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Original Article

Sinensetin Shows Cardioprotective Activity against Isoproterenol-Induced Acute Myocardial Infarction in Rats via Regulation of Inflammatory Pathways

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ABSTRACT

Background: Myocardial Infarction (MI), or heart attack, is a severe complication resulting from a sudden and prolonged interruption of blood flow to a portion of the myocardium, causing cellular ischemia and subsequent necrosis. The increasing incidence of MI is a significant public health issue worldwide. **Objectives:** In this work, we established the Isoproterenol (ISO)-induced MI model in rats, demonstrating that sinensetin treatment exhibited considerable protective activity against MI in rats. **Materials and Methods:** The experimental rats received ISO (85 mg/kg) to induce MI and were co and pre-treated with sinensetin. The concentrations of biochemical markers such as uric acid, C-Reactive Protein (CRP), and total protein was assessed. The tissue injury marker enzymes and antioxidant levels were analyzed utilizing kits. The concentrations Na^+, Ca^{2+}, and K^+ ions, as well as inflammatory cytokine levels were analyzed using kits. The levels of HO-1/NQO-1 and NF-κB was assessed using appropriate kits. **Results:** The present results indicated that sinensetin treatment resulted in a decreased uric acid and CRP levels with increased total protein levels in the MI rats. The serum concentrations of cardiac tissue injury marker enzymes were markedly diminished, although these levels in cardiac tissues was elevated by the sinensetin in the MI rats. In addition, sinensetin treatment considerably elevated antioxidant levels, diminished inflammatory cytokines, and modulated Na^+, Ca^{2+} and K^+ ion concentrations in MI rats. Furthermore, the sinensetin treatment significantly increased the decrease NF-κB and regulated HO-1/NQO-1 concentrations in the MI rats. **Conclusion:** The current findings indicate that sinensetin treatment can ameliorate and protect the ISO-induced cardiac damage in rats. Consequently, sinensetin treatment may serve as a novel salutary candidate to treat MI.

Keywords: Cardiac injury, HO-1/NQO-1 Pathway, Isoproterenol, Inflammation, Sinensetin.

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INTRODUCTION

Myocardial Infarction (MI), generally known as a heart attack, constitutes a critical medical emergency arising from an abrupt and sustained disruption of blood flow to a segment of the myocardium, resulting in cellular ischemia and subsequent necrosis.[1] This ischemic insult typically stems from thrombotic occlusion of a coronary artery, often superimposed on a pre-existing atherosclerotic plaque. The ensuing deprivation of oxygen and essential nutrients precipitates a cascade of detrimental cellular events, culminating in irreversible damage to the cardiomyocytes, the functional contractile units of the heart. The prompt restoration of coronary perfusion represents the cornerstone of acute MI management, aiming to recover exposed myocardium and mitigate the extent of irreversible injury.[2] The precipitating event in most MI is the rupture or erosion of an atherosclerotic plaque within a coronary artery. This exposes the thrombogenic subendothelial matrix to circulating blood, triggering the rapid development of a thrombus that can partially or completely block the vessel lumen. The pathophysiology of MI is a complex interplay of factors, commencing with the gradual buildup of lipids and inflammatory cells within the arterial intima, resulting in the development of atherosclerotic plaques over decades. These plaques, often asymptomatic for many years, can become vulnerable to rupture due to factors such as inflammation, shear stress, and plaque composition.[3]

The global prevalence of MI is a substantial public health concern, exhibiting considerable variation across geographical regions and demographic groups. Epidemiological studies reveal a higher incidence in developed countries, attributable to factors such as aging populations, lifestyle choices, and the prevalence of cardiovascular risk factors. However, the incidence is rapidly increasing in developing nations, mirroring the adoption of Westernized diets and sedentary lifestyles. Age is a paramount

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risk factor, with the incidence of MI escalating significantly with advancing years. Men generally exhibit a higher propensity for MI compared to women, although this disparity diminishes with age, particularly after menopause.[4] Genetic predisposition also contributes to the risk profile, with individuals possessing a family history of premature coronary artery disease facing an elevated likelihood of experiencing MI. Smoking, hypertension, hyperlipidemia, diabetes mellitus, obesity, and physical inactivity are well-established modifiable risk factors that significantly amplify the risk of MI. The burden of MI extends beyond the immediate morbidity and mortality, encompassing substantial long-term consequences.[5]

Contemporary treatment strategies for MI are multifaceted, encompassing immediate interventions aimed at restoring coronary blood flow, alongside long-term management plans designed to prevent future cardiac events. The cornerstone of acute MI treatment lies in the rapid restoration of blood flow to the affected myocardium, typically achieved through pharmacological thrombolysis or percutaneous coronary intervention. Thrombolytic agents, such as Tissue Plasminogen Activator (tPA), are administered intravenously to dissolve blood clots blocking coronary arteries, thus re-establishing blood flow and minimizing myocardial injury.[6] Percutaneous coronary intervention, a minimally invasive procedure, involves the insertion of a catheter into a peripheral artery, typically in the groin or arm, and threading it to the site of the blockage in the coronary artery. A balloon-tipped catheter is then inflated to compress the plaque against the artery wall, widening the artery lumen and restoring blood flow. In several incidences, a stent, a small, expandable metal mesh tube, is deployed to provide structural support to the artery and prevent it from narrowing again.[7] Following acute interventions, long-term management strategies are implemented to mitigate the risk of recurring MI and improve overall well being. These strategies often involve a combination of lifestyle changes, such as adopting a heart-healthy diet, frequent exercise, and abstaining from smoking, alongside pharmacological therapies, including antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors, and statins.[8]

While current treatment options have significantly improved outcomes for patients with MI, they are not without limitations and potential drawbacks. Moreover, the efficacy of current treatment options may vary depending on individual patient characteristics, such as age, comorbidities, and genetic factors, highlighting the need for personalized approaches to MI management.[9] Despite the advancements in conventional therapies, the quest for novel and complementary approaches to MI treatment remains a priority, with an increasing interest in the potential of plant-derived bioactive compounds to modulate various aspects of cardiovascular health.[10] Sinensetin is a well known bioactive polymethoxylated flavonoid compound widely present in Orthosiphon aristatus (Lamiaceae) and several citrus fruits. The biological properties of the sinensetin was already well reported, such as anticancer activity,[11] anti-inflammatory activity,[12] hepatoprotective activity,[13] and protected against periodontitis[14] and pulmonary fibrosis.[15] The cardioprotective effect of sinensetin against MI remains largely unexplored. Consequently, we established the Isoproterenol (ISO)-induced MI model in rats, demonstrating that sinensetin pretreatment demonstrated a considerable protective activity against MI in rats.

MATERIALS AND METHODS

Experimental rats

The current study was performed on male Wistar rats with an estimated weight of 230±10 g. The rats were maintained in a regulated laboratory setting with meticulous consideration for their safety. The conditions were sustained at a temperature of 22-26°C, humidity of 40-70%, and a 12-hr light-dark cycle. Throughout the experimental phase, rats were provided with purified water and standard rodent feed. Before initiating the study, a one-week acclimatization period was allotted for the rats to adjust to the laboratory setting.

Experimental groups

The acclimated rats were arbitrarily allocated into four groups with six rats in each. Group I comprised control rats that received 0.1% NaCl. Group-II rats were administered ISO (85 mg/kg; i.p.) on the 19th and 20th days to initiate MI. Groups III and IV were treated oral co- and pre-treatment of 10 and 20 mg/kg of sinensetin for 20 days, respectively with ISO administered on the 19th and 20th days. Upon completion of the treatments, the rats were euthanized, and blood was then taken for serum preparation. All heart tissues were excised and rinsed with saline solution. The excised heart was weighed to determine any alterations in weight. The cardiac tissues underwent histological analysis, while the remaining tissue samples were utilized to create homogenates for further biochemical assessments.

Analysis of biochemical marker levels

The serum concentrations of uric acid, C-Reactive Protein (CRP), and total protein in experimental animals were analyzed using assay kits as per the manufacturer's instructions (Elabscience, USA). The activities of ALT, GGT, AST, and CK were evaluated in both serum and cardiac tissue homogenates of the experimental rats utilizing commercially available assay kits (Abcam, USA). The studies were conducted according to the manufacturer's procedural requirements.

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Analysis of oxidative stress and antioxidant biomarkers

The levels of NF-κB, NQO-1, and HO-1 proteins in cardiac tissue homogenates were evaluated utilizing specific assay kits. The studies was done in triplicate in accordance with the manufacturer's specifications (MyBioSource, USA). The levels of SOD, GSH, CAT in the heart tissue homogenates of the rats were analyzed using assay kits (Abcam, USA). The tests were conducted according to the manufacturer's specifications.

Analysis of Na^+, Ca^{2+}, and K^+ ions

The quantities of Na^+, Ca^{2+}, and K^+ ions in the heart tissue homogenates of the rats were assessed using commercially available kits (MyBioSource, USA). The studies were conducted according to the manufacturer's procedural requirements.

Analysis of inflammatory cytokines

Assay kits were employed to evaluate the inflammatory cytokines, including IL-6, TNF-α, and IL-1β in the serum of the experimental rats. The manufacturer's recommendations from Elabscience, USA, were adhered to in conducting the assays in triplicates.

Statistical analysis

The results are portrayed as mean±SD of triplicates. The values are examined utilizing GraphPad Prism software. The variations in the values were evaluated using a one-way ANOVA and Tukey's *post hoc* test. A significance level of $p<0.05$ was established for group comparisons.

RESULTS

Sinensetin regulates uric acid, total protein, and CRP levels in experimental rats

Figure 1 depicts the effect of sinensetin on the uric acid, total protein, and CRP concentrations in the ISO-induced MI rats. The concentrations of uric acid and CRP was observed to be elevated, while total protein level was reduced in ISO-induced MI rats in comparison to control. Whereas, both co- and pre-treatment of 10 and 20 mg/kg of sinensetin markedly diminished the uric acid and CRP concentrations and elevated the protein levels in MI rats.

Sinensetin regulates the tissue injury markers in experimental rats

Figure 2 illustrates the concentrations of tissue injury markers in both serum and cardiac tissue homogenates of the rats. The serum concentrations of ALT, GGT, AST, and CK was considerably elevated in the MI rats in comparison to control. Contrastingly, the concentrations of these enzymes were notably reduced in the hearts of MI rats, which evidences the cardiac tissue injury. Captivatingly, the 10 and 20 mg/kg of sinensetin was effectively

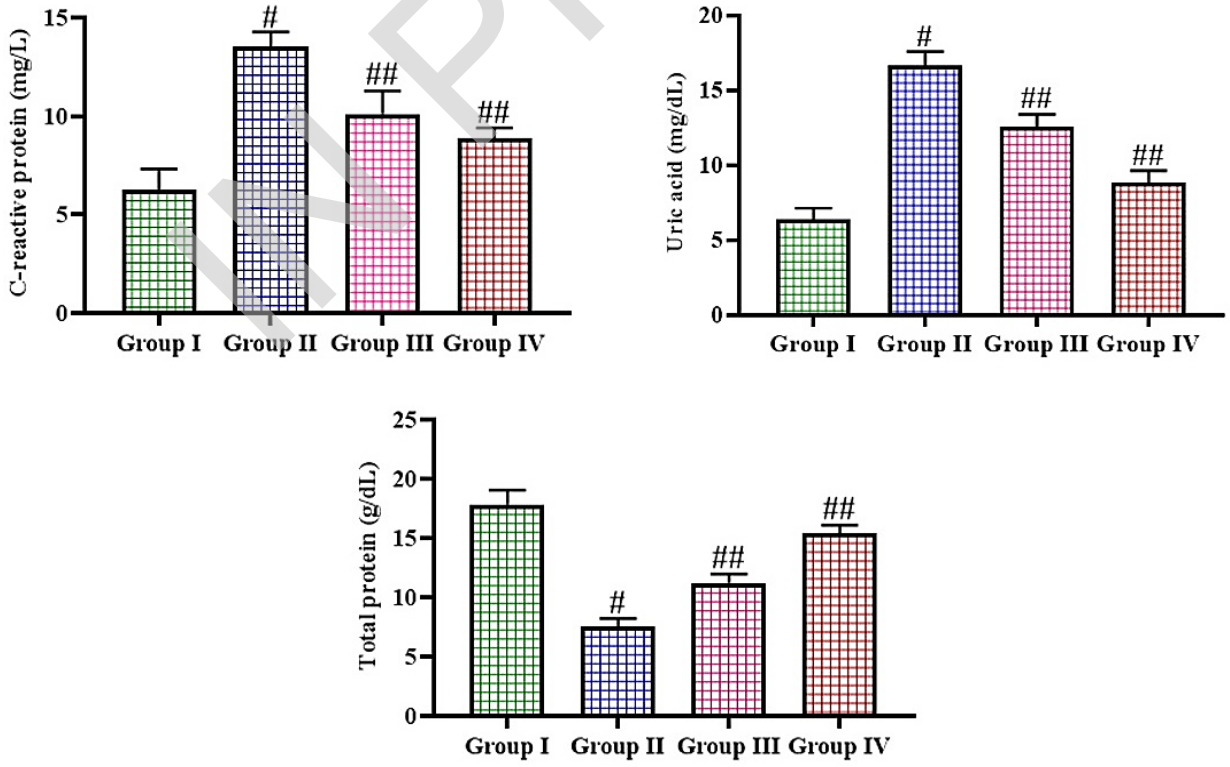


Figure 1: Effect of sinensetin on the uric acid, total protein, and CRP levels in the experimental rats. The values represented in each bar denote the mean±SD of triplicates, statistically evaluated using one-way ANOVA and Tukey's *post hoc* test. '#' indicates that values significantly differ at $p<0.01$ from control; '##' signifies that values significantly differ at $p<0.05$ from ISO-induced MI rats.

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reduced these marker enzymes in serum and augmented these enzymes in the hearts of MI rats. These findings evidenced that the sinensetin protected the ISO-induced cardiac damage in rats.

Sinensetin increases the antioxidants in cardiac tissues of experimental rats

The concentrations of antioxidant markers in the heart tissues of MI rats were evaluated, and the results are presented in Figure 3. The results of this study indicated that the ISO-induced MI rats had a significant diminution in GSH, SOD, and CAT concentrations in their heart tissues compared with control. Interestingly, the 10 and 20 mg/kg of sinensetin exhibited a consistent increase in GSH, SOD, and CAT levels, as illustrated in Figure . These studies indicated the antioxidant potential of sinensetin.

Sinensetin regulates the Na^+, Ca^{2+}, and K^+ ion levels in cardiac tissues of experimental rats

Figure 4 depicts the impact of sinensetin on the Na^+, Ca^{2+}, and K^+ ion concentrations in the hearts of experimental rats. The MI rats demonstrated increased Na^+ and Ca^{2+} ion levels, together with reduced K^+ ions, in comparison with control. Remarkably, the 10 and 20 mg/kg of sinensetin remarkably reduced the concentrations of Na^+ and Ca^+ ions, along with the increased K^+ ions in the hearts of MI rats.

Sinensetin decreases the inflammatory markers in experimental rats

Figure 5 illustrates the concentrations TNF-α, IL-6, and IL-1β in the experimental rats. Increased inflammatory cytokine levels were observed in the serum of ISO-induced MI rats in comparison to the control. Contrastingly, the 10 and 20 mg/kg of sinensetin markedly reduced these cytokine concentrations in the serum of MI rats, which witnesses its anti-inflammatory properties.

Effect of sinensetin on the HO-1/NQO-1 and NF-κB levels in the experimental rats

Figure 6 presents the levels of HO-1/NQO-1 and NF-κB in the hearts of experimental rats. The current findings indicate that the levels of NQO-1 and NF-κB was considerably increased while the HO-1 level was reduced in the cardiac tissues of MI rats in comparison to the control. Nonetheless, the treatment of sinensetin at 10 and 20 mg/kg of concentrations led to a considerable diminution in the NQO-1 and NF-κB concentrations and elevation in the HO-1 concentrations in the cardiac tissues of MI rats.

DISCUSSION

MI remains a primary cause of morbidity and mortality globally, presenting a significant burden on healthcare systems and individual well-being. Despite advancements in early pharmacological and medical device interventions aimed at reducing myocardial loss following infarction, the viable cardiomyocytes within the ischemic zone and adjacent areas continue to experience heightened workload and metabolic stress, which can lead to heart failure characterized by further cell loss and pathological myocardial remodeling. The acute event of MI is typically triggered by an abrupt reduction or cessation of coronary blood flow, leading to an imbalance between oxygen delivery and demand in the myocardial tissue, ultimately impairing cardiomyocyte function and survival.[16] Prompt re-establishment of blood flow to the ischemic myocardium is crucial for recovering jeopardized tissue and improving patient outcomes, yet the reperfusion itself can paradoxically induce additional injury, known as myocardial ischemia/reperfusion injury. Conventional treatments, such as thrombolytic therapy and percutaneous coronary intervention, have exhibited effectiveness in decreasing infarct size and improving clinical outcomes by restoring blood flow. However, these interventions do not fully eliminate the risk of subsequent heart failure or other complications, underscoring the necessity for novel therapeutic

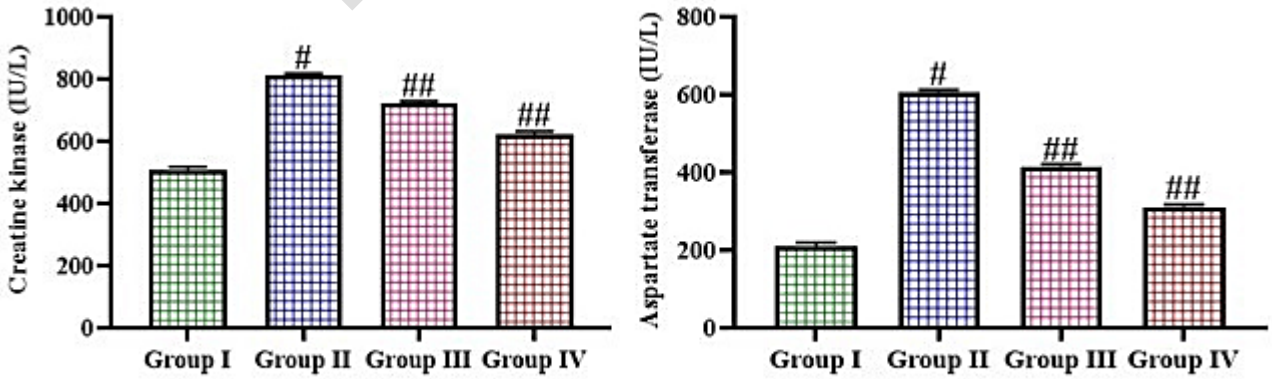


Figure 2: Effect of sinensetin on the tissue injury markers in the experimental rats. The values represented in each bar denote the mean±SD of triplicates, statistically evaluated using one-way ANOVA and Tukey's *post hoc* test. '#' indicates that values significantly differ at $p<0.01$ from control; '##' signifies that values significantly differ at $p<0.05$ from ISO-induced MI rats.

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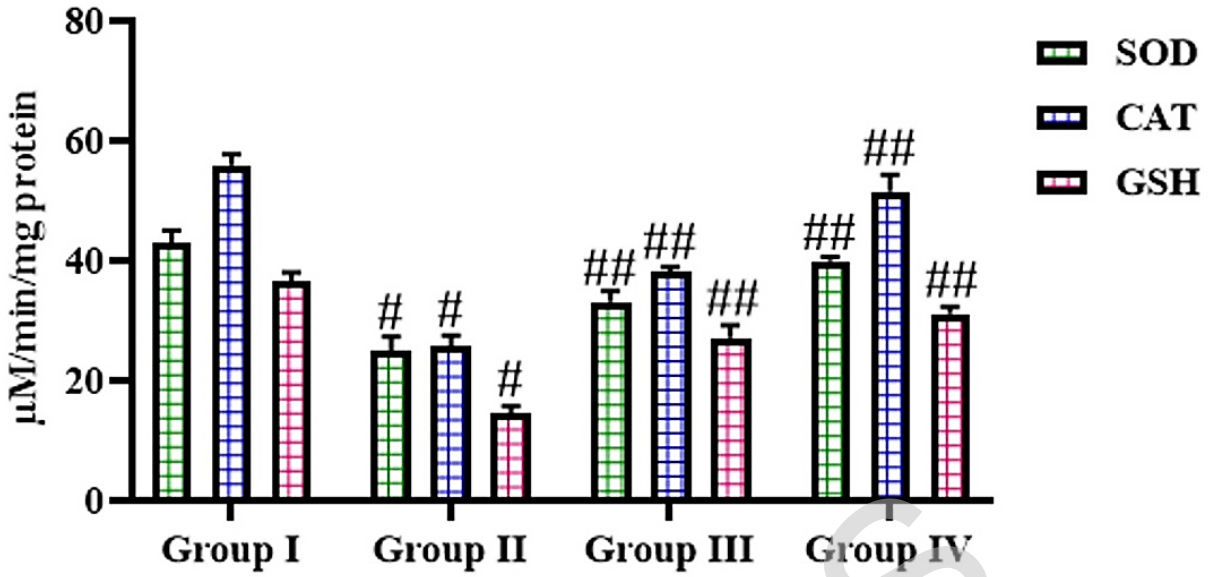


Figure 3: Effect of sinensetin on the antioxidant levels in the heart tissues of experimental rats. The values represented in each bar denote the mean±SD of triplicates, statistically evaluated using one-way ANOVA and Tukey's *post hoc* test. '#' indicates that values significantly differ at $p<0.01$ from control; '##' signifies that values significantly differ at $p<0.05$ from ISO-induced MI rats.

strategies that can complement existing approaches.[17] Thus, we developed the ISO-induced MI model in rats, illustrating that sinensetin pretreatment provided a substantial protective effect against MI in rats.

The evaluation of tissue injury marker levels in serum and cardiac tissues holds paramount importance in the context of MI in rats, serving as a crucial tool for assessing the extent of cardiac damage and dysfunction. AST and ALT are transaminases that catalyze the transfer of amino groups from amino acids to alpha-keto acids, serving a pivotal role in amino acid metabolism and gluconeogenesis.[18] AST is also instrumental in diagnosing and estimating the severity of MI. The evaluation of AST and ALT in serum has been a cornerstone in the assessment of cardiac, hepatic, and muscular disorders, reflecting enzymatic alterations at the cellular level within the respective tissues. Elevated levels of these enzymes in serum are indicative of cellular damage and leakage from the affected tissues, providing valuable insights into the pathophysiology of MI.[19]

GGT, a membrane-bound enzyme involved in glutathione metabolism and the transport of amino acids, is another key indicator of tissue damage. Its elevation in serum has been observed in cardiac disorders, suggesting its potential involvement in MI.[20] CK, an enzyme that catalyzes the reversible transfer of phosphate between creatine and ATP, plays a crucial role in energy homeostasis in muscle tissues, including the heart. Specifically, CK isoenzymes, such as CK-MB, are highly specific to cardiac muscle and are extensively used as biomarkers for MI. Upon MI, the compromised integrity of cardiac cells leads to the release of CK into the bloodstream, resulting in elevated serum levels that serve as a hallmark of cardiac injury. The combined analysis of these enzymes provides a comprehensive assessment of the extent of tissue damage in ISO-induced MI.[21] The present results demonstrated increased serum concentrations of ALT, GGT, AST, and CK and a reduction in these enzymes in the hearts of MI rats. Whereas, the sinensetin treatment notably decreased these marker enzymes in the serum and augmented these enzymes in the hearts of MI rats. These results witnessed that the sinensetin treatment protected the ISO-induced cardiac injury in rats.

The imbalance between oxygen demand and delivery during ischemia initiates a complex series of cellular events that culminates in oxidative stress. Oxidative stress, characterized by an overproduction of ROS/or a deficiency in antioxidant defenses, plays a major role in the onset of MI. The initial ischemic insult triggers a cascade of events, including the disruption of mitochondrial function, calcium overload, and activation of inflammatory pathways, each contributing to the generation of ROS.[22] If the production of oxidant species overwhelms the antioxidant system, then membranes, lipids, proteins and nucleic acids are altered. The reperfusion phase, while essential for restoring blood flow, ironically exacerbates oxidative stress, leading to further cellular damage. The surge of oxygen during reperfusion fuels the mitochondrial respiratory chain, resulting in a burst of ROS production, overwhelming the endogenous antioxidant defense mechanisms.[23]

SOD, CAT, and GSH are crucial components of the cellular antioxidant defense system, working synergistically to mitigate the damaging effects of ROS. SOD converts the superoxide radicals into hydrogen peroxide and oxygen, acting as a first line of defense against ROS-mediated injury. CAT, primarily located in peroxisomes, facilitates the conversion of hydrogen peroxide into water and oxygen, effectively neutralizing this potentially

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harmful ROS.[24] GSH functions as a major intracellular antioxidant, scavenging ROS and participating in various detoxification reactions. These antioxidants play a primary role in regulating redox homeostasis and protecting cardiomyocytes from oxidative damage. Deficiencies in any of these key antioxidant enzymes can significantly impair the ability of cardiomyocytes to cope with oxidative stress, making them more susceptible to oxidative damage. Targeting oxidative stress and enhancing antioxidant defenses represent promising therapeutic strategies for mitigating MI and improving patient outcomes.[25] The findings of this study demonstrated that the MI rats had a considerable diminution in GSH, SOD, and CAT in their heart tissues. Captivatingly, the sinensetin administration illustrated the elevated antioxidants in MI rats, which supports its antioxidant properties.

The intricate interplay of Na^+, Ca^{2+}, and K^+ ions is critical for maintaining normal cardiac function, and disruptions in their homeostasis are intricately linked to the pathophysiology of MI. The severity and extent of myocardial damage during an infarction are significantly influenced by the dysregulation of ion homeostasis, particularly involving Na^+, Ca^{2+}, and K^+ ions, all of which play essential roles in cardiomyocyte electrophysiology, contractility, and cellular integrity. Understanding the roles of these ions is essential to develop effective therapies to mitigate myocardial damage and improve outcomes following infarction.[26] Ca overload is a central feature of MI pathophysiology, contributing to both ischemic and reperfusion injury. During ischemia, the compromised function of the sarcolemma and sarcoplasmic reticulum Ca pumps results in an uncontrolled elevation in intracellular Ca levels. K+ ions also play an essential role in the pathophysiology of MI, primarily through their influence on cardiomyocyte excitability and the development of arrhythmias.[27] Na overload can trigger Ca overload through the reverse mode operation of the Na-Ca exchanger. The altered K homeostasis during ischemia affects cardiomyocyte excitability, predisposing to arrhythmias and increasing the risk of sudden cardiac death. The imbalance of Na^+, Ca^{2+}, and K^+ leads to arrhythmias, cellular damage, and ultimately cell death. Understanding the intricate interactions between these ions and their effect on cellular function is crucial to develop potential therapeutic strategies to protect the myocardium during and after infarction. Targeting the dysregulation of these ions represents a promising avenue for therapeutic intervention in MI.[28] The current results demonstrated the elevated Na^+ and Ca^{2+} ions with decreased K^+ ions in the heart of MI rats. Interestingly, the sinensetin administration decreased Na^+ and Ca^+ levels and increased K^+ levels in the heart tissues of MI rats.

The pathophysiology of MI is intricate process involves a complex interplay of inflammatory responses, orchestrated by various cytokines, that can either promote healing or exacerbate myocardial dysfunction. The sterile inflammatory response, triggered by cellular necrosis and the release of damage-associated molecular patterns, is essential for clearing cellular debris and initiating tissue repair. However, dysregulation of this inflammatory response can lead to adverse remodeling and heart failure.[29] TNF-α, IL-6, and IL-1β are key pro-inflammatory markers implicated in the pathophysiology of MI, exerting diverse and often overlapping effects on cardiac cells and the surrounding microenvironment. These cytokines, released from resident cardiac cells, infiltrating immune cells, and even remote organs, contribute to both the beneficial and detrimental aspects of the inflammatory response.[30] ROS, produced in the ischemic myocardium particularly during reperfusion, activate signal transduction pathways that induce the release of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, initiating a host response. The excessive and prolonged

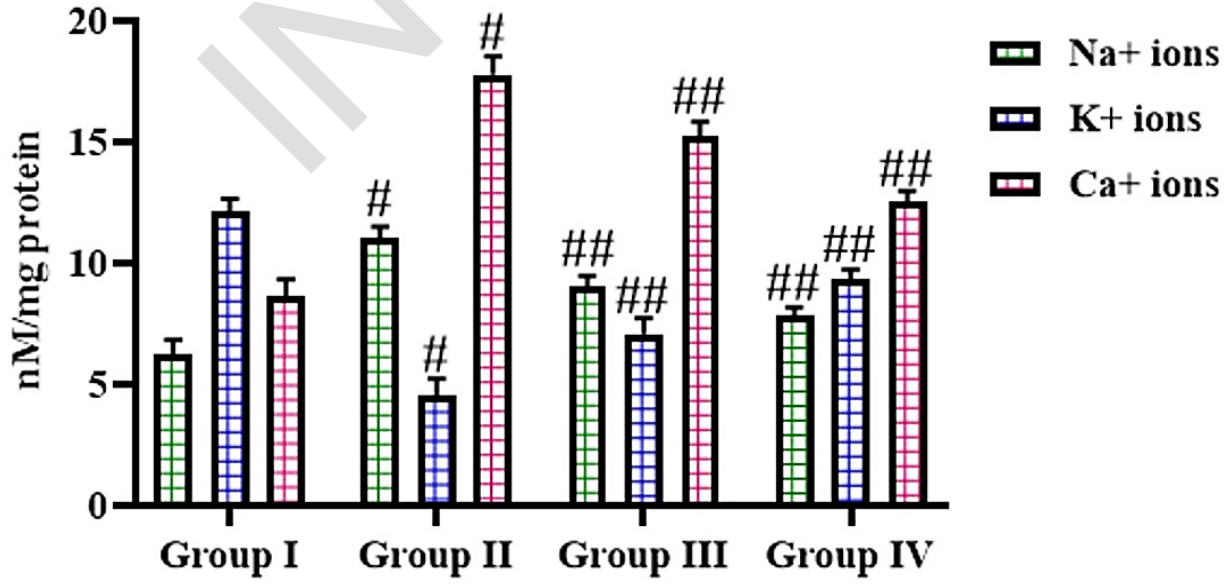


Figure 4: Effect of sinensetin on the Na^+, K^+, and Ca^{2+} ion levels in the cardiac tissues of experimental rats. The values represented in each bar denote the mean±SD of triplicates, statistically evaluated using one-way ANOVA and Tukey's *post hoc* test. '#' indicates that values significantly differ at $p<0.01$ from control; '##' signifies that values significantly differ at $p<0.05$ from ISO-induced MI rats.

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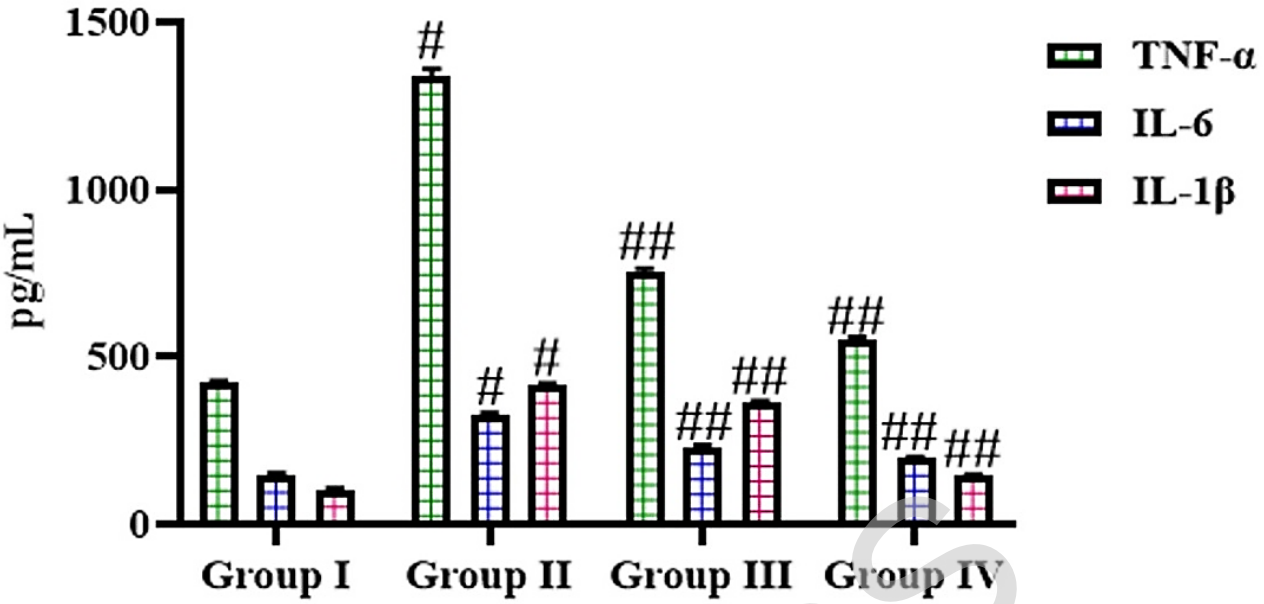


Figure 5: Effect of sinensetin on the inflammatory markers in the experimental rats. The values represented in each bar denote the mean±SD of triplicates, statistically evaluated using one-way ANOVA and Tukey's *post hoc* test. '#' indicates that values significantly differ at $p<0.01$ from control; '##' signifies that values significantly differ at $p<0.05$ from ISO-induced MI rats.

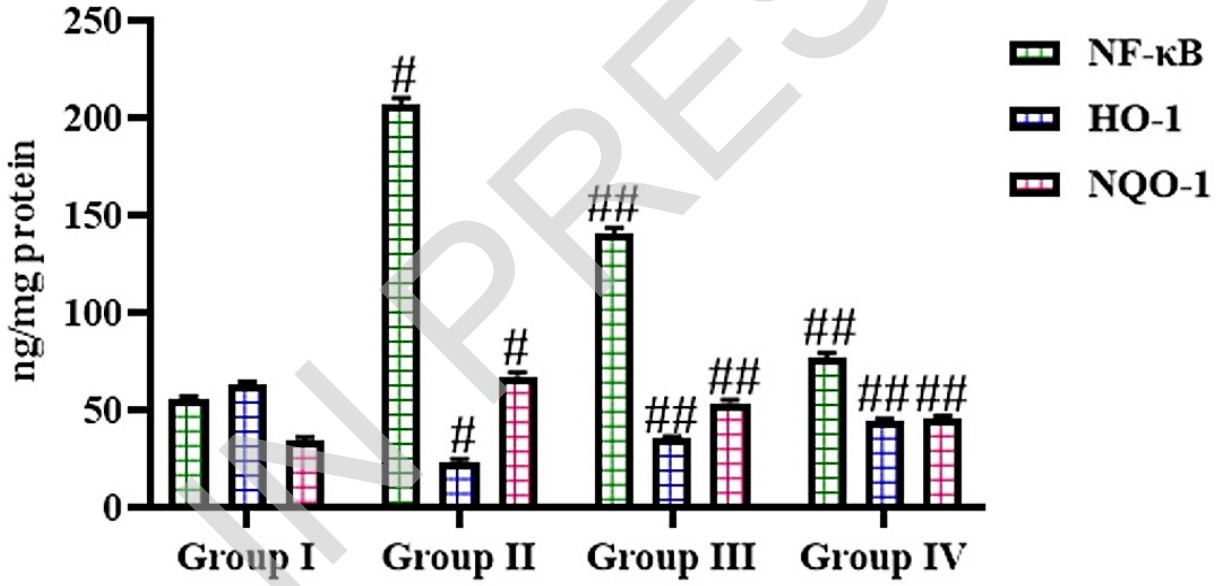


Figure 6: Effect of sinensetin on the HO-1/NQO-1 and NF-κB levels in the experimental rats. The values represented in each bar denote the mean±SD of triplicates, statistically evaluated using one-way ANOVA and Tukey's *post hoc* test. '#' indicates that values significantly differ at $p<0.01$ from control; '##' signifies that values significantly differ at $p<0.05$ from ISO-induced MI rats.

production of pro-inflammatory cytokines following MI can have negative inotropic effects, exacerbating myocardial dysfunction. Understanding the intricate interplay between inflammation, inflammatory cytokines, and cardiac remodeling is essential for developing targeted therapies to improve outcomes following MI.[31] In this work, the increased concentrations of IL-1β, TNF-α, and IL-6 were seen in the serum of MI rats. However, the sinensetin treatment remarkably decreased these cytokine concentrations in the MI rats, which supports its anti-inflammatory properties.

HO-1 and NQO-1 are pivotal cytoprotective enzymes that play significant roles in the cellular defense against oxidative stress and inflammation, both of which are key contributors to the pathophysiology of MI. HO-1, an inducible enzyme, catalyzes the degradation of heme into biliverdin, carbon monoxide, and ferrous iron, each of which exhibits distinct biological activities.[32] NQO-1, a flavoprotein, catalyzes the two-electron reduction of quinones, preventing the formation of semiquinones and the subsequent generation of superoxide radicals. NQO1 also plays a role in the detoxification of various xenobiotics and electrophiles, further contributing to its antioxidant and cytoprotective functions. Both HO-1 and NQO1 contribute significantly to maintaining intracellular redox status and averting oxidative stress-induced damage.[33] NF-κB plays an essential role in

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controlling the gene expressions involved in inflammation, immunity, and cell survival, and is typically sequestered in the cytoplasm in an inactive state, bound to inhibitory proteins called IκBs. Upon stimulation by various stimuli, like inflammatory cytokines, ROS, or pathogen-associated molecular patterns, IκBs are phosphorylated, ubiquitinated, and degraded, resulting in the release and nuclear translocation of NF-κB. Within the nucleus, NF-κB associates with particular DNA sequences in the promoter regions of target genes, therefore commencing their transcription.[34] These target genes encode a wide array of proteins, such as pro-inflammatory cytokines, chemokines, and anti-apoptotic factors, which collectively contribute to the inflammatory response and regulate cell fate. Aberrant activation of NF-κB has been implicated in numerous pathological conditions, including chronic inflammatory diseases, autoimmune disorders, and cancer. NF-κB activation promotes the transcription of pro-inflammatory mediators, exacerbating myocardial damage and hindering the healing process.[35] The interplay between HO-1/NQO-1 and NF-κB signaling pathways is complex and context-dependent, with evidence suggesting both synergistic and antagonistic interactions.[36] Targeting these pathways offers potential therapeutic strategies for mitigating MI, with approaches aimed at enhancing HO-1/NQO-1 activity or inhibiting NF-κB activation showing promise in preclinical studies.[37] In this work, the findings illustrated the increased levels of NQO-1 and NF-κB and reduced HO-1 in the hearts of MI rats. Captivatingly, the sinensetin treatment considerably reduced the NQO-1 and NF-κB levels and increased the HO-1 levels in the heart tissues of MI rats.

CONCLUSION

The current findings indicate that sinensetin treatment can ameliorate and protect the ISO-induced cardiac damage in rats. The beneficial effect of sinensetin may stem from its significant antioxidant and anti-inflammatory properties. Consequently, sinensetin treatment may serve as a novel therapeutic candidate to treat MI. To improve our comprehension of the antioxidant, anti-inflammatory, cardioprotective activities of sinensetin in mitigating MI, additional studies are necessary in the future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

Nil.

ETHICAL APPROVAL

This work has approved by the institutional animal ethical committee by Department of Cardiovascular, Xi'an 5th Hospital, No. 112 Xiguanzheng street, Xi'an, 710000, China.

ABBREVIATIONS

MI: Myocardial Infarction; **ISO:** Isoproterenol; **CRP:** C-Reactive Protein; **CK:** Creatine Kinase; **SOD:** Superoxide Dismutase; **GSH:** Glutathione; **IL:** Interleukin; **HO-1:** Heme Oxygenase-1; **NQO1:** NAD(P)H:quinone Oxidoreductase 1.

SUMMARY

Myocardial Infarction (MI) is a severe medical condition caused by a sudden and prolonged interruption of blood flow to the myocardial regions, leading to cellular ischemia and subsequent necrosis. MI continues to be a primary cause of morbidity and mortality worldwide, imposing a considerable burden on healthcare systems and individual health. The present findings demonstrate that sinensetin treatment can mitigate and protect against ISO-induced cardiac injury in rats. The advantageous effect of sinensetin may arise from its notable antioxidant and anti-inflammatory characteristics. Thus, sinensetin may be a novel therapeutic option for the treatment of MI.

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