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Original Article

Antioxidant and Anti-Inflammatory Efficacy of Dipsacoside B in Ameliorating Myocardial Infarction in an *in vivo* Model

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ABSTRACT

Background: Myocardial Infarction (MI) is a severe coronary ailment associated with a great risk of mortality, often contributing to sudden cardiac death. Cardiovascular diseases account for approximately 32% of global deaths, with MI representing 85% of these cases, necessitating immediate and extensive medical intervention. **Objectives:** In this study, we investigated the therapeutic efficacy of the triterpenoid saponin dipsacoside B in alleviating myocardial infarction. **Materials and Methods:** Myocardial Infarction (MI) was induced in healthy male rats using Isoproterenol (ISO). Following this, the rats received treatment with two distinct concentrations of dipsacoside B. The study utilized both pre-treatment and co-treatment protocols with dipsacoside B in the ISO-induced MI rats. The cardioprotective and anticholesteremic effects of dipsacoside B were evaluated through hemodynamic assessments and serum lipid profile analysis. To determine the compound's oxidative stress scavenging potential, antioxidant levels were quantified in the experimental animals. Furthermore, the therapeutic effectiveness of dipsacoside B was evaluated by analyzing important myocardial biomarkers such as TGF-β, cTnI, BNP, MYO, H-FABP, GP-BBP, and CK-MB. **Results:** The anti-inflammatory and anti-apoptotic properties were investigated by measuring levels of inflammatory proteins and caspases in the MI-induced rats receiving dipsacoside B treatment. To confirm the antioxidant defense potential of dipsacoside B, Nrf2 protein levels were analyzed. The results demonstrated that dipsacoside B effectively regulated serum lipid profiles and improved hemodynamic parameters in MI-induced rats. Treatment with dipsacoside B significantly reduced critical MI mediators, restored antioxidant levels, and mitigated oxidative stress. Furthermore, dipsacoside B suppressed inflammation and apoptosis, as evidenced by reduced inflammatory markers and caspase activity. Importantly, Nrf2 protein expression was markedly upregulated, confirming the antioxidant defense capacity of dipsacoside B. **Conclusion:** In conclusion, our findings indicate that dipsacoside B exhibits strong antioxidant, anti-inflammatory, and cardioprotective properties, making it a promising therapeutic agent for alleviating myocardial infarction.

Keywords: Myocardial infarction, ISO MI *in vivo* model, Phytochemical, Dipsacoside, Antioxidant, Anti-inflammatory agent.

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INTRODUCTION

Cardiovascular Diseases (CVDs) pose a major global health challenge, accounting for around 17.9 million deaths in 2019, which represents roughly 32% of all deaths worldwide.[1] As of 2019, there were over 500 million cases of CVD worldwide, nearly double the number in 1990, with Ischemic Heart Disease (IHD), stroke, and hypertensive heart disease being among the most prevalent conditions.[2] Projections suggest that global cardiovascular mortality could rise significantly, with MI anticipated to affect 471 million people by 2050. CVDs also account for nearly 40% of the 17 million premature deaths attributed to non-communicable diseases, with around 18.6 million deaths estimated annually.[3] The majority of risk factors associated with CVDs are modifiable and primarily stem from unhealthy lifestyles and habits. In addition to individual factors, broader socio-economic and geographic influences also play a role in disease trends.[4,5]

Myocardial Infarction (MI), usually known as a heart attack, is characterized by an inadequate blood circulation and oxygen to the cardiac tissue, resulting in the death of cardiomyocytes and a heightened risk of heart failure.[6] This pathological condition arises from an imbalance between myocardial oxygen demand and

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coronary blood flow, leading to substantial cardiac remodeling that impairs overall heart function.[7] A pivotal factor in the progression of MI is the dynamic interaction between oxidative stress, inflammation, and hypoxia, which collectively drive maladaptive left ventricular remodeling.[8,9] Oxidative stress occurs due to an overproduction of free radicals, particularly under ischemic conditions, which disrupt myocardial homeostasis and exacerbate cellular injury.[10,11] Reactive Oxygen Species (ROS) and inflammatory processes, regulated through key signaling pathways such as Mitogen-Activated Protein Kinases (MAPK) and Nuclear Factor Kappa B (NF-κB), contribute to further cardiomyocyte necrosis and myocardial damage. These molecular events amplify myocardial dysfunction and remodeling, ultimately compromising cardiac performance.[12]

Phytochemicals are essential bioactive compounds with significant potential in the cardiovascular diseases amelioration.[13] These compounds are particularly effective in reducing the low-density lipoprotein oxidation, thereby improving lipid metabolism and regulating apoptotic pathways within endothelial cells. Recent studies by Ciumărnean *et al.*,[14] have demonstrated that flavonoids can modulate lipid profiles by inhibiting LDL oxidation and enhancing endothelial function through mechanisms that promote vasodilation and regulate apoptosis. Similarly, Yamagata *et al.*[15] reported the antioxidant and anti-inflammatory effects of flavonoids, which play a pivotal role in mitigating cardiovascular risk factors. Additional studies have shown that polyphenols and carotenoids can attenuate inflammation and oxidative stress, leading to improved endothelial function, reduced blood pressure, decreased platelet aggregation, and enhanced insulin sensitivity.[16] Phytochemicals modulates diverse signaling pathways and interact with key protein targets, emphasizing their therapeutic potential as complementary agents in the amelioration of cardiovascular diseases.

Dipsacoside B is an oleanane-type pentacyclic triterpenoid saponin derived from plants such as Lonicerae flos and Dipsacus asper.[17] Dipsacoside B demonstrated neuroprotective activity[18] and ameliorated cognitive impairments[19] in animal models. It exhibits ameliorative effect against acetaminophen induced liver damage and alleviates ischemic stroke.[20] Dipsacoside B renders positive vascular effects, including the prevention of Vascular Smooth Muscle Cell (VSMC) migration and proliferation, following balloon injury in rats.[21] These findings suggest that dipsocaside may have a significant impact on mitigating vascular-related morbidities. Therefore, in this research we analyzed the cardioprotective effect of dipsacoside B against myocardial infraction induction in rat model.

MATERIALS AND METHODS

Chemicals

Dipsacoside B and isoproterenol was purchased from Sigma Aldrich, USA. The assay kits for biochemical estimations were acquired from Invitrogen and Elabscience, USA, respectively.

Experimental Animals

Male Wistar albino rats weighing between 150 and 220 g were acclimatized for one week prior to the start of the treatment. They were kept in a controlled environment within the experimental animal facility, which maintained a temperature range of 19-25°C, relative humidity levels of 30-70%, and a light/dark cycle of approximately 12 hr. Throughout the study, a maximum of six rats were housed per cage in sterilized polypropylene cages topped with a stainless-steel mesh, equipped with provisions for water bottles and feed. Clean autoclaved corn cob was used for bedding. Free access to standard rodent pellet diet and clean water was provided to the experimental animals.

Myocardial Infraction Stimulation

Myocardial infarction was induced in the healthy experimental animals following the protocol established by El-Gohary and Allam.[22] Two sequential doses of 85 mg/kg of isoproterenol were administered intraperitoneally on days 19 and 20 of the experiment.

Treatment Protocol

Healthy acclimatized rats were assorted into four (n=6 each). Control rats received saline as treatment throughout the experimental period. The Myocardial Infarction (MI) group was given saline orally for 18 days and then subjected to MI induction with Isoproterenol (ISO) on days 19 and 20. The MI + LD Dipsacoside B group received 10 mg/kg body weight of Dipsacoside B orally for 20 days, followed by MI stimulation with ISO on days 19 and 20. Similarly, the MI + HD Dipsacoside B group was treated with 20 mg/kg body weight of Dipsacoside B orally for 20 days and underwent MI induction on days 19 and 20 using ISO. The animals were subjected to euthanasia procedure after 24 hr of the last treatment. Blood samples and the heart tissue were collected for further examination.

Assessment of hemodynamic changes

Arterial cannula connected to a pressure transducer was placed on the femoral artery of the anesthetized experimental rats. The pulsatile arterial pressure is recorded through the pressure transducer, and the resulting waveforms are analyzed using a data acquisition system. Mean Arterial Pressure (MAP), Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), and Heart Rate (HR) values were calculated from the recorded pulsatile arterial pressure data.

Analysis of serum lipids

Total cholesterol, Triglcerides, high and low density lipoproteins were quantified in the MI stimulated untreated and dipsacoside B treated animals. The serum lipids were quantified using the colorimetric assay kit purchased from Elabscience. Total cholesterol is measured by quantifying the red quinone compounds of benzoquinone imine phenizone formed, at 510 nm. Triglycerides were quantified by measuring the quinones formed, at 510 nm absorbance. Both the LDL cholesterol and HDL-cholesterol were quantified at 546 nm.

Assessment of Oxidative Imbalance

The oxidative imbalance in myocardial infarction was evaluated in both untreated and dipsacoside-treated animals by quantifying levels of Thiobarbituric Acid-Reactive Substances (TBARS) using the method described by Ohkawa *et al.*[23] Catalase (CAT) activity was assessed following Aebi's protocol,[24] and Superoxide Dismutase (SOD) activity was determined using the method from Madesh and Balasubramanian.[25] The content of reduced Glutathione (GSH) was measured using Ellman's method,[26] activities of Glutathione Peroxidase (GPx) and Glutathione Reductase (GR) were evaluated according to Hafeman *et al.*[27] The assay for Glutathione S-Transferase (GST) was conducted using the method developed by Habig *et al.*[28]

Assessment of critical mediators of MI

Transforming Growth Factor-beta (TGF-β), Cardiac Troponin I (cTnI), and B-type Natriuretic Peptide (BNP) are critical biomarkers and mediators involved in the pathophysiology and diagnosis of MI. The above markers were quantified using the ELISA purchased from Invitrogen. The assay was performed in accordance with the kit manual protocol.

Assessment of biomarkers of MI

Myoglobin (MYO), Heart-Type Fatty Acid-Binding Protein (H-FABP), Glucose-Regulated Protein 78 (GRP78 or GP-BBP), and Creatine Kinase-MB (CK-MB) were quantified to diagnose myocardial infarction and to monitor the degree of myocardial damage. These biomarkers were quantified in the MI stimulated untreated and dipsacoside treated rats. ELISA kits procured from Elabscience were utilized to quantify the levels of biomarkers. The test were done as per the instructions provided in the kits.

Assessment of cardiac tissue inflammation

Inflammatory-stimulating cytokines TNF-α, IL-1β, IL-6, NF-κB, apoptotic inducers Caspase 3, Caspases 9 and Nuclear factor erythroid 2-related factor 2 (Nrf2), key regulatory of antioxidant defense were quantified in the MI stimulated untreated and dipsacoside treated rats. The levels of cardiac inflammatory markers were quantified with the ELSIA kits procured from Invitrogen.

Statistical analysis

The data obtained with our various analysis were statistically assessed using the software GraphPad Prism version 8.2.1. One way ANOVA was applied to analyze the intergroup comparison and Tukey's HSD test were done to analyze intra group comparison. Statistical significance was set up at $p<0.05$.

RESULTS

Dipsacoside B regulated hemodynamic changes in MI stimulated rats

Hemodynamic changes occurred in the MI stimulated untreated and dipsacoside B treated were analyzed and the results were depicted in Figure 1. Dipsacoside B treatment increased both SAP and DAP in the MI stimulated rats which was considerably reduced in the MI stimulated untreated rats. The MAP were recorded to be 78±0.03 mmHg and 98±0.06 mmHg respectively in the 10 and 20 mg/kg dipsacoside B treated whereas the MI stimulated untreated shown considerably decreased MAP of 52±0.03 mmHg. Control rats shown 125±0.02 mmHg of MAP and 410±0.2 mmHg of heart rate. The heart rate was also considerably decreased to 220±0.3 mmHg in the MI stimulated untreated rats whereas treatment with dipsacoside B increased to 285±0.2 mmHg and 310±0.4 mmHg respectively with 10 and 20 mg/kg bwt treatment.

Dipsacoside normalized serum lipid in MI stimulated rats

The results of serum lipid profile analysis performed in the MI stimulated untreated and dipsacoside B treated rats were illustrated in the Figure 2. MI stimulation enhanced the levels of total cholesterol to 3.1±0.0003 mmol/L whereas 10 and 20 mg/kg dipsacoside B treatment decreased the total cholesterol to 2.4±0.0001 and 1.9±0.0006 mmol/L respectively. MI stimulation increased the triglycerides to 8±0.0001 whereas treatment with dipsacoside B decreased the triglyceride levels to 6.4±0.0004 and 5.1±0.0003 mmol/L respectively with 10 and 20 mg/kg treatment. Treatment with dipsacoside B also decreased the levels of LDL and increased the HDL levels in the MI stimulated rats. Control rats exhibited 1.20.0001 mmol/L of total cholesterol and 0.8±0.0001 mmol/L of triglycerides. The levels of LDL was significantly reduced and the HDL levels were increased in the control rats compared to the other group experimental rats.

Dipsacoside enhanced antioxidant levels in MI stimulated rats

Figure 3 represents the antioxidant status and the levels of oxidative stress induced damage in MI stimulated untreated and dipsacoside treated rats. TBARS, which indicates the level of lipid peroxidation in cells were significantly enhanced with MI stimulation whereas treatment with dipsacoside B decreased the levels TBARS. Both SOD and CAT levels were considerably

increased with dipsacoside treatment which was reduced in MI stimulated untreated. Dipsacoside B treatment had a positive impact on the glutathione system, it increased the levels of GSH, GPx, GR and GST. The increase in glutathione system was observed in dose dependent manner.

Dipsacoside attenuated critical mediators of MI

MI stimulation increased the levels of TGF-β and cTnI to 1100±5.2 and 0.24±0.00008 pg/mL respectively. Dipsacoside treatment decreased the TGF-β to 760±2.5 and 0.18±0.00002 pg/mL and cTnI to 680±1.5 and 0.14±0.00004 pg/mL levels respectively with 10 and 20 mg/kg dosage treatment. The BNP levels were also increased to 1980±4.8 pg/mL with MI stimulation and upon dipsacoside treatment the levels were decreased to 1590±3.5 and 1390±6.5 pg/mL with 10 and 20 mg/kg dosage treatment. The control rats exhibited 520±1.5 pg/mL of TGF-β, 0.08±0.00003 pg/mL of cTnI and 1250±2.5 pg/mL of BNP (Figure 4).

Dipsacoside ameliorated myocardial infraction

Figure 5 depicts the levels of biomarkers of myocardial infraction in the MI stimulated untreated and dipsacoside treated rats. The myoglobin levels were significantly enhanced in the MI stimulated untreated rats (6.2±0.007 ng/mL), whereas treatment with dipsacoside treatment decreased the levels of MYO in both 10 mg/kg (5.7±0.005 ng/mL) and 20 mg/kg (4.2±0.009 ng/mL) dosage treated rats. Dipsacoside treatment significantly enhanced the levels of H-FABP and GP-BBP levels to 7.7±0.002 ng/mL and 49±0.02 ng/mL upon 10 mg/kg dosage treatment and 5.8±0.007 ng/mL and 42±0.07 ng/mL with 20 mg/kg dosage treatment. MI stimulated rats exhibited increased level of H-FABP (8.1±0.003 ng/mL) and GP-BBP (57±0.04 ng/mL) than the control rats (4.3±0.002 ng/mL and 32±0.05 ng/mL respectively). CK-MB levels were significantly enhance in the MI stimulated rats (28±0.005 ng/mL) compared to healthy control rats (11±0.001 ng/mL), whereas treatment with dipsacoside treatment decreased the levels of CK-MB to 18±0.002 and 14±0.002 ng/mL respectively with 10 and 20 mg/kg dosage treatment.

Dipsacoside attenuated inflammation in MI stimulated rats

The inflammatory stimulating cytokines levels were quantified in the MI stimulated untreated and dipsacoside treated rats, the results were illustrated in Figure 6. Stimulation of MI in rats with ISO treatment significantly enhanced the inflammatory stimulating cytokines TNF-α, IL-1β, IL-6 and NF-κB levels whereas the treatment with dipsacoside decrease the inflammatory stimulating cytokine levels in a dose dependent manner. Dipsacoside treatment also decreased the levels of caspases 3 and 9 inducers of apoptosis which were significantly enhanced in MI stimulated untreated rats. Nrf2, regulator of antioxidant defense was significantly decreased with MI stimulation and it was comparatively increased with dipsacoside treatment.

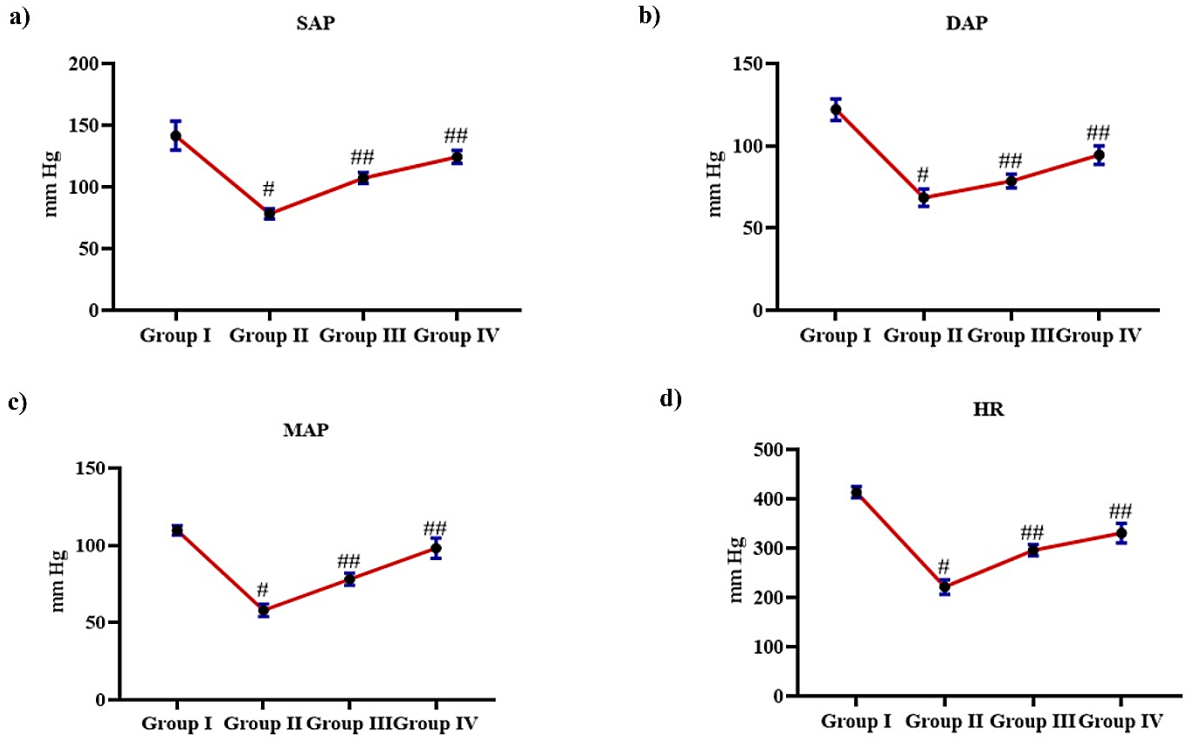

Figure 1: Dipsacoside B regulated hemodynamic changes in MI stimulated rats. a) Systolic Arterial Pressure (SAP), b) Diastolic Arterial Pressure (DAP), c) Mean Arterial Pressure (MAP), d) Heart Rate (HR) in control, MI stimulated untreated rats, MI stimulated+10 mg/kg Dipsacoside treated and MI stimulated+20 mg/kg Dipsacoside treated rats. # Control vs Others, ## MI stimulated untreated rats vs MI stimulated+10 mg/kg Dipsacoside treated and MI stimulated+20 mg/kg Dipsacoside treated rats. Statistical significance $p<0.05$.

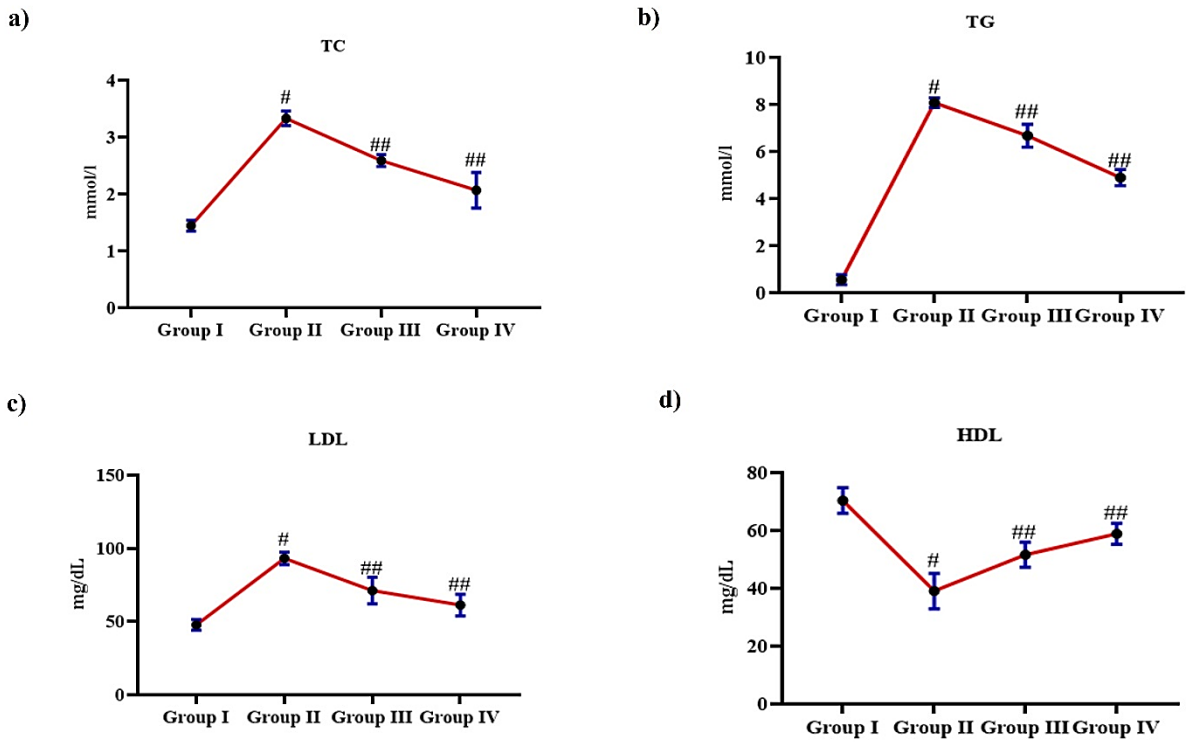

Figure 2: Dipsacoside normalized serum lipid in MI stimulated rats. a) Total Cholestrol, b) Triglycerides, c) Low Density Lipoprotein (LDL), d) High Density Lipoproteim (HDL) levels in control, MI stimulated untreated rats, MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. # Control vs Others, ## MI stimulated untreated rats vs MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. Statistical significance $p<0.05$.

DISCUSSION

Recent advancements in medical therapies have significantly improved the prediction for acute myocardial infarction over the past few decades.[29,30] Despite these improvements, acute MI remains a leading cause of mortality globally, indicating that further enhancements in treatment are necessary.[31] Common pharmacological treatments include aspirin, ACE inhibitors, angiotensin receptor blockers, statins and diuretics.[32] The most effective current approaches for managing MI are Coronary Artery Bypass Grafting (CABG) and Percutaneous Coronary Intervention (PCI), enhances blood flow to the ischemic heart.[33] However, these procedures won't be suitable of patients with iodinated contrast agent allergies and with widespread coronary artery stenosis. Additionally, even successful CABG procedures can only reduce MI by an average of 30%,[34] while about 46% of patients with PCI experience complications related to ischemia-reperfusion.[35] As a result, there is a pressing necessity for innovative treatment strategies to tackle the challenges related to myocardial infarction.

Myocardial infarction is a complex pathological condition characterized by the heart muscle tissue death due to sustained ischemia, often caused by coronary artery disease. The underlying mechanisms include atherosclerotic plaque formation, rupture, and thrombosis, leading to obstruction of blood flow.[36] Metabolic changes that impair myocardial function, oxidative stress, inflammation, and apoptosis were stimulated by ischemia.[37] Recent research emphasizes the significance of post-MI healing processes, which can lead to cardiac fibrosis and chronic heart failure if maladaptive remodeling occurs.[38] Ongoing studies focus on potential therapeutic strategies targeting inflammation, oxidative stress, and myocardial repair to improve outcomes for MI patients.[39] Phytochemicals which possess multifaceted therapeutic efficacy are the potent candidates which effectively targets the varied pathological signaling and render a ameliorative effect in myocardial infarction condition.[40] Therefore in our study we hypothesized to evaluate the efficacy of dipsacoside B, a saponin on alleviating myocardial infarction in rat model.

ISO triggered MI model is considered to be reliable non-invasive model with low mortality incidence. ISO administration induces hypoxia, hypotension, overloads calcium, triggers free radical synthesis and caused energy depletion in cardiomyocytes leading to cardiac myocytes damages. The pathological condition exhibited with ISO administration mimics human myocardial infarction,[41,42] therefore we utilized ISO triggered MI model to analyzed the potency of dipsacoside B in MI condition.

Hypercholesterolemia significantly contributes to be a prime initiator of heart disease.[43,44] Numerous prospective researches indicate a direct connection between plasma cholesterol levels and the risk of cardiac arrest.[45] Research has shown that high cholesterol levels adversely affect coronary heart disease outcomes and left

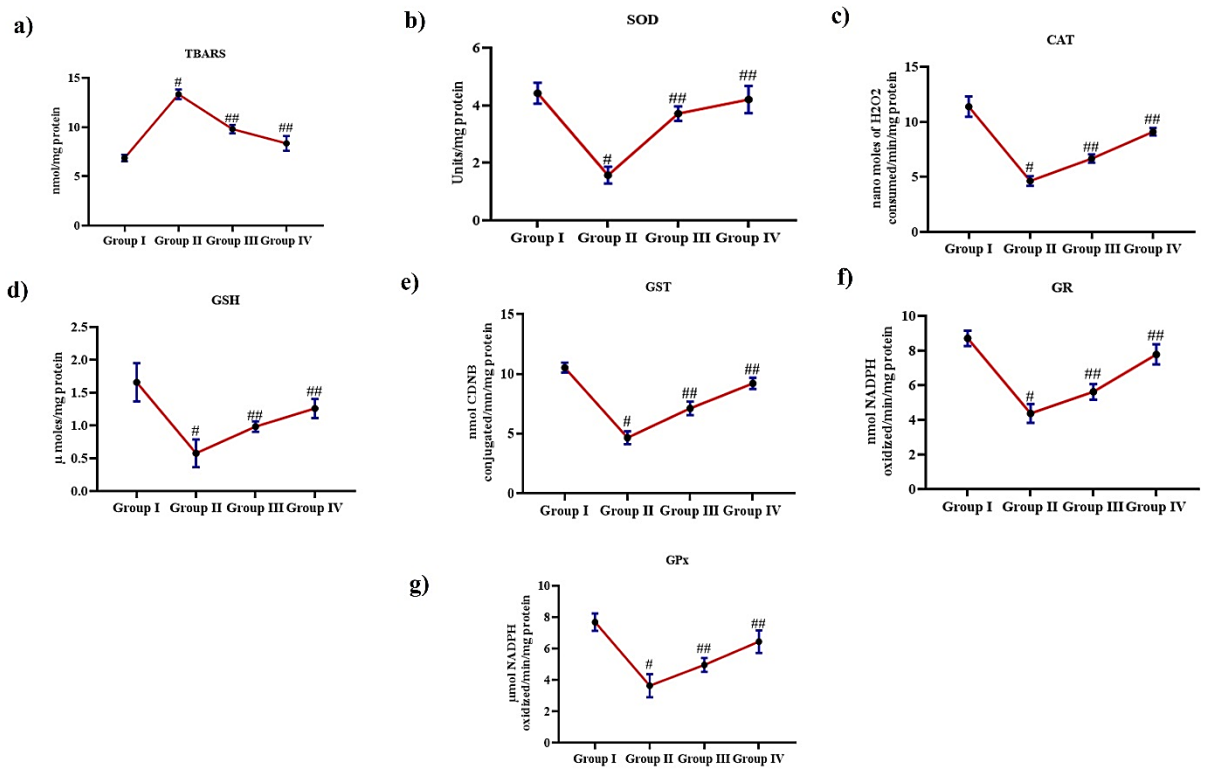

Figure 3: Dipsacoside enhanced antioxidant levels in MI stimulated rats. a) Thiobarbituric Acid-Reactive Substances (TBARS), b) Catalase (CAT), c) Superoxide Dismutase (SOD), d) Reduced glutathione (GSH), e) Glutathione Peroxidase (GPx), f) Glutathione Reductase (GR), g) Glutathione S-Transferase (GST) levels in control, MI stimulated untreated rats, MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. # Control vs Others, ## MI stimulated untreated rats vs MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. Statistical significance $p<0.05$.

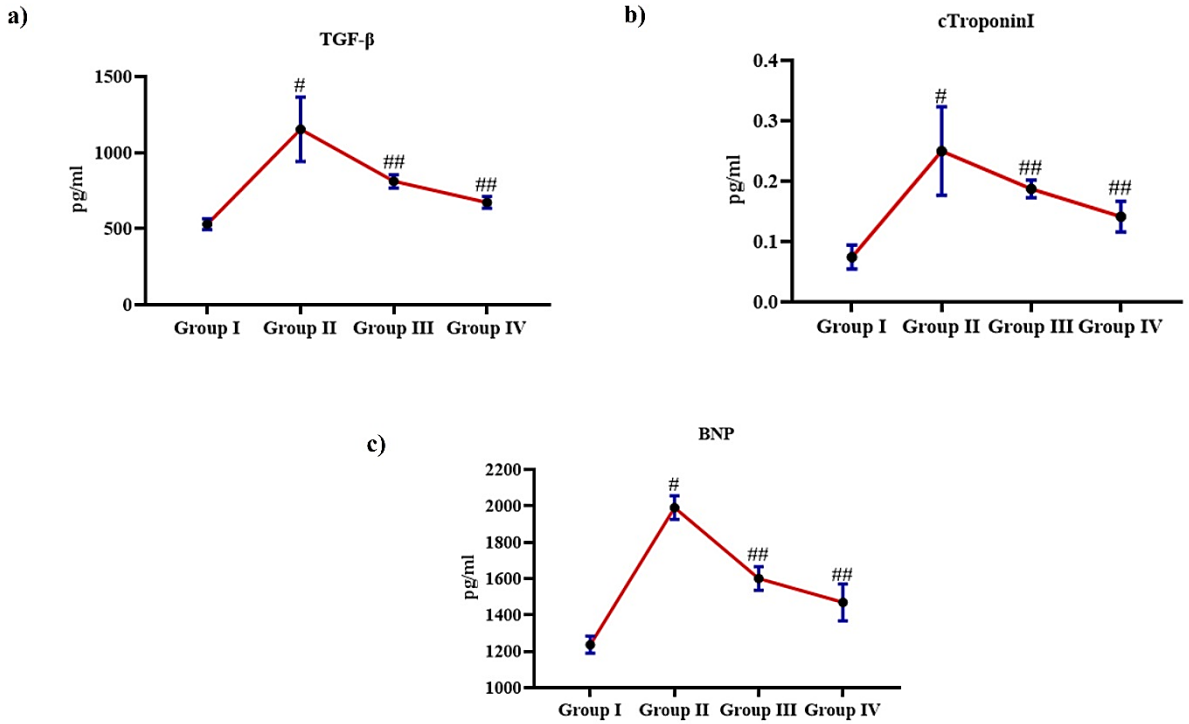

Figure 4: Dipsacoside attenuated critical mediators of MI. a) Transforming Growth Factor-beta (TGF-β), b) Cardiac Troponin I (cTnI), c) B-type Natriuretic Peptide (BNP) levels in control, MI stimulated untreated rats, MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. # Control vs Others, ## MI stimulated untreated rats vs MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. Statistical significance $p<0.05$.

ventricular systolic function following a myocardial infarction, while lipid-lowering therapies have been found beneficial.[46] Statins, which inhibit HMG-CoA reductase, effectively reduce cholesterol production and can help mitigate dyslipidemia and related health issues.[47] While conventional medications like statins primarily target LDL cholesterol, phytochemicals offer a holistic approach via lowering blood pressure, improving lipid profiles and exhibiting anti-inflammatory and antioxidant properties with fewer side effects.[48] Dipsacoside B treatment significantly lowered cholesterol, triglycerides, and LDL levels while increasing HDL levels in rats with myocardial infarction. Additionally, the administration of dipsacoside B effectively regulated hemodynamic changes, demonstrating its cardioprotective effects through lipid-lowering properties.

Oxidative stress occurs at the ischemic site upon the reestablishment of circulation, as the influx of oxygen causing excessive ROS generation, which can be detrimental to the affected area. The increase in ROS during reperfusion after ischemia alters cellular and tissue metabolism, contributing to dysfunction and even cell death in cases of myocardial infarction.[49] Therefore, reducing oxidative stress may help mitigate ischemia-reperfusion injury.[50,51] MDA is a recognized marker of oxidative stress that indicates the Coronary Artery Disease (CAD) and plaque vulnerability.[52] Studies show that MDA levels are elevated and antioxidants were reduced with Acute Coronary Syndrome (ACS).[53,54] SOD plays a crucial role by converting superoxide radicals into Hydrogen Peroxide (H_2O_2), which is subsequently broken down into water and oxygen by the catalase enzyme system.[55] Research has found that both SOD activity and catalase levels are reduced with acute MI.[56,57] Furthermore, the glutathione system, is essential for defending the heart from oxidative stress and regulating redox balance.[58] Dipsacoside treatment significantly enhanced the antioxidant levels and attenuated lipid peroxidation in myocardial infraction confirming counteracting potency against ISO induced oxidative stress.

Nrf2 belongs to the NF-E2 family of nuclear basic leucine zipper transcription factors which aids in the process of pro-oxidants detoxification. In ischemic condition Nrf2 plays vital via rendering antioxidant defense and mice deficient with Nrf2 were reported to be prone to oxidative stress induced cardiac injury.[59] Dipsacoside treatment had significantly enhanced the levels of Nrf2 and it also attenuated the caspases 3 and 9 levels in MI triggered rats which confirms the antioxidant induced anti-apoptotic potency of dipsocapside B., promotes the detoxification of pro-oxidative stressors.

Inflammatory and apoptotic intracellular signaling pathways were triggered by free radicals.[60] Following MI, tissue damage and necrosis initiate a robust inflammatory response.[61] These pro-inflammatory cytokines activate myocardial cells and recruit additional immune cells to the site of injury, thereby exacerbating myocardial damage and imposing additional stress on cardiac function.[62] Cardiac pathology is multifaceted with

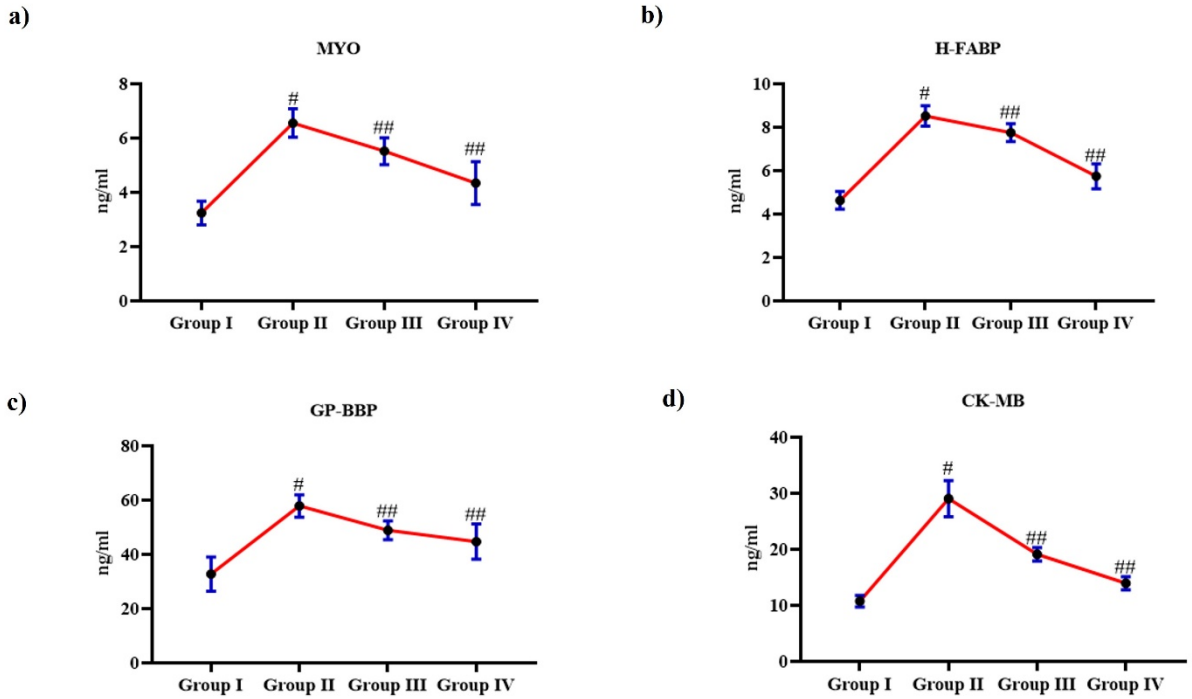

Figure 5: Dipsacoside ameliorated myocardial infraction. a) Myoglobin, b) Heart-Type Fatty Acid-Binding Protein (H-FABP), c) Glucose-regulated protein 78 (GP-BBP), d) Creatine Kinase-MB (CK-MB) levels in control, MI stimulated untreated rats, MI stimulated+10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. # Control vs Others, ## MI stimulated untreated rats vs MI stimulated+10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. Statistical significance $p<0.05$.

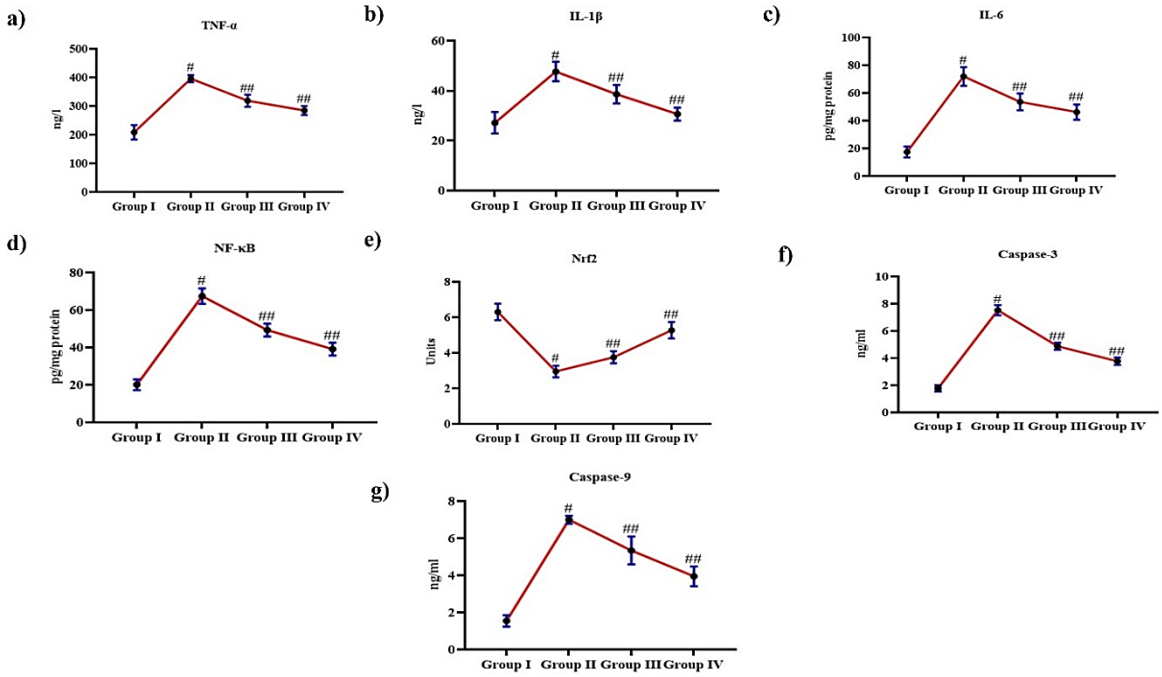

Figure 6: Dipsacoside attenuated inflammation in MI stimulated rats. a) Tumor Necrosis Factor alpha (TNF-α), b) Interleukin 1beta (IL-1β), c) Interleukin 6 (IL-6), d) Nuclear Factor kappa B (NF-κB), e) Nrf2, f)caspase-3 and g) caspase-9 levels in control, MI stimulated untreated rats, MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. # Control vs Others, ## MI stimulated untreated rats vs MI stimulated + 10 mg/kg Dipsacoside treated and MI stimulated + 20 mg/kg Dipsacoside treated rats. Statistical significance $p<0.05$.

action of inflammatory mediators and free radicals.[63] Elevated serum levels of TNF-α, along with increased concentrations of pro-inflammatory cytokines and oxidative stress markers observed in patients with myocardial infarction, suggest a bidirectional relationship. Inflammation appears to amplify oxidative stress while concurrently impairing the body's endogenous antioxidant defense systems, further propagating myocardial injury and dysfunction.[64] In our study also treatment with ISO enhanced the inflammatory stimulating cytokines IL-6, IL-1β, TNF-α and NFκB whereas the dipsacoside B administration attenuated the synthesis of inflammatory cytokines and prevented the oxidative stress induced inflammation in cardiac tissue.

TGF-β regulates fibroblast activity and extracellular matrix remodeling in myocardial infarction by promoting collagen and fibronectin synthesis while inhibiting matrix degradation via protease inhibitors.[65] Dipsacoside B treatment reduced the levels of TGF-β in MI triggered rats hence we further analyzed the impact of dipsacoside B on critical mediators of MI. Electrocardiogram (ECG) findings, including ST changes or pathological Q-waves, alongside elevated cardiac troponins and CK-MB, confirm MI diagnosis.[66] H-FABP, a cytoplasmic protein in cardiomyocytes, is rapidly released into circulation which aids Non-ST Elevation Myocardial Infarction (NSTEMI) detection, outperforming traditional biomarkers like cTnI and CK-MB in early diagnostics.[67,68] GPBB demonstrates superior sensitivity and specificity to CK-MB and myoglobin for AMI diagnosis within 4 hr of symptom onset, highlighting its utility as an early biomarker.[69] Dipsacoside treatment had reduced the levels of cTnI, Ck-MB and it also exhibit significant reduction of H-FABP and GBPP in MI triggered rats. Elevated BNP levels in acute myocardial infarction correlate with infarct severity, left ventricular dysfunction, and potential heart failure.[70,71] Myoglobin, an early but transient marker of myocardial injury, rises quickly but is cleared within 24 hr.[72] The BNP and myoglobin levels were also decreased with dipsacoside B treatment proving its cardioprotective effect. Analysis of critical mediators in dipsacoside B treated authentically confirms the ameliorative potency of the drug against myocardial infarction.

CONCLUSION

The research highlights the significant ameliorative efficacy of dipsacoside B in addressing myocardial infarction. The compound not only improved serum lipid profiles and hemodynamic parameters in isoproterenol-induced MI in rats but also demonstrated potent antioxidant properties by scavenging oxidative stress and enhancing antioxidant levels. Additionally, dipsacoside B effectively reduced key inflammatory markers and caspase activity, indicating its anti-inflammatory and anti-apoptotic effects. The marked enhancement of Nrf2 protein further supports its role in bolstering the body's antioxidant defenses. Overall, our result indicates dipsacoside B could serve as a valuable intervention for myocardial infarction, offering a

multifaceted approach to cardioprotection that warrants further investigation in clinical settings.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ISO: Isoproterenol; **MI:** Myocardial infraction; **i.p:** Intraperitoneal Injection; **MAP:** Mean Arterial Pressure; **SAP:** Systolic Arterial Pressure; **DAP:** Diastolic Arterial Pressure; **HR:** Heart rate; **TBARS:** Thiobarbituric Acid-Reactive Substances; **CAT:** Catalase; **SOD:** Superoxide Dismutase; **GSH:** Reduced Glutathione; **GPx:** Glutathione Peroxidase; **GR:** Glutathione Reductase; **GST:** Glutathione S-Transferase; **TGF-β:** Transforming Growth Factor-beta; **cTnI:** Cardiac Troponin I; **BNP:** B-Type Natriuretic Peptide; **MYO:** Myoglobin; **H-FABP:** Heart-Type Fatty Acid-Binding Protein; **GP-BBP:** Glucose-Regulated Protein 78; **CK-MB:** Creatine Kinase-MB; **TNF-α:** Tumor Necrosis Factor Alpha; **IL-1β:** Interleukin 1beta; **IL-6:** Interleukin 6; **NF-κB:** Nuclear Factor Kappa B; **CVD:** Cardiovascular Disease; **MI:** Myocardial Infraction; **IHD:** Ischemic Heart Disease; **BMI:** Body Mass Index; **ROS:** Reactive Oxygen Species; **MAPK:** Mitogen-Activated Protein Kinases; **NFkB:** Nuclear Factor Kappa B; **VSMC:** Vascular Smooth Muscle Cell; **PCI:** Percutaneous Coronary Intervention; **CABG:** Coronary Artery Bypass Grafting; **CAD:** Coronary Artery Disease; **ACS:** Acute Coronary Syndrome; **H_2O_2:** Hydrogen Peroxide; **ECG:** Electrocardiogram; **NSTEMI:** Non-ST Elevation Myocardial Infarction.

ETHICAL APPROVAL

This work has approved by the institutional animal ethical committee by Xinchang County People's Hospital, Shaoxing Zhejiang, 312500, China.

SUMMARY

Myocardial Infarction (MI), usually known as a heart attack, is characterized by an inadequate blood circulation and oxygen to the cardiac tissue, resulting in the death of cardiomyocytes and a heightened risk of heart failure. Dipsacoside B effectively reduced key inflammatory markers and caspase activity, indicating its anti-inflammatory and anti-apoptotic effects.

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