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Original Article

Cardioprotective Effects of Piperlongumine against Doxorubicin-Induced Myocardial Infarction via Down-Regulating Cardiac Biomarkers in Rats

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ABSTRACT

Background: Doxorubicin, an extensively utilized antineoplastic agent, has been a significant contributor to the remarkable advancements in cancer treatment over the past several decades. However, the clinical usefulness of this powerful drug is often restricted by its well-documented cardiotoxic effects. **Objectives:** The present research work was focused at unveiling the therapeutic roles of piperlongumine against doxorubicin-induced cardiotoxicity. **Materials and Methods:** The experimental rats were received 2.5 mg/kg of doxorubicin to induce cardiotoxicity, subsequently treated with 50 mg/kg of piperlongumine. Plethysmography via the tail-cuff was employed to assess hemodynamic parameters. The oxidative and antioxidative biomarkers, and cardiac function markers, were quantified using a commercial assay kits. The concentrations of inflammatory biomarkers and apoptotic proteins were also assessed using the kits. **Results:** The piperlongumine treatment considerably enhanced the heart and body weights of the doxorubicin-induced rats. The piperlongumine treatment significantly lowered the hemodynamic parameters in rats with doxorubicin-induced cardiotoxicity. Furthermore, the piperlongumine treatment markedly reduced the activities of cardiac function markers and inflammatory biomarkers in the doxorubicin-induced rats. **Conclusion:** The present findings exhibited that piperlongumine can mitigate the biochemical and cardiotoxic effects induced by doxorubicin in rats via its robust antioxidant and anti-inflammatory effects. Thus, piperlongumine may serve as an novel treatment option in conjunction with doxorubicin to mitigate its cardiotoxic effects.

Keywords: Cardiotoxicity, Piperlongumine, Cardiomyocytes, Hemodynamic markers, Heart weight.

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INTRODUCTION

Doxorubicin, a highly effective anthracycline chemotherapeutic agent, has been widely utilized to treat numerous malignancies. Though, the clinical usefulness of doxorubicin is significantly restricted by its increasing cardiotoxicity, which can result in permanent and potentially life-threatening complications such as cardiomyopathy and congestive heart failure.[1] Doxorubicin-induced cardiac toxicity refers the harmful impacts of this chemotherapeutic drug on the cardiovascular system, resulting in cardiomyopathy and heart failure. The primary mechanism underlying this condition involves the excessive production of ROS and the disruption of cellular signaling pathways, which ultimately result in cardiomyocytes necrosis and impaired cardiac activity.[2] The development of doxorubicin-induced cardiotoxicity is multifactorial, with both patient-specific and treatment-associated causes participating in the risk. Patient-related factors include advanced age, underlying cardiovascular conditions, and genetic predisposition, while treatment-related factors include cumulative dose, concomitant use of other cardiotoxic agents, and administration route.[3] The adverse effects of doxorubicin-induced cardiotoxicity can be profound, impacting the patient's quality of life. Patients may experience a range of symptoms, including decreased exercise tolerance, heart failure, and arrhythmias, which can lead to hospitalization, reduced treatment efficacy, and increased mortality. Moreover, the management of doxorubicin-induced cardiotoxicity can be challenging, often requiring close monitoring, early intervention, and the use of cardioprotective agents.[4]

The mechanisms of doxorubicin-induced cardiac toxicity are intricate and multifaceted, encompassing the production of ROS, impairment of mitochondrial activity, and stimulation of inflammatory pathways. Doxorubicin primarily induces cardiotoxicity by the accumulation of ROS following oxidative

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stress. Doxorubicin can interact with cellular enzymes, like NADPH oxidases, resulting in the generation of ROS. These reactive species can damage major cell components, ultimately resulting in cardiomyocyte dysfunction and apoptosis.[5] Another contributing factor to doxorubicin-induced cardiotoxicity is the disruption of mitochondrial function. Doxorubicin has been shown to impair mitochondrial respiration, leading to decreased ATP production and increased oxidative stress within cardiomyocytes. This mitochondrial dysfunction can also trigger the release of pro-apoptotic markers, further exacerbating apoptosis and cardiac dysfunction. Understanding these underlying mechanisms is crucial to developing techniques to attenuate the deleterious cardiac effects of doxorubicin and improve the clinical management of cancer patients receiving this chemotherapeutic agent.[6]

While current treatment strategies aim to address this problem, they are often hampered by their limited potential and the potential for adverse effects. Despite the advancements, the search for more effective and safer alternatives continues, with increasing attention being directed towards the potential of plant-derived bioactive compounds. These naturally occurring molecules have demonstrated promising cardioprotective properties, making them an attractive option for managing doxorubicin-induced cardiotoxicity.[7] One of the essential mechanisms underlying doxorubicin's cardiotoxicity is its potential to trigger oxidative stress and inflammation within the myocardium. Many plant-based compounds exhibit significant antioxidant and anti-inflammatory characteristics, making them intriguing options for alleviating these detrimental consequences.[8] Piperlongumine is a primary bioactive alkaloid compound present in the fruits and roots of the *Piper longum* plant. The various pharmacological properties of the piperlongumine was already well reported in numerous previous studies, including anticancer,[9] anti-atherosclerosis,[10] immunosuppressive,[11] anti-arthritis,[12] anti-lupus nephritis[13] properties, and mitigated the encephalomyelitis.[14] However, the therapeutic effects of piperlongumine against drug-induced cardiotoxicity was not assessed yet. Therefore, the present research work was focused at unveiling the therapeutic roles of piperlongumine against doxorubicin-induced cardiotoxicity.

MATERIALS AND METHODS

Experimental Rats

The 10 to 12 weeks aged Wistar rats were housed in well-sanitized conditions with a 12-hr light/dark sequence, a temperature of 21-24°C, and humidity of 50-60%. They were provided with free access to pellet food and water. Before the commencement of the investigation, rats were acclimated to the laboratory environment for seven days.

Treatment groups

The acclimated rats was categorized into four groups as follows. Group I: control; Group II: rats subjected to cardiotoxicity induction through the administration of doxorubicin (2.5 mg/kg) for 14 days;[15] Group III: rats was treated with 50 mg/kg of piperlongumine for 3 days before and along with the doxorubicin challenge via oral gavage; Group-IV: rats were received only piperlongumine (50 mg/kg) without any other treatments. The body weight of the each rat was meticulously measured before and after the treatments. At the conclusion, rats were sacrificed following anesthesia, and blood was collected for serum preparation by centrifuging at 10,000 rpm for 15 min. The serum was stored at 4°C for additional experiments. A sample of cardiac tissues was stored at -20°C for biochemical experiments.

Analysis of hemodynamic parameters

The control and experimental rats were subjected to measure the blood pressure indicators. Tail-cuff plethysmography and a pressure meter were employed to assess the Systolic Arterial Pressure (SAP), Mean Arterial Pressure (MAP), Diastolic Arterial Pressure (DAP), and Heart Rate (HR) levels of the experimental rats.

Analysis of oxidative stress markers

The oxidative stress and antioxidant biomarkers in the cardiac tissues were evaluated using the commercial kits. The concentrations of TBARS, Superoxide Dismutase (SOD), Catalase (CAT), Glutathione (GSH), Glutathione-S-Transferase (GST), Glutathione Reductase (GR), and glutathione peroxidase (GPx) were examined utilizing the commercial diagnostic kits. The assays were performed with three replicates using the specifications suggested by the manufacturer (Abcam, USA).

Analysis of serum cardiac biomarkers

The serum cardiac biomarker concentrations, Specifically Aspartate Transaminase (AST), Lactate Dehydrogenase (LDH), and Creatine Kinase (CK) in both control and experimental rats were analyzed using commercial test kits as per the manufacturer's specifications (MyBioSource, USA).

Analysis of cardiac biomarkers

The serum concentrations of Heart-Type Fatty Acid Binding Protein (H-FABP), Glycogen Phosphorylase isoenzyme BB (GP-BB), and Creatine Kinase MB Enzyme (CK-MB) in the experimental rats were analyzed using the kits as per the manufacturer's recommendations (Elabscience, USA).

Analysis of inflammatory biomarkers

The serum concentrations of inflammatory biomarkers, including Interferon-γ (INF-γ), Monocyte Chemoattractant Protein-1 (MCP-1), Tumor Necrosis Factor-α (TNF-α), and Interleukin-1β

(IL-1β) in the control and experimental rats were assessed using the test kits and adhering to the manufacturer's protocols (MyBioSource, USA).

Analysis of apoptotic proteins

The apoptotic protein concentrations, such as Bad and caspase-3 in the cardiac tissue homogenates of the experimental rats was studied using the commercial assay kits by the guidelines of manufacturer (Abcam, USA).

Statistical analysis

The values were illustrated as mean±SD from three individual assays. One-way ANOVA and Tukey's *post hoc* assay was utilized to assess the significance between treatment groups, with $p<0.05$ being significant.

RESULTS

Effect of piperlongumine on the heart and body weight changes in the experimental rats

In response to doxorubicin-induced cardiotoxicity, the rats exhibited a decline in both heart and body weight. Conversely, the 50 mg/kg of piperlongumine treatment demonstrated significant enhancement in the heart and body weight of doxorubicin-induced rats. The rats treated alone with piperlongumine had no significant alterations in heart and body weight, resembling the control group (Figure 1).

Effect of piperlongumine on hemodynamic parameters in experimental rats

Figure 2 demonstrates that the blood pressure indicators, namely SAP, DAP, MAP, and HR significantly decreased in rats experiencing doxorubicin-induced cardiac damage. Interestingly, the piperlongumine (50 mg/kg) treatment significantly mitigated these alterations and notably enhanced the SAP, DAP, MAP, and HR in the doxorubicin-treated rats with cardiotoxicity. Additionally, the rats treated with piperlongumine alone did not display significant changes in blood pressure markers (Figure 2).

Effect of piperlongumine on oxidative stress biomarkers in heart tissues of the experimental rats

The biomarkers of oxidative stress was assessed in the cardiac tissues, and findings are displayed in Figure 3. The rats with doxorubicin-induced cardiotoxicity demonstrated increased TBARS levels, whilst the antioxidant levels were markedly diminished relative to the control group. Captivatingly, the 50 mg/kg of piperlongumine treatment significantly reduced the TBARS levels and enhanced antioxidant concentrations, including GSH, GPx, GST, GR, CAT, and SOD in the heart tissues of doxorubicin-induced rats. No significant alterations were observed in these markers in the piperlongumine alone-treated rats, which closely resembled the control (Figure 3).

Effect of piperlongumine on serum cardiac biomarkers in experimental rats

The serum concentrations of cardiac biomarkers, including LDH, AST, and CK were analyzed, with the results depicted in Figure 4. The doxorubicin-treated rats exhibited a considerable elevation in LDH, AST, and CK concentrations when compared with control. Intriguingly, the piperlongumine (50 mg/kg) treatment exhibited reduced LDH, AST, and CK concentrations. The LDH, AST, and CK levels in rats treated with piperlongumine (50 mg/kg) alone did not substantially differ from the control group.

Effect of piperlongumine on cardiac biomarkers in experimental rats

Figure 5 illustrates that the serum concentrations of GP-BB, H-FABP, and CK-MB was remarkably increased in the doxorubicin-treated rats. In contrast, the rats with of piperlongumine (50 mg/kg) treatment exhibited a considerable decrease in the concentrations GP-BB, H-FABP, and CK-MB in the doxorubicin-treated rats. There were no major differences in these markers in the rats with piperlongumine alone treatment, resembling the control group (Figure 5).

Effect of piperlongumine on inflammatory markers in serum of experimental rats

Figure 6 demonstrated that the serum concentrations of inflammatory markers, specifically IL-1β, TNF-α, INF-γ, and MCP-1 was drastically augmented in the doxorubicin-treated rats in comparison to the control. The piperlongumine (50 mg/kg) treatment significantly reduced the IL-1β, TNF-α, INF-γ, and MCP-1 concentrations in the serum of doxorubicin-induced rats. The rats treated with piperlongumine alone and control rats exhibited similar amounts of these markers compared with control (Figure 6).

Effect of piperlongumine on apoptotic proteins in experimental rats

Figure 7 demonstrates that the doxorubicin-treated rats displayed a notable elevation in the levels of Bad and caspase-3 in their cardiac tissues. Interestingly, the piperlongumine (50 mg/kg) treatment appreciably diminished the concentrations of Bad and caspase-3 in the cardiac tissues of doxorubicin-induced rats. Furthermore, the rats treated with piperlongumine alone did not exhibit significant alterations in the Bad and caspase-3 concentrations compared with control (Figure 7).

DISCUSSION

Doxorubicin, a widely used chemotherapeutic agent, has been associated with a significant adverse effect known as cardiotoxicity. This condition can lead to cardiomyopathy, a deterioration of the heart's structure and function, which can be life-threatening. Researchers have highlighted the importance of understanding the

underlying mechanisms of doxorubicin-induced cardiotoxicity to develop effective strategies for mitigating this complication.[16] A crucial aspect of this context is the examination of alterations in body and heart weights, which might yield significant insights into the advancement of doxorubicin-induced cardiac toxicity. Doxorubicin has been shown to disrupt mitochondrial activity, leading to increased accumulation of ROS and subsequent cell death in cardiomyocytes.[17] This cardiotoxic effect can result in the loss of heart muscle weight, ultimately leading to a decrease in heart weight. Additionally, doxorubicin-induced cardiotoxicity can also affect the overall body weight, as the drug can interfere with various physiological processes, including metabolism and energy homeostasis.[18] Examining alterations in body weight and heart weight within the framework of doxorubicin-induced cardiotoxicity facilitates a more comprehensive evaluation of the underlying pathogenic mechanisms. This information can facilitate the creation of targeted therapies to lessen the cardiac toxicity effects of doxorubicin and enhance the overall well-being

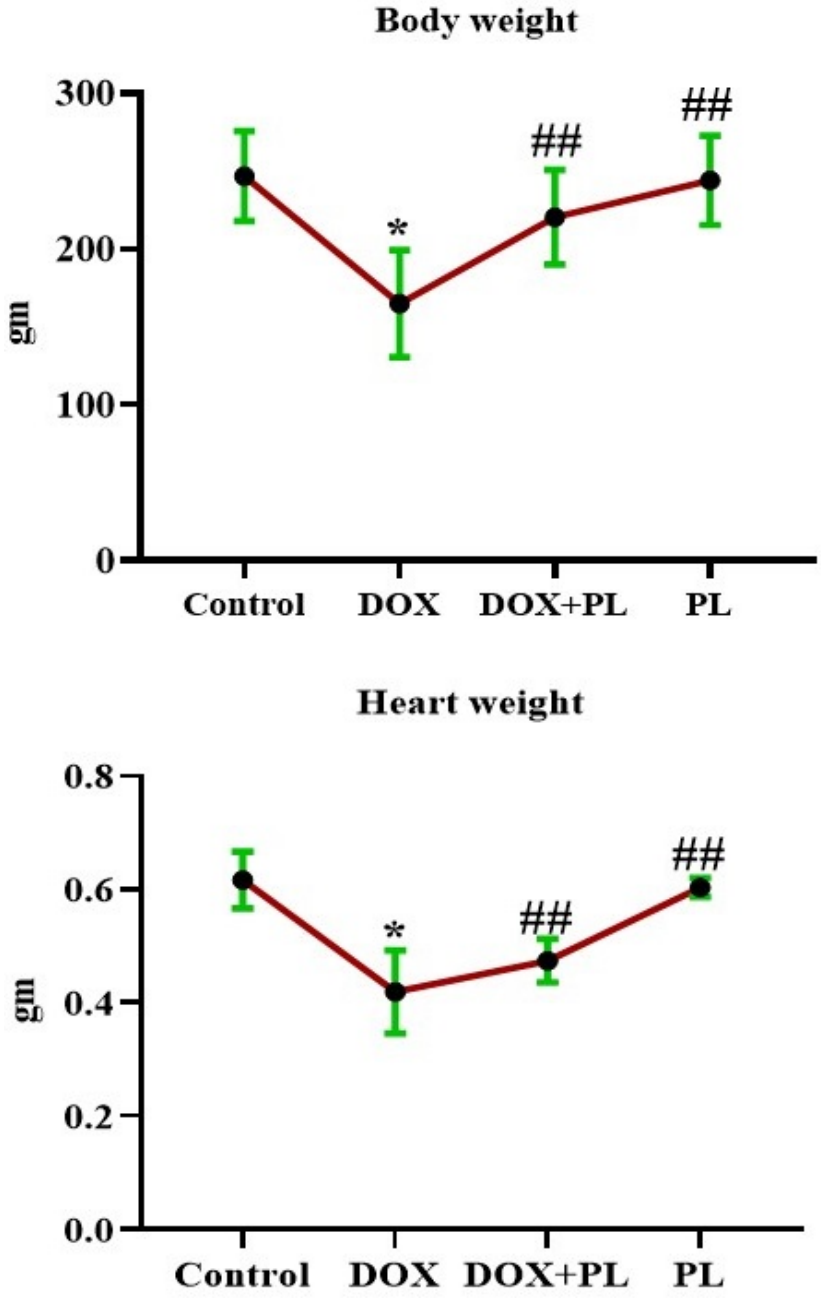

Figure 1: Effect of piperlongumine on the heart and body weight changes in the experimental rats.The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

of cancer patients receiving this treatment.[19] The outcomes of this work exhibited decreased heart and body weight in the rats with doxorubicin-induced cardiotoxicity. Whereas, the piperlongumine treatment considerably enhanced the heart and body weight of doxorubicin-induced rats (Figure 1).

The mechanisms of doxorubicin-induced cardiac toxicity are intricate and multifaceted, with oxidative stress and antioxidant defense imbalance being pivotal factors.[20] Doxorubicin has been demonstrated to provoke the production of ROS in cardiac tissues, resulting in oxidative injury to cellular macromolecules. Oxidative stress can compromise mitochondrial function, affect calcium homeostasis, and trigger apoptotic pathways, ultimately resulting in cardiomyocyte death. Furthermore, doxorubicin can also interfere with the antioxidant mechanisms, like SOD, CAT, and GPx, further worsening the oxidative stress.[21] One of the key oxidative stress markers that has been widely studied in doxorubicin-induced cardiotoxicity is TBARS, which are an indicator of lipid peroxidation. Increased levels of TBARS in the heart tissues can indicate the occurrence of oxidative injury and cellular dysfunction. In addition, the analysis of primary antioxidants can provide valuable insights into the body's defense mechanisms against the oxidative stress induced by doxorubicin.[22] In addition to oxidative injury, doxorubicin-induced cardiotoxicity has also been connected with the activation of inflammation and the accumulation of potentially cardiotoxic metabolites. These causes may lead to heart dysfunction and remodeling. Various treatments targeting oxidative stress and antioxidant imbalance have been investigated to mitigate doxorubicin-induced cardiac toxicity. One method involves the administration of antioxidant supplements, including vitamins, minerals, and phytochemicals.[23] The current findings revealed elevated TBARS levels and reduced antioxidants in the heart tissues of rats administered doxorubicin (Figure 3). The piperlongumine treatment significantly reduced TBARS and increased antioxidant levels in the heart tissues of rats subjected to doxorubicin induction.

Doxorubicin's cardiotoxic effects have been well documented, with its potential to trigger oxidative stress, inflammation, and mitochondrial dysfunction as the primary drivers of myocardial injury. However, the assessment of serum biomarkers remains crucial for the early diagnosis of doxorubicin-induced

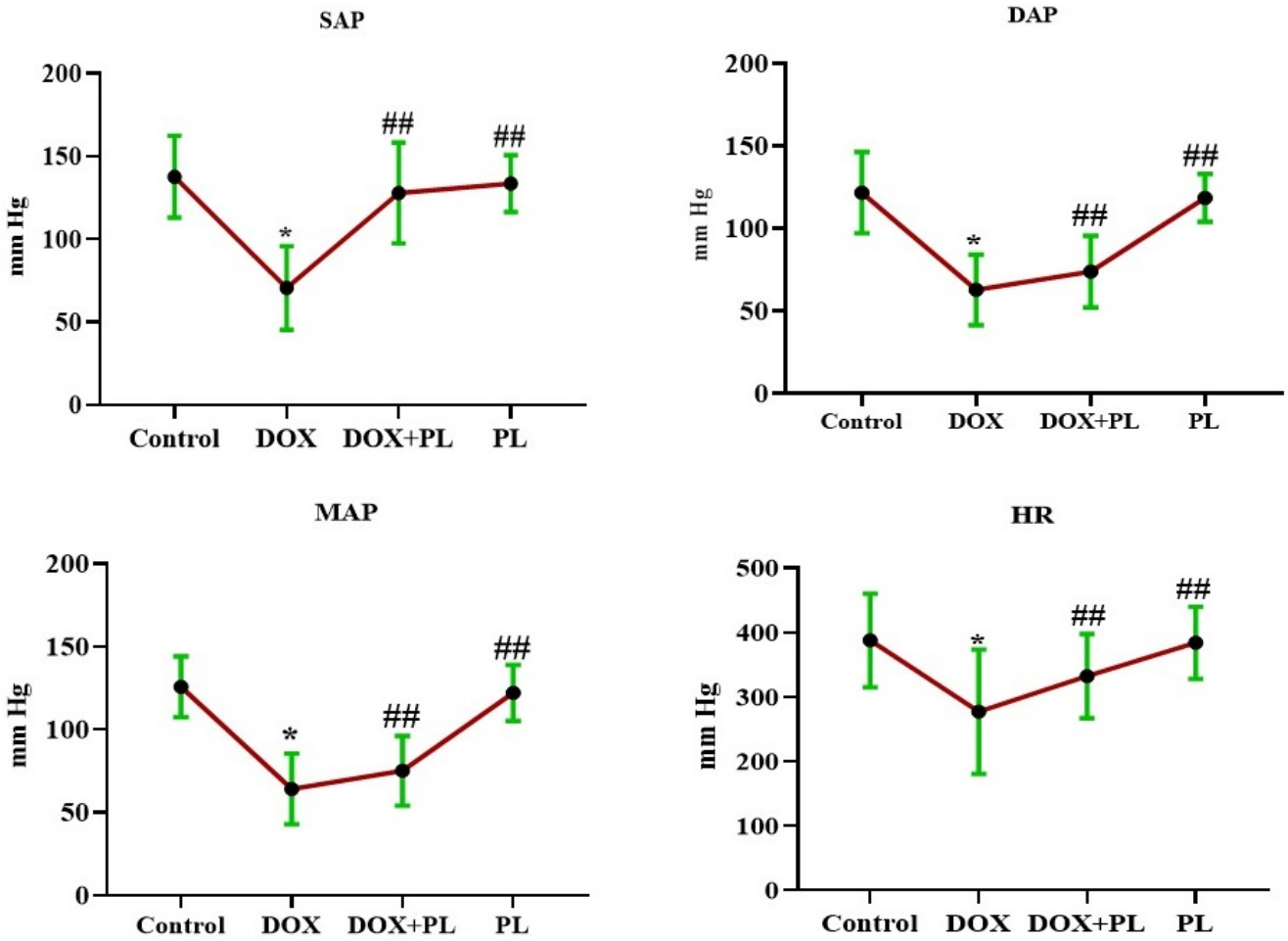

Figure 2: Effect of piperlongumine on the hemodynamic parameters in the experimental rats. The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

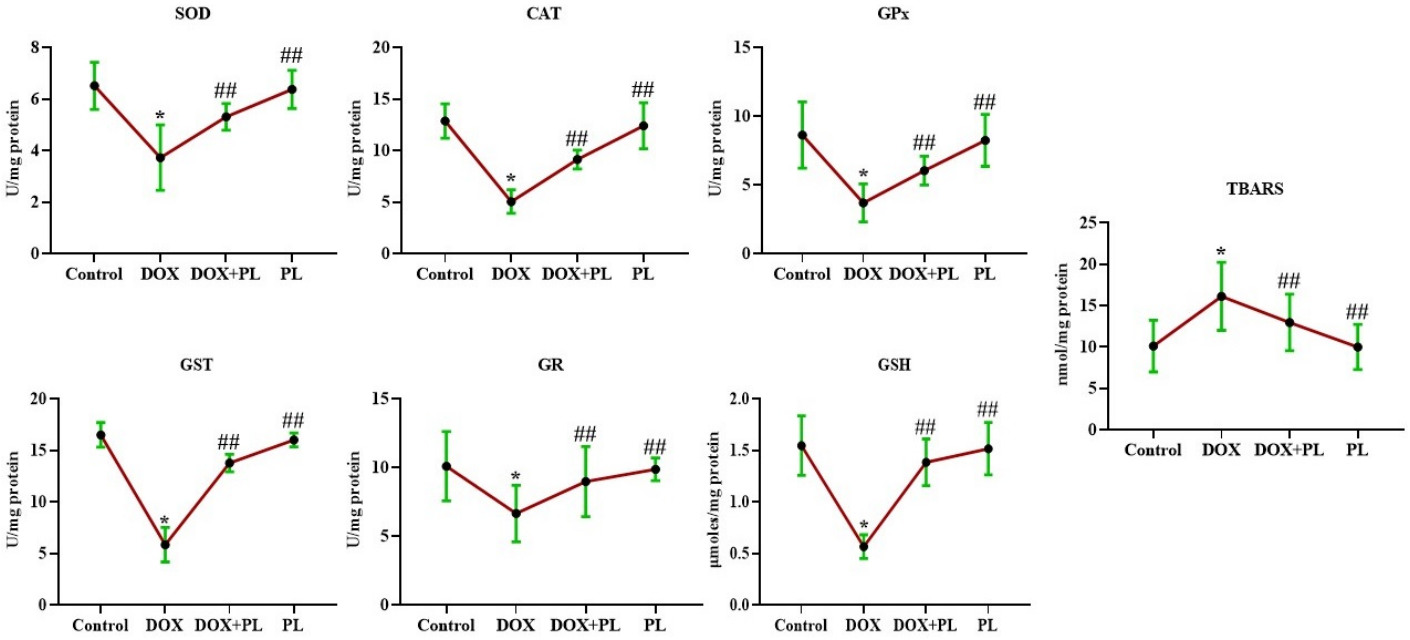

Figure 3: Effect of piperlongumine on the oxidative stress markers in the heart tissues of the experimental rats. The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

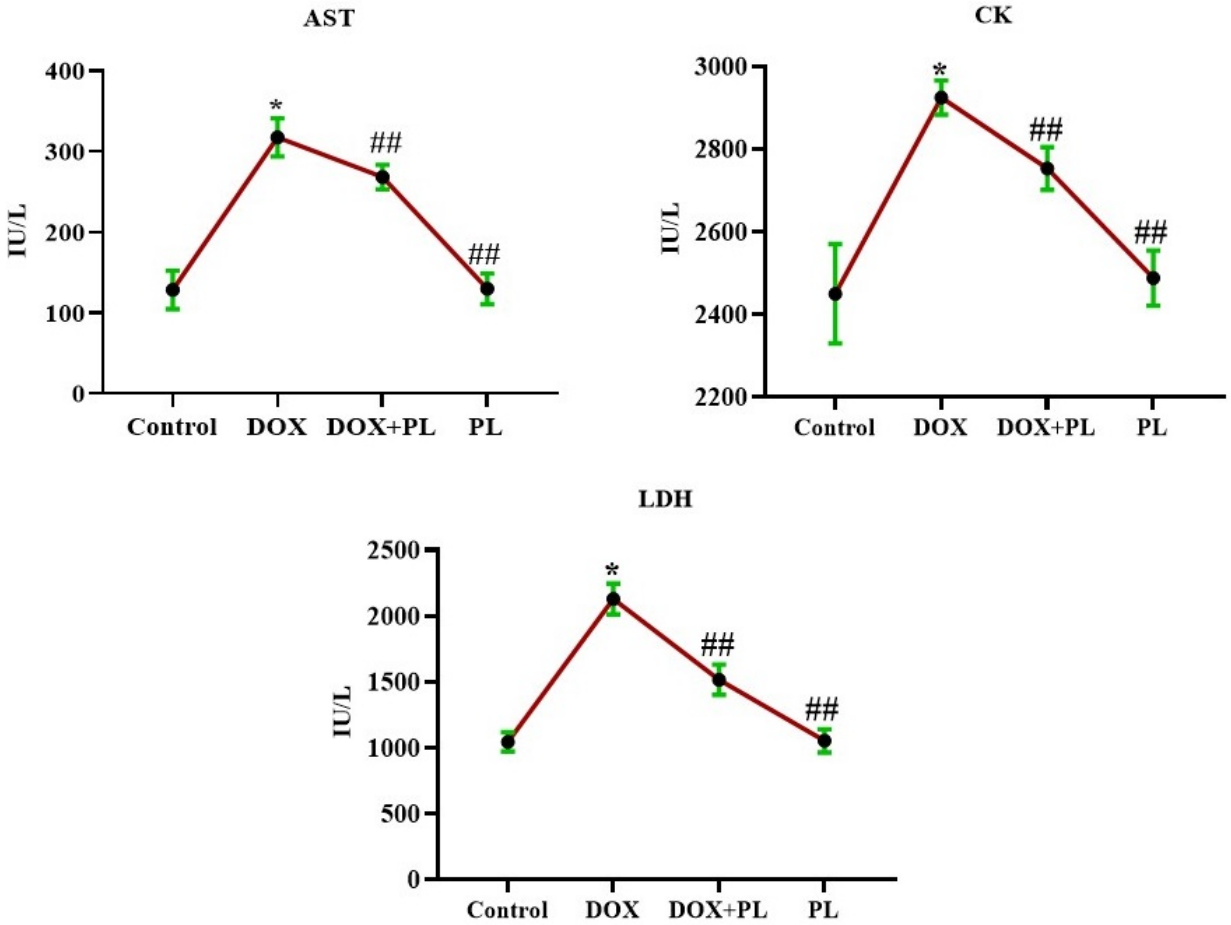

Figure 4: Effect of piperlongumine on the serum cardiac biomarker levels in the experimental rats. The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

cardiotoxicity. AST is an enzyme present in various tissues, including the heart, liver, and skeletal muscle.[24] Elevated AST levels in the serum can be indicative of myocardial injury, as doxorubicin-induced oxidative stress can result in the release of this enzyme into the bloodstream. Similarly, LDH, an enzyme involved in energy metabolism, has been shown to be augmented during the doxorubicin-induced cardiotoxicity, reflecting the disruption of myocardial function and energy production. CK, an enzyme primarily found in the skeletal and cardiac muscle, is also a well-established marker of myocardial injury. The analysis of serum biomarkers, including AST, LDH, and CK is crucial for the early detection of doxorubicin-induced cardiac damage.[25] The present findings evidenced the elevated concentrations of LDH, AST, and CK in the doxorubicin-treated rats. Fascinatingly, the treatment with piperlongumine exhibited reduced LDH, AST, and CK concentrations in the rats with doxorubicin-induced cardiotoxicity (Figure 4).

In the context of doxorubicin-induced cardiac damage, the analysis of specific serum biomarkers has emerged as a crucial strategy to monitor and mitigate the development of doxorubicin-induced cardiotoxicity. H-FABP is a small cytoplasmic protein that is predominantly expressed in the myocardium. Elevated levels of H-FABP in the serum can offer as an early marker of heart injury, as the protein is rapidly released into the bloodstream upon cardiomyocyte damage.[26] Similarly, GP-BB is an enzyme that is specific to the myocardium and its increased serum concentrations can reflect ongoing myocardial injury. CK-MB, on the other hand, is a cardiac-specific isoenzyme of CK, and its elevation in the serum is a well-established marker of myocardial necrosis.[27] The importance of these serum biomarkers in the milieu of doxorubicin-induced cardiac damage has been highlighted in several studies. The analysis of serum biomarkers, such as H-FABP, GP-BB, and CK-MB, provides valuable insights into the early detection of doxorubicin-induced cardiac toxicity. This information can aid in the advancement of targeted methods to prevent or lessen the side effects of the doxorubicin, ultimately improving the overall prognosis and quality of life for cancer patients.[28] The current work evidenced the increased serum concentrations of GP-BB, H-FABP, and CK-MB in the doxorubicin-induced cardiotoxicity rats (Figure 5). Interestingly, the rats treated with piperlongumine exhibited a considerable

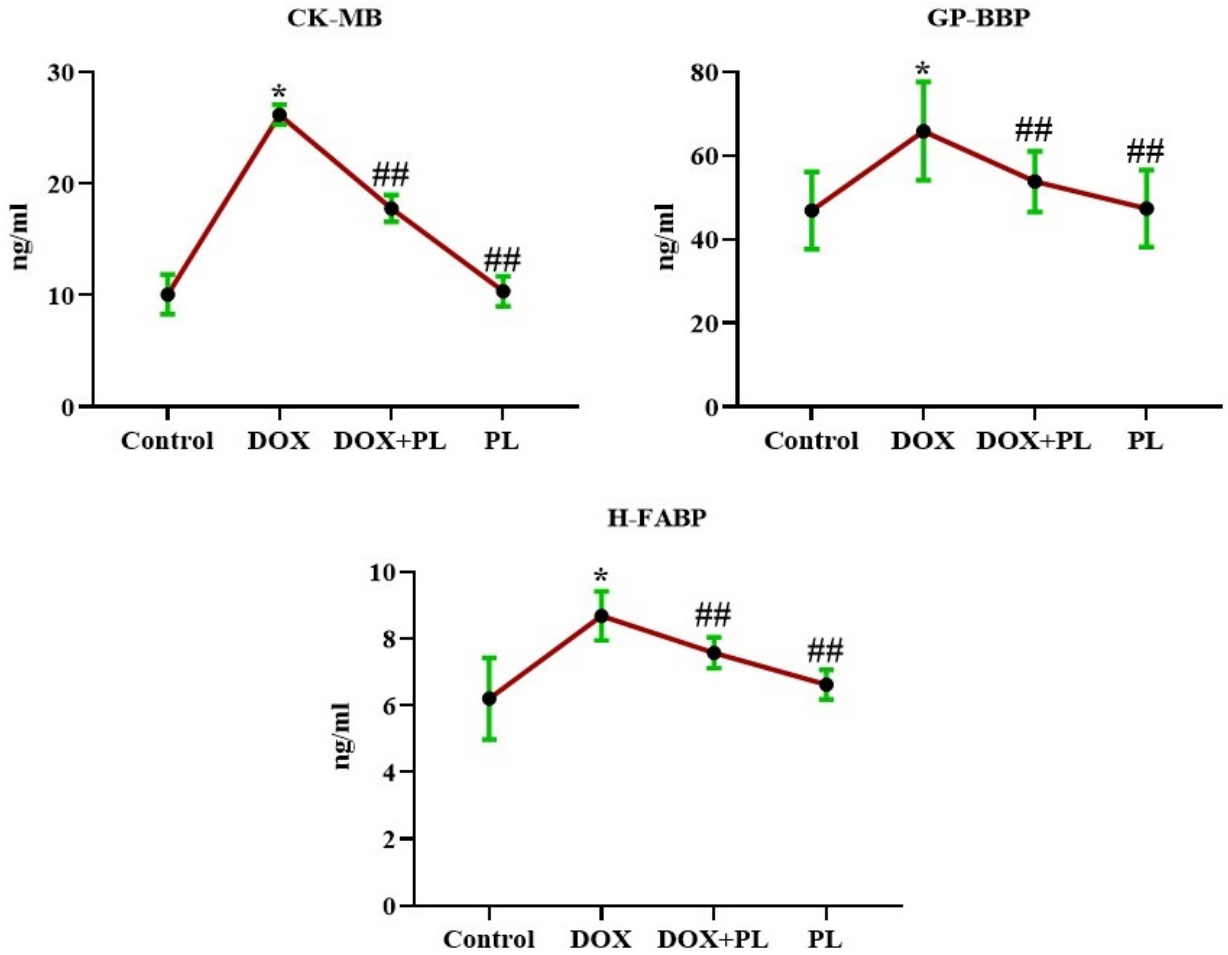

Figure 5: Effect of piperlongumine on the cardiac biomarker levels in the experimental rats. The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

diminution in the GP-BB, H-FABP, and CK-MB concentrations in the serum of doxorubicin-treated rats.

The causes of doxorubicin-induced cardiotoxicity are complex, with the dysregulation of critical inflammatory cytokines implicated in its pathogenesis. The augmented inflammatory biomarkers, like IF-γ, MCP-1, TNF-α, and IL-1β have been participated in the onset of the doxorubicin-induced cardiotoxicity. These inflammatory mediators can contribute to the stimulation of signaling cascades that leads to cardiomyocyte necrosis and the development of cardiac dysfunction.[29] Emerging data highlights that the production of IL-1β by macrophages in response to doxorubicin treatment plays a central role in the initiation of the inflammatory response. Doxorubicin activates the NLRP3 inflammasome, leading to the processing and production of IL-1β, which then induces the release of additional proinflammatory cytokines, including TNF-α and MCP-1.[30] In addition to IL-1β, MCP-1 and TNF-α have also been implicated in the pathological processes underlying doxorubicin-induced cardiotoxicity. MCP-1, a chemokine responsible for the recruitment of monocytes and macrophages, has been shown to be upregulated in response to doxorubicin exposure, potentially exacerbating the inflammatory milieu in the myocardium. Furthermore, TNF-α has been noted to play a role in the induction of cardiomyocyte apoptosis and mitochondrial dysfunction, which are hallmarks of doxorubicin-induced cardiotoxicity.[31] Strategies focused at attenuating the adverse effects of these inflammatory cytokines have demonstrated promising results in mitigating doxorubicin-induced cardiotoxicity. In similar manner, the drastically increased concentrations of IL-1β, TNF-α, INF-γ, and MCP-1 were observed in the serum of doxorubicin-treated rats (Figure 6). However, the treatment with piperlongumine considerably reduced the concentrations of these inflammatory markers in the doxorubicin-induced rats.

The disruption of cellular signaling pathways is one of the key mechanisms underlying doxorubicin-induced cardiac toxicity, which can result in apoptosis and ultimately heart failure. The Bad protein, part of the Bcl-2 protein family, is essential in the regulation of apoptosis. Bad is a pro-apoptotic protein that facilitates apoptosis by attaching to and inhibiting the anti-apoptotic proteins Bcl-2 and Bcl-xL. The activation of Bad has been recognized as a contributing component to cardiomyocytes apoptosis.[32] Doxorubicin has been demonstrated

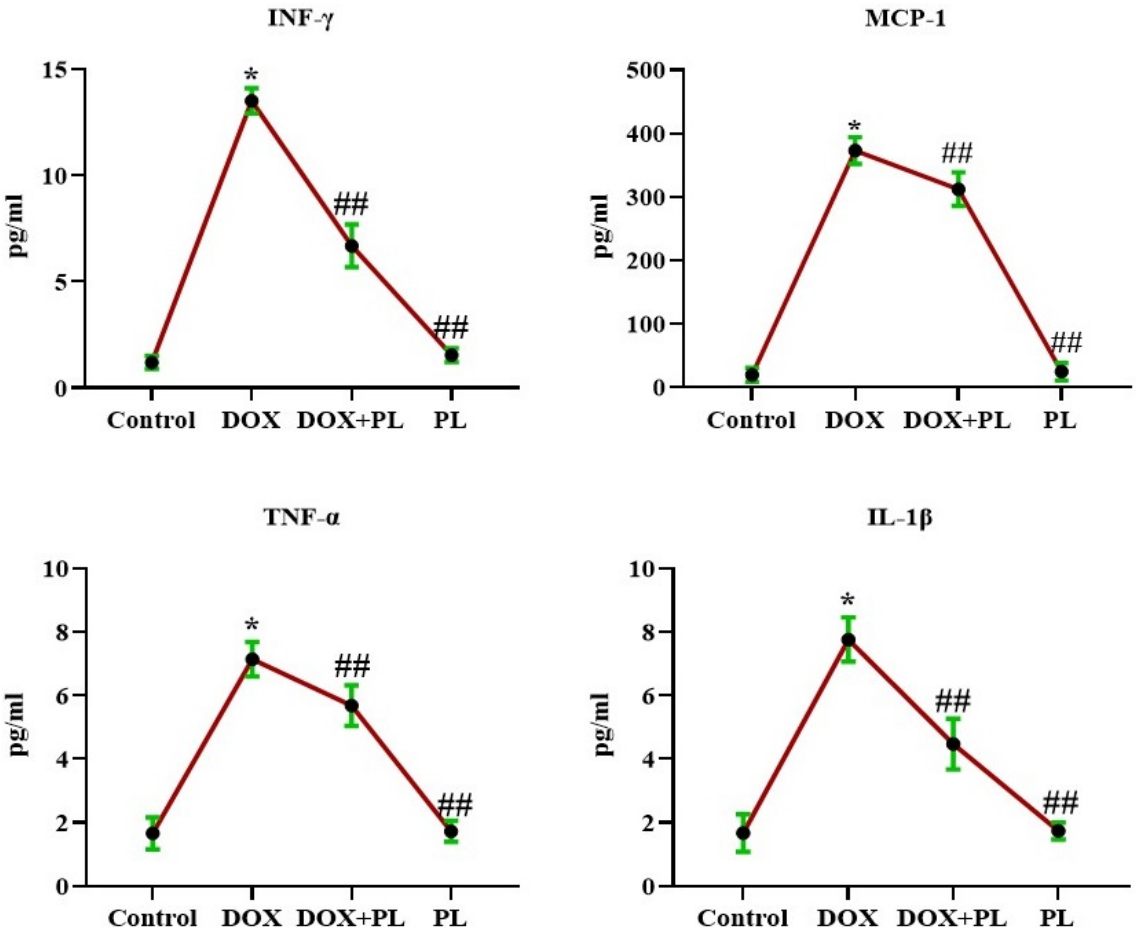

Figure 6: Effect of piperlongumine on the inflammatory marker levels in the serum of experimental rats. The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

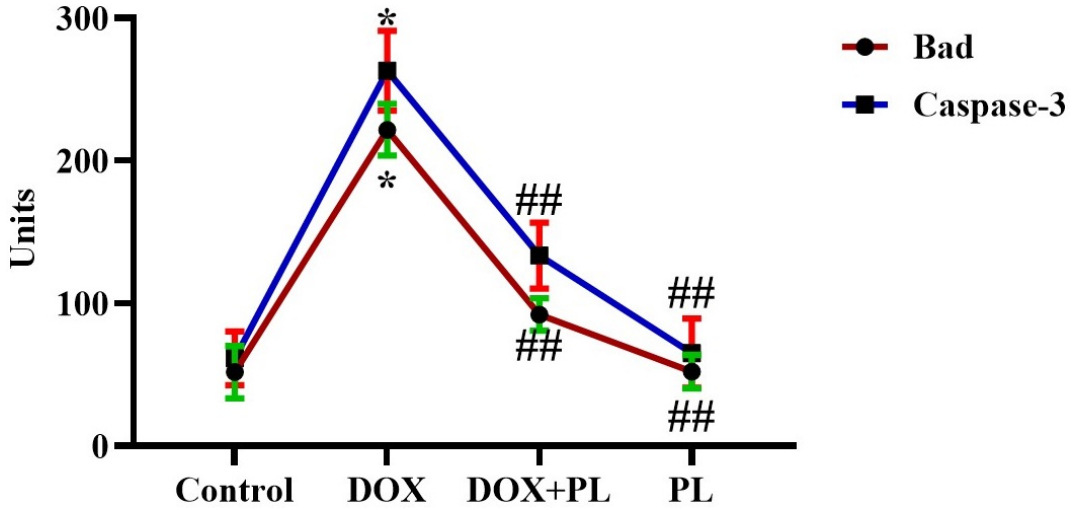

Figure 7: Effect of piperlongumine on the apoptotic protein levels in the experimental rats. The results are presented as a mean±SD from three replicate tests. All data are subjected to statistical analysis using one-way ANOVA and Tukey's *post hoc* tests. '*' indicates that the results are significant at $p<0.01$ relative to the control group; '##' indicates that the results are significant at $p<0.05$ relative to the doxorubicin-induced group. DOX: Doxorubicin; PL: Piperlongumine.

to activate Bad, resulting in the release of cytochrome-c from the mitochondria and the resulting activation of caspase-3, a principal executor of apoptosis. This sequence of events ultimately leads to the demise of cardiomyocytes, the principal cells accountable for heart function.[33] Caspase-3, an essential executioner caspase, mediates the proteolytic cleavage of many cellular substrates, culminating in cell death. The activation of caspase-3 signifies doxorubicin-induced cardiomyocyte apoptosis. The activation of caspase-3 induces the destruction of structural and regulatory proteins, leading to the typical morphological alterations connected with apoptosis.[34] Taken together, the available evidence suggests that the Bad and caspase-3 proteins are a critical players in the pathophysiology of doxorubicin-induced cardiac toxicity.[35] Targeting these molecular pathways and understanding the intricate interplay between apoptotic regulators may lead to the advancement of more talented strategies to prevent or alleviate the devastating cardiac complications associated with doxorubicin treatment.[36] In this work, the increased concentrations of Bad and caspase-3 was observed in the heart tissues of doxorubicin-treated rats. Interestingly, the piperlongumine remarkably down-regulated the Bad and caspase-3 concentrations in the heart tissues of doxorubicin-induced rats (Figure 7). These findings evidenced that piperlongumine can protect the cardiomyocytes from the doxorubicin-induced apoptosis.

CONCLUSION

In summary, the present results exhibited that piperlongumine treatment can mitigate the biochemical and cardiotoxic effects induced by doxorubicin in rats via its robust antioxidant and anti-inflammatory effects. Consequently, piperlongumine may serve as an novel treatment option in conjunction with doxorubicin to mitigate its cardiotoxic effects. Further investigations are necessary to enhance understanding of the anti-inflammatory and antioxidant mechanisms of piperlongumine in relation to doxorubicin-induced cardiotoxicity.

ACKNOWLEDGEMENT

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ABBREVIATIONS

ROS: Reactive Oxygen Species; **SAP:** Systolic Arterial Pressure; **DAP:** Diastolic Arterial Pressure; **HR:** Heart Rate; **SOD:** Superoxide Dismutase; **GST:** Glutathione-S-Transferase; **AST:** Aspartate Transaminase; **LDH:** Lactate Dehydrogenase: **CK:** Creatine Kinase; **H-FABP:** Heart-Type Fatty Acid Binding Protein; **GP-BB:** Glycogen Phosphorylase Isoenzyme BB; **INF-γ:** Interferon-γ; **MCP-1:** Monocyte Chemoattractant Protein-1; **IL:** Interleukin.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

This work has approved by the institutional animal ethical committee by The Third People's Hospital of Yibin, Sichuan Province, 644000, China.

SUMMARY

Doxorubicin, a commonly utilized chemotherapeutic drug, is linked to notable side effects, majorly cardiotoxicity. This disorder may result in cardiomyopathy, a decline in the heart's structure and function, potentially posing a life-threatening risk. Piperlongumine is a principal bioactive alkaloid found in the

fruits and roots of the Piper longum plant. The current findings demonstrate that piperlongumine therapy can alleviate the biochemical and cardiotoxic effects caused by doxorubicin in rats through its potent antioxidant and anti-inflammatory properties.

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