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Noscapine protects the heart from isoprenaline-induced toxicity

Mohaddeseh Sadat Alavi[1,2], Fereshte Torabi[3], Mohammad Mahdi Dabaghi[4], Amir-Hossein Mohebbi[2], Azar Hosseini[1,2,*]

[1]*Pharmacological Research Center of Medicinal Plants, Basic Sciences Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Department of Pharmacology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Anatomy and Cell Biology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4]*Student Research Committee, School of Pharmacy, Mashhad University of Medical Science, Mashhad, Iran*

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**** Corresponding Author:***
Tel: +985138828566
Fax: +985138828567
Hosseiniaz@mums.ac.ir

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Abstract

Objective: Cardiovascular disease is the major cause of mortality and morbidity. Various studies have shown that oxidative stress plays a major role in myocardial infarction. This study investigated the cardio-protective effect of noscapine against isoprenaline-induced cardiotoxicity.

Materials and methods: Rats received noscapine (5 and 50 mg/kg) or vitamin E (positive control) orally from day 1 to 9. In the pre-treatment group, isoprenaline was injected subcutaneously at a dose of 85 mg/kg on the 8^{th} and 9^{th} days. In the co-treatment group, isoprenaline was administered on the 2^{nd} and 3^{rd} days. On the 10^{th} day, rats were anesthetized, and blood was collected from the heart to determine lactate dehydrogenase (LDH), creatine kinase muscle-brain (CK-MB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lipid profile. The levels of superoxide dismutase (SOD), catalase, malondialdehyde (MDA), and thiol were measured in cardiac tissue. A histopathological study was also performed on cardiac tissue.

Results: Isoprenaline increased LDH, CK-MB, and MDA, while reducing SOD, thiol, and catalase ($P<0.001$ for all cases). Isoprenaline led to the infiltration of inflammatory cells and necrosis. In pre- and co-treatment groups, noscapine reduced MDA, lipid profile, and cardiac markers while increasing anti-oxidant activity and high density lipoprotein (HDL). Vitamin E, as a positive control, decreased lipid peroxidation and oxidative stress, and modulated lipid profile.

Conclusion: Noscapine attenuated isoprenaline-induced cardiac toxicity in the tissue. The protective effect of noscapine was partly mediated by reducing oxidative stress, suggesting a role in the modulation of isoprenaline-induced cardiotoxicity.

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Introduction

Cardiovascular diseases (CVD) and ischemic heart diseases (IHD) are important causes of death worldwide and can lead to disability. According to the World Health Organization (WHO) predictions, cardiovascular diseases will cause more than 23.6 million deaths annually, most of which will be due to myocardial infarction (MI) (Organization 2013). Myocardial infarction can lead to serious and fatal complications including myocardial fibrosis and hypertrophy of the heart chambers (Fishbein et al. 2022). Myocardial infarction is a phenomenon that widely influences the function, structure, and biochemical parameters of the cardiac system (Lüscher 2015). As a result, myocardial cells undergo cell death through both controlled mechanisms (apoptosis, autophagy, and necroptosis) and uncontrolled pathway (cell necrosis). The most important mechanisms involved in atherosclerosis are spasms of the coronary arteries (Severino et al. 2020), inflammation, oxidative stress, accumulation of free radicals, and cell apoptosis (Neri et al. 2015). A common treatment for MI includes the use of angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic antagonists, and antiplatelet agents (Strauss, Hall and Narkiewicz 2023). Studies have shown that most biological substances of natural origin have different pharmacological properties and have lower side effects on patients (Chopra and Dhingra 2021). Therefore, the use of new and complementary agents for treating heart attacks and controlling their complications is discussed, especially in developed countries (David, Wolfender and Dias 2015). There are different methods for inducing myocardial ischemia in the laboratory environment, for example, the occlusion of coronary arteries through surgery. Another common method of inducing myocardial ischemia in the laboratory environment is the injection of a high dose of isoprenaline (Jiang et al. 2021; Lindsey et al. 2018). Isoprenaline is a beta-adrenoceptor agonist applied in emergencies, asthma attacks, bradycardia, arrest of the heart, and eye problems (Khan 2007). Besides these therapeutic effects, isoprenaline, especially in high doses, can have serious side effects, such as the induction of MI (Hosseini et al. 2022). Isoprenaline can cause an increase in the heart need for oxygen and serious heart damage through mechanisms, for example, elevation of free radicals, generation of inflammatory factors, and apoptosis (Qi et al. 2019). Researchers have found that isoprenaline-induced myocardial abnormalities in the hearts of laboratory animals are similar to what occurs in human myocardial ischemia (Noushida et al. 2024). Therefore, isoprenaline is widely used as a standardized model to induce MI in rats to investigate the beneficial effects of compounds on the MI process (Zaafan et al. 2013). Different studies have reported that opioid receptors can have a role in the management of cardiovascular diseases and cause cardio-protection (Johnson 2019). Co-administration of morphine and verapamil reduced myocardial injury (Joukar et al. 2011). Also, administration of morphine, fentanyl, and remifentanil attenuated myocardial infarct size (Kim, Jang and Kim 2011). Noscapine is a benzyl-isoquinoline alkaloid compound with the chemical formula $C_{22}H_{23}NO_7$, found in Berberidaceae, Papaveraceae, and Ranunculaceae (Priyadarshani 2022). This compound was first isolated from opium in 1803 by Jean-François Derosne. Noscapine is found in plants that are rich in alkaloids. Its properties in the central nervous system (CNS) are minimal and do not lead to respiratory depression, euphoria, or addiction (Akhter et al. 2022). Noscapine has different properties, such as reduced cough and inflammation, free radicals, and anti-cancer (Rida et al. 2015). Also, studies have reported anti-fibrotic (Kach et al. 2014), anti-tumor (Chougule et al. 2011), reduction of blood glucose (Wei and Zheng 2025) and neuroprotective (Jayaraj et al. 2021a) effects of noscapine. There is only one *in vitro* study that showed noscapine has a cardioprotective effect (Vahabzadeh et al. 2020).

In this study, we investigated the cardioprotective effect of noscapine against isoprenaline in rats by evaluating oxidative stress parameters. Additionally, cardiac markers, liver enzymes, lipid profile and histopathological modification were evaluated.

Materials and Methods

Adult male Wistar rats weighing 200 to 250 g were bought from the Animal Research Center of Mashhad University of Medical Sciences, Mashhad, Iran. The temperature of the storage room was 22±4°C with a 12-hr day/night cycle. Water and food were available to animals. The Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (NIH) was used to perform all tests. This proposal was approved by the Animal Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1400.104). The male rats were randomly divided into ten groups (8 animals in each group). This research utilized two experimental protocols: pre-treatment and co-treatment.

Preparation of noscapine

Noscapine with high purity (>99.5%) was bought from FaranShimi® Company (CAS number: 128-62-1)

Stimulation of MI

Isoprenaline was administrated subcutaneously at a dose of 85 mg/kg on the 8th and 9th to stimulate MI in the pre-treatment group (El-Gohary and Allam 2017). In the co-treatment group, rats subcutaneously received isoprenaline on the 2nd and 3rd days.

Pre-treatment protocol

This experiment was done in five groups, each one including eight male rats. Normal saline 0.9% was intraperitoneally injected for 9 days for group 1. In group 2, normal saline was given for 9 days, and then, isoprenaline (85 mg/kg) was administrated subcutaneously (S.C.) on the 8th and 9th days. Treatment groups 3 and 4 received noscapine at 5 or 50 mg/kg of gavage for 9 days (Bosak et al. 2025; Kawadkar et al. 2021; Wei and Zheng 2025); then, isoprenaline was administrated on the 8th and 9th days as S.C. As a positive group, the fifth group received vit E at the dose of 100 mg/kg orally for 9 days and isoprenaline on the 8th and 9th days.

Co-treatment protocol

In this experiment, 40 male rats were used, including five groups (8 rats). Normal saline was administrated as i.p. for 9 days. Next, 85 mg/kg of isoprenaline was administrated as S.C. (0.3 ml) on the 2nd and 3rd with an interval of 24 hr. Treatment groups 3 and 4 received noscapine orally at two doses, including 5 or 50 mg/kg for 9 days, and isoprenaline was administrated on the 2nd and 3rd. The fifth group received vitamin E at a dose of 100 mg/kg orally, and isoprenaline was administered on the 2nd and 3rd days.

Sample collection

On the 10th day, ketamine hydrochloride (80 mg/kg)/xylazine (8 mg/kg) was applied to anesthetize rats (Alavi et al. 2026). Then, blood samples were collected intracardially, and serum was separated immediately and stored in a freezer at -20 °C. The heart tissue was separated and kept in formalin to study pathological changes. Also, a part of the heart was stored in a freezer to measure biochemical markers.

Evaluation of malondialdehyde

To determine malondialdehyde (MDA), a tissue sample (0.5 ml) was mixed with trichloroacetic acid 10% (1 ml) and thiobarbituric acid (TBA) 0.67% (1.5 ml). The mixture was heated (40 min) in a water bath and then cooled. After adding HCl (0.025 ml) and *n*-butanol (1.5 ml), the samples were centrifuged (10 min, 1000 g). The absorbance was read at 535 nm, and the concentration was calculated according to

absorbance/(1.56 $\times 10^5$ $cm^{-1}M^{-1}$)
(Boroushaki et al. 2019).

Measurement of thiol content

According to recent studies, the thiol amount was measured in cardiac tissue. Tris-EDTA buffer (pH 8.6) was added to the tissue homogenate (50 µL). Then, absorbance was read at 412 nm as A1. After adding 5,5′-Dithiobis-(2-nitrobenzoic) acid (DTNB) to this mixture, the absorbance was again determined as A2. The concentration of thiol (mM) was calculated using:

(A2-A1-B)×0.7)/0.05×14
(Boroushaki et al. 2019).

Catalase activity

The determination of catalase activity was carried out via the Aebi method. The method is based on detecting hydrogen peroxide destruction by measuring its absorbance attenuation at 240 nm/min. The activity was presented as K (constant) per liter (Aebi 1984; Bergmeyer 2012).

Superoxide dismutase activity

The amount of superoxide dismutase (SOD) was measured via the Madesh and Balasubramanian methods. The base of this procedure is the conversion of tetrazolium dye to formasan compound through SOD, whose absorbance was read at 570 nm (Madesh and Balasubramanian 1998).

Evaluation of enzyme markers

After centrifugation of blood, the serums were isolated and kept in a freezer to evaluate enzyme markers including lactate dehydrogenase (LDH), creatine kinase muscle-brain (CK-MB), , aspartate aminotransferase (AST), and alanine aminotransferase (ALT) by standard kits (Hosseini et al. 2018).

Determination of lipid profile

The amounts of lipids such as triglyceride (TG), cholesterol (chol), low density lipoprotein (LDL), and high-density lipoprotein (HDL) were evaluated in serum according to manufacturer's protocol (Pars Azmun Co., Karaj, Iran).

Histopathological examination

Heart samples were rapidly dissected out and fixed in 10% formalin. After fixation, samples were paraffin-embedded, sectioned at 5 µm, and stained with hematoxylin and eosin (H&E). In the following, the sections were examined by light microscopic analysis.

Statistical analysis

Results were analyzed by GraphPad Prism software version 8 (GraphPad Software, San Diego, CA) and presented as means ± SD. Significance was determined by One-Way ANOVA followed by Tukey-Kramer's test.

Results

Noscapine reduced lipid peroxidation

In this research, we evaluated the effect of noscapine on MDA levels in both the pre-treatment and co-treatment groups (Figure 1A and 1B). As shown in Figures 1A-B, isoprenaline significantly increased the level of MDA ($p<0.001$ vs. control). Administration of noscapine at the dose of 5 mg/kg did not markedly reduce MDA in both A and B experiments compared to isoprenaline ($p>0.05$). In comparison with the isoprenaline group, noscapine at 50 mg/kg meaningfully decreased the level of MDA in pre-treatment ($p<0.05$, Figure 1A) and co-treatment groups ($p<0.01$, Figure 1B). Also, Vit E, as the positive control group at 100 mg/kg, notably attenuated MDA compared to isoprenaline ($p<0.001$).

Effect of noscapine on the level of thiol content

Thiol content was measured in both experiments and shown in Figures 2A-B. In comparison with the control group, isoprenaline decreased the level of thiol in both pre- and co-treatment experiments ($p<0.001$ for all cases). As shown in Figures 2A-B, noscapine (5 mg/kg) had no significant effects on thiol content ($p>0.05$), while 50 mg/kg of noscapine significantly increased the level of thiol in pre-treatment ($p<0.05$, vs. isoprenaline) and co-treatment ($p<0.01$ vs. isoprenaline). As expected, Vit E markedly increased the level of thiol ($p<0.001$, Figures 2A-B).

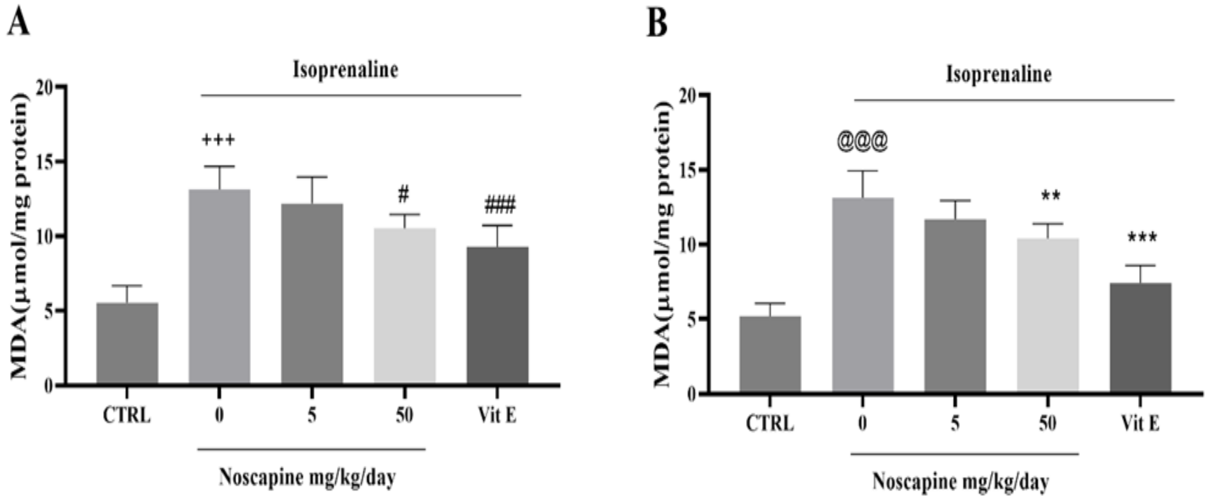

Figure 1. Effect of noscapine on MDA level in pre-treatment (A) and co-treatment (B) in heart tissue. The level of MDA was measured in heart tissue. Results are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. **p<0.01, ***p<0.001, #p<0.05 and ###p<0.001 in comparison with isoprenaline. + or @: statistical difference *vs* control and * or #: in comparison *vs* isoprenaline. Abbreviation: CTRL: control; Vit E: vitamin E; MDA: Malondialdehyde.

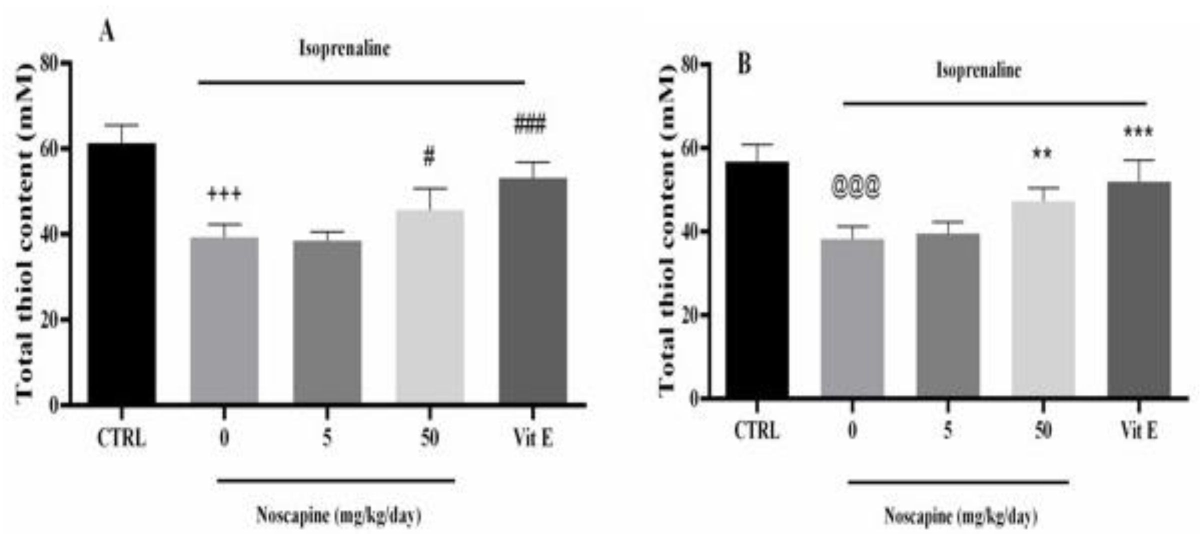

Figure 2. Effect of noscapine on thiol level in pre-treatment (A) and co-treatment (B) in heart tissue. The level of thiol was determined in heart tissue. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. **p<0.01, ***p<0.001, #p<0.05 and ###p<0.001 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control; Vit E: vitamin E.

Noscapine increased the activity of catalase

The activity of catalase was measured in heart tissue in pre-treatment (Figure 3A) and co-treatment (Figure 3B) experiments. Isoprenaline decreased the activity of catalase in both experiments in comparison with the control groups (p<0.001). Noscapine (5 mg/kg) significantly increased catalase in the pre-treatment group (p<0.05, Figure 3A), while the elevation of catalase in the co-treatment experiment at the same dose was not significant (p>0.05, Figure 3B The elevation of catalase activity at a dose of 50 mg/kg of noscapine was significant in both experiments compared to isoprenaline group, (p<0.001, for all cases, Figures 3A-B).

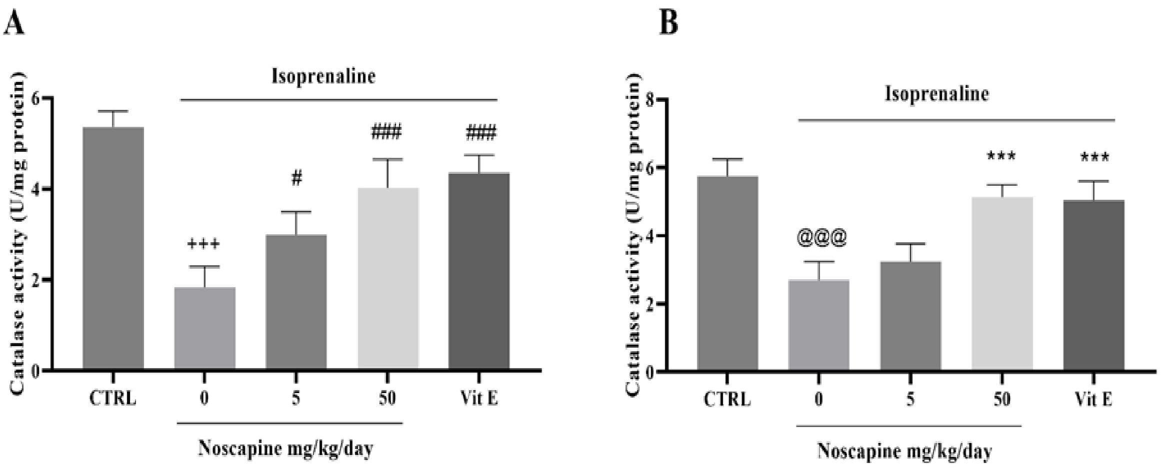

Figure 3. Effect of noscapine on catalase activity in pre-treatment (A) and co-treatment (B) in heart tissue. The activity of catalase was measured in heart tissue. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. ***p<0.001, #p<0.05 and ###p<0.001 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control; Vit E: vitamin E.

Effect of noscapine on SOD activity

We evaluated the effect of noscapine on SOD activity in heart tissue after isoprenaline-induced toxicity. As shown in Figures 4A and B, isoprenaline markedly reduced the activity of SOD compared to control (p<0.001 for both experiments, Figures 4A-B). The obtained results revealed noscapine at the dose of 50 mg/kg significantly elevated SOD activity in both experiments (p<0.01, Figure 4A; p<0.001, Figure 4B) following isoprenaline treatment, which acted similarly to the Vit E group (p<0.001) compared to the isoprenaline group.

Effect of noscapine on cardiac markers

As shown in Figure 5, isoprenaline causes the elevation of LDH (Figure 5 A - B) and CK-MB (Figure 5 C -D) in both experiments compared to the control group (p<0.001 for all cases, Figures 5 A-D). Administration of noscapine at the dose of 5 mg/kg markedly decreased LDH (p<0.05, Figure 5B) and CK-MB (P<0.01, Figure 5D) in the co-treatment assay, while in the pre-treatment evaluation of LDH and CK-MB were insignificant (p>0.05). In comparison with the isoprenaline group, noscapine at the dose of 50 mg/kg attenuated LDH (p<0.001: Figures 5 A-B) and CK-MB (p<0.01, Figure 5 C, and p<0.001, Figure 5D) in both experiments. Vit E significantly decreased cardiac markers in pre- and co-treatment compared with the isoprenaline group (p<0.001 for all cases, Figures 5A-D).

Effect of noscapine on liver enzymes

In comparison with control group, isoprenaline elevated the level of AST (Figure 6 A-B) and ALT (Figure 6 C- D) as significantly in two models of experiment ($p<0.001$, Figure 6 A-D). In pre-treatment group, high dose of noscapine decreased the level of AST ($p<0.01$, Figure 6A) and ALT ($p<0.05$, Figure 6C) while in co-treatment group (Figure 6 B and D) noscapine markedly attenuated AST and ALT in both of doses (5 mg/kg, $p<0.01$; 50 mg/kg, $p<0.001$). In two models of the study, Vit E decreased the level of liver enzymes significantly ($p<0.001$ for all cases, Figures 5 A-D).

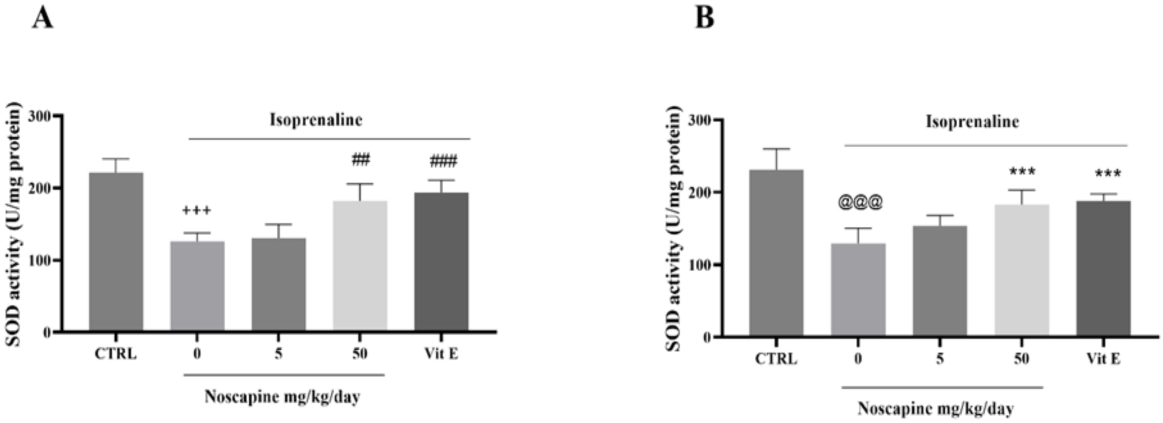

Figure 4. Effect of noscapine on SOD activity in pre-treatment (A) and co-treatment (B) in heart tissue. The activity of SOD was evaluated in heart tissue. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. ***p<0.001, ##p<0.01 and ###p<0.001 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control; Vit E: vitamin E; SOD: Superoxide Dismutase.

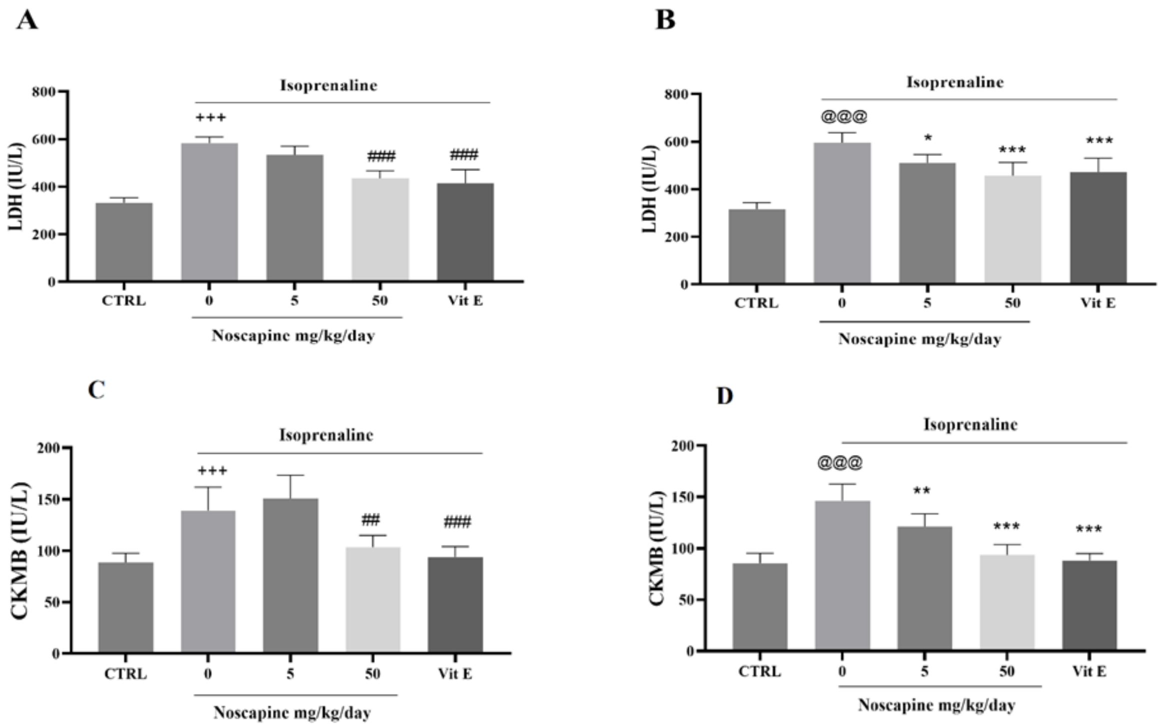

Figure 5. Effect of noscapine on LDH and CKMB in serum. The levels of cardiac markers were evaluated in pre and co-treatment. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. ***p<0.001, ##p<0.01 and ###P<0.001 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control; Vit E: vitamin E; CKMB: Creatine Kinase-MB; LDH: Lactate Dehydrogenase.

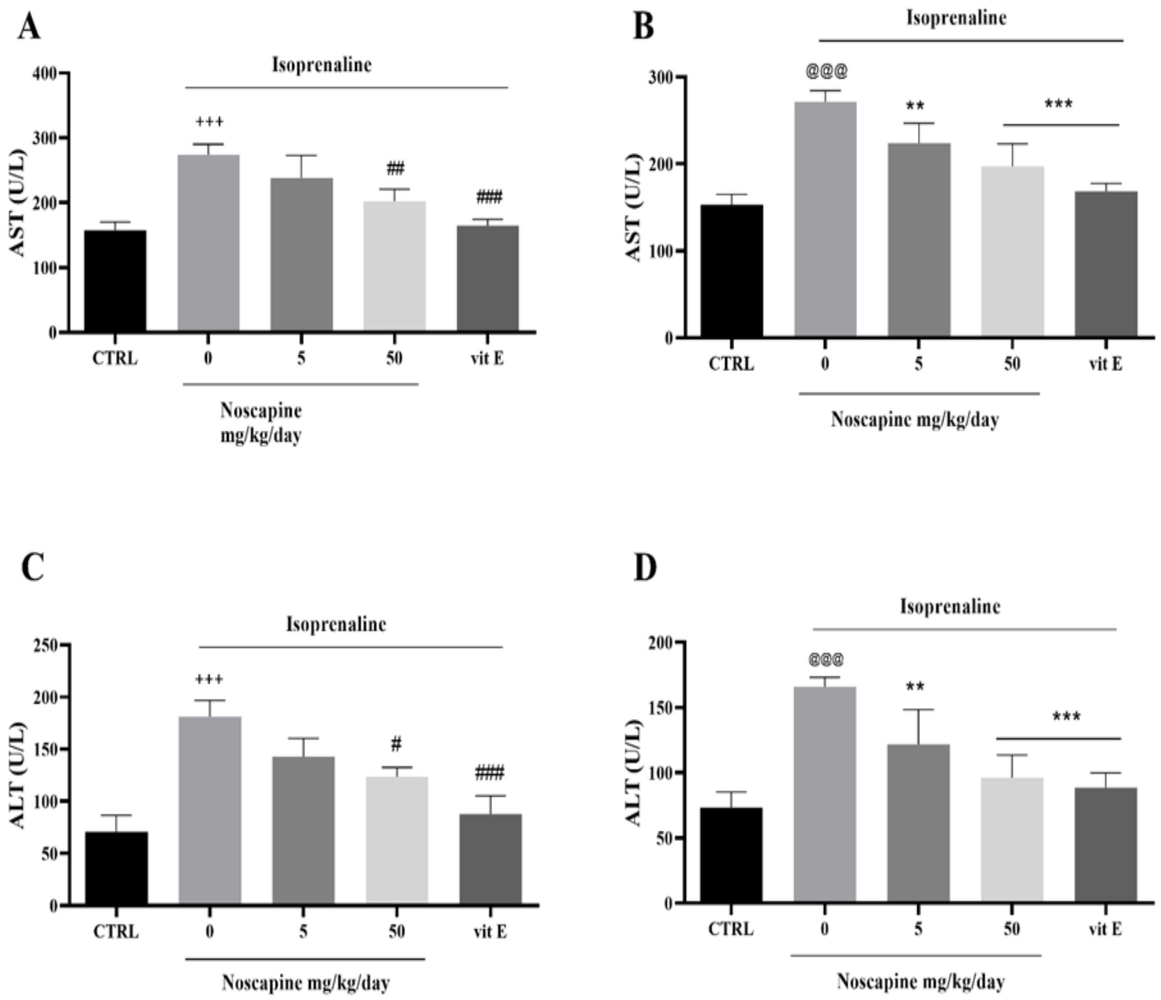

Figure 6. Effect of noscapine on AST and ALT in serum. The levels of AST and ALT were evaluated in pre and co-treatment. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. **p<0.01 and ***p<0.001, #P<0.05 and ###p<0.001 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control; Vit E: vitamin E; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Influence of noscapine on lipid profile

In Figures 7-10, the level of lipid profile is shown in pre- and co-treatment groups. In comparison to the control group, isoprenaline increased the level of TG, cholesterol, and LDL significantly, while HDL reduced (p<0.001). In pre-treatment group, noscapine reduced the level of TG (5 mg/kg, p<0.05 and 50 mg/kg, p<0.001, Figure 7A), cholesterol (50 mg/kg; p<0.01, Figure 8A), LDL (50 mg/kg, p<0.001; Figure 9A) and increased HDL (50 mg/kg, p<0.001, Figure 10A). In co-treatment group, noscapine reduced the level of TG (5 mg/kg, p<0.01; 50 mg/kg, p<0.001, Figure 7B), cholesterol (50 mg/kg, p<0.001; Figure 8B), LDL (5 mg/kg, p<0.05 and 50 mg/kg, p<0.01, Figure 9B) and increased HDL (5 mg/kg, p<0.05 and 50 mg/kg, p<0.01, Figure 10B). Vit E decreased the level of TG, LDL, and cholesterol in both models while increasing HDL significantly (p<0.001, Figures 7-10).

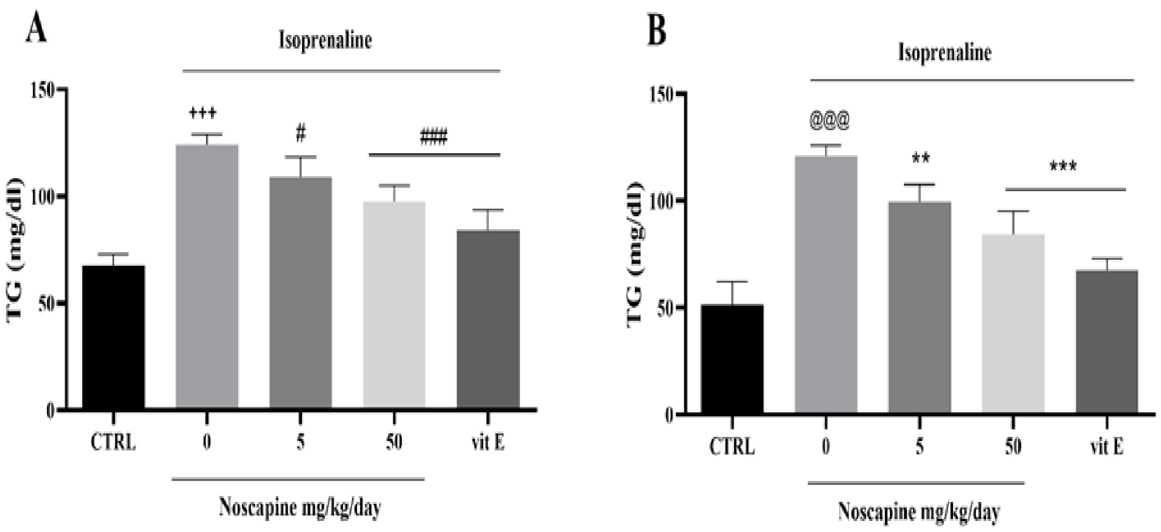

Figure 7. Effect of noscapine on level of triglyceride in pre-treatment (A) and co-treatment (B) in serum. The level of triglyceride was measured in serum. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. **p<0.01, ***p<0.001, #p<0.05 and ###p<0.001 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control; TG: triglyceride

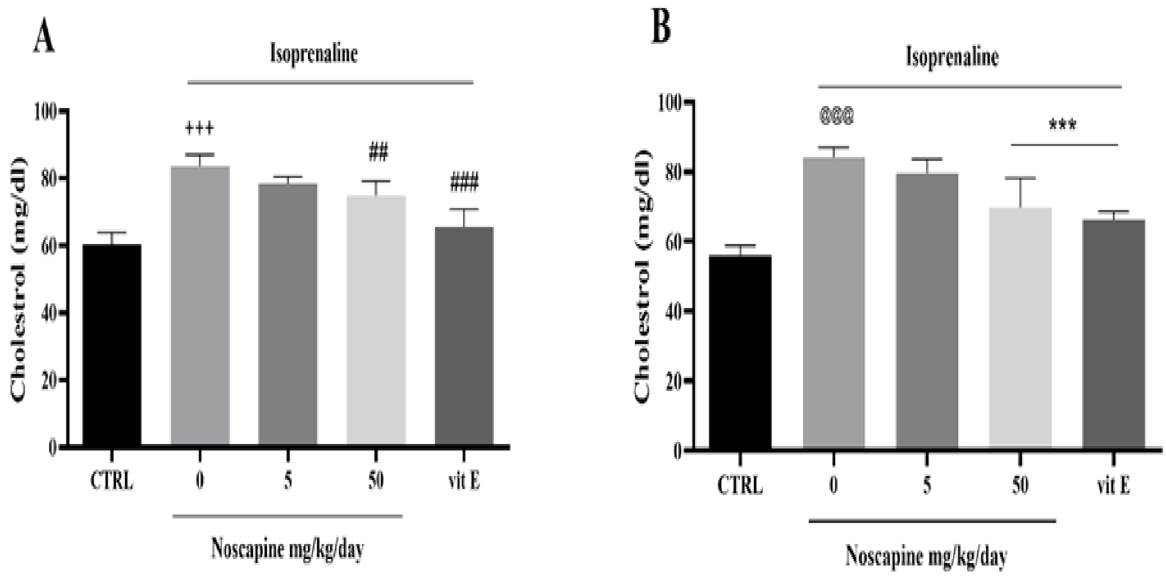

Figure 8. Effect of noscapine on level of cholesterol in pre-treatment (A) and co-treatment (B) in serum. The amount of cholesterol was measured in serum. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. ***p<0.001 and ***P<0.001in comparison with isoprenaline. *+ or @: statistical difference vs control and * or #: in comparison vs isoprenaline*. Abbreviation: CTRL: control

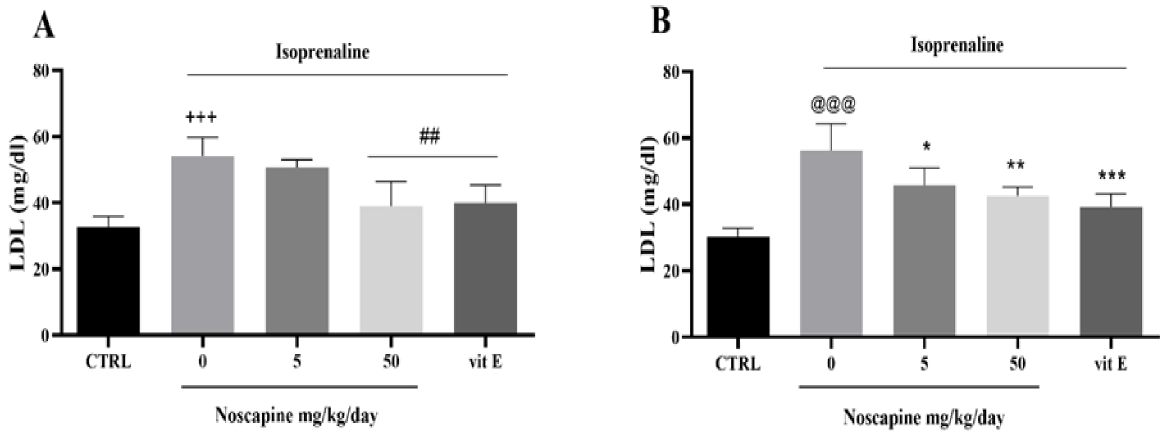

Figure 9. Effect of noscapine on LDL in pre-treatment (A) and co-treatment (B) in serum. The level of LDL was evaluated in serum. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. *p<0.05, **p<0.01, ***p<0.001 and ##p<0.01 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control

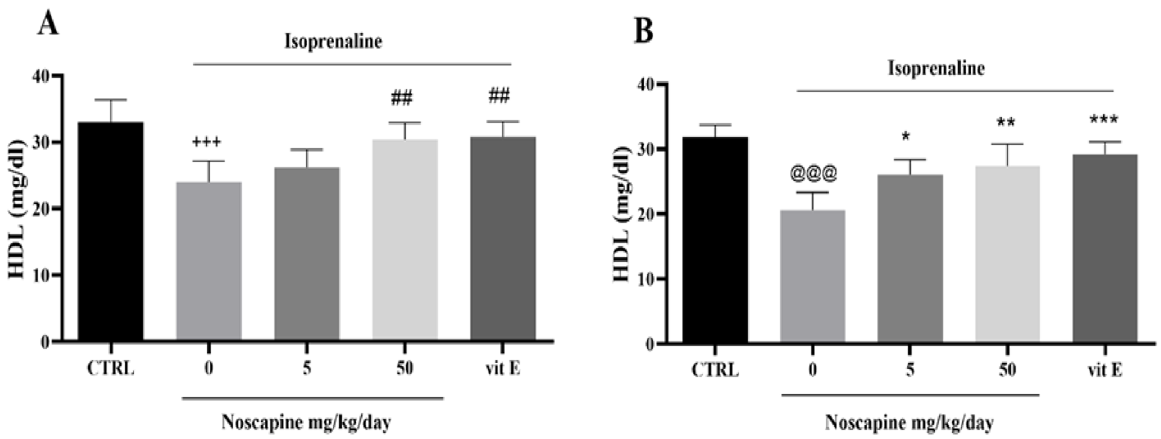

Figure 10. Effect of noscapine on HDL in pre-treatment (A) and co-treatment (B) in serum. The level of HDL was determined in serum. Data are expressed as mean ±SD. +++p<0.001, @@@p<0.001 in comparison with the control group. *p<0.05, **p<0.01, ***p<0.001 and ##p<0.01 in comparison with isoprenaline. + or @: statistical difference vs control and * or #: in comparison vs isoprenaline. Abbreviation: CTRL: control

Effect of noscapine on histopathology in the pre-treatment experiment

As shown in Figure 11, as pre-treatment, the heart tissue from the control group showed normal cardiac fibers without any infarction. The isoprenaline group showed widespread myocardial structure disorders and sub-endocardial necrosis with massive inflammatory infiltration and vascular congestion. Noscapine 5 mg/kg decreased the degree of infiltration of inflammatory cells. However, the heart tissue from the isoprenaline + Noscapine 50 mg/kg and isoprenaline + Vit E groups revealed improved morphology and minimal damage with mild inflammatory infiltrate.

Effect of noscapine on histopathology in co-treatment experiment

As shown in Figure 12, the heart tissue from the control group showed normal cardiac fibers without any infarction. The isoprenaline group showed widespread myocardial structural disorder and sub-endocardial necrosis with inflammatory infiltration. In contrast, 5 mg/kg of noscapine presented moderate inflammatory infiltrates and vascular congestion. The heart tissue from the noscapine 50 mg/kg and Vit E groups showed minimal inflammatory infiltration and vascular congestion.

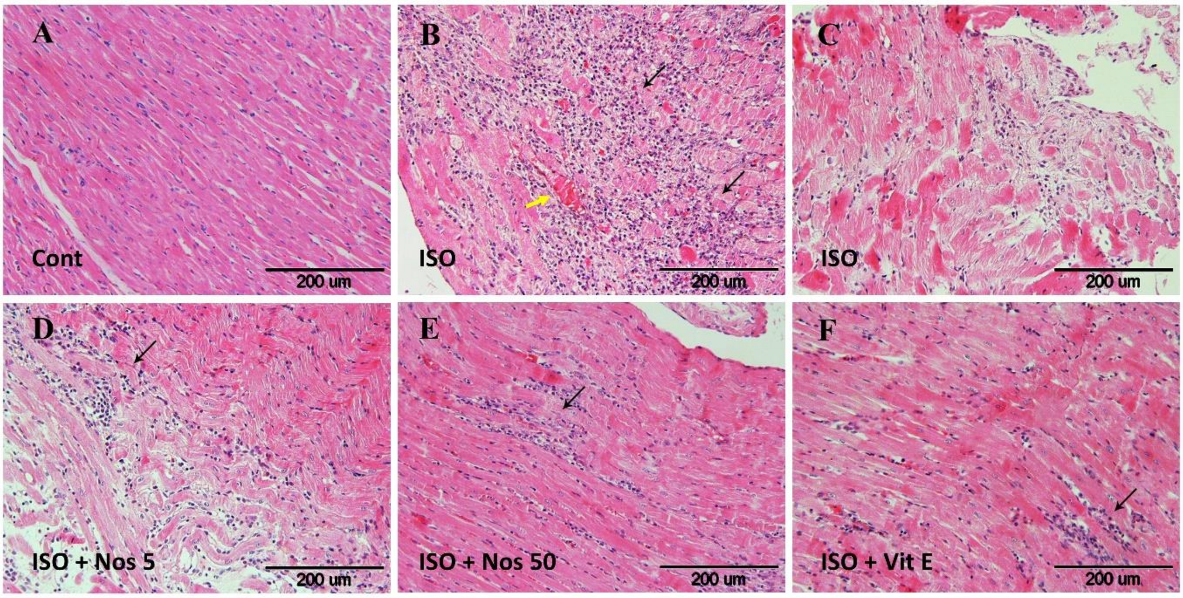

Figure 11. Effect of noscapine on histological changes of heart tissue in the pre-treatment group. Control group (A); isoprenaline group (B and C) showed widespread myocardial structure disorder and sub-endocardial necrosis with massive inflammatory infiltration (black arrow) and vascular congestion (yellow arrow). ISO + NOS 5 (D) decreased the degree of infiltration of inflammatory cells (black arrow). ISO +Nos 50 and ISO + Vit E groups (E and F) revealed improvement of the morphology and minimal damage with mild inflammatory infiltrate (black arrow). (H&E × 200). Abbreviation: Cont: control; Vit E: vitamin E; Nos: noscapine; ISO: Isoprenaline.

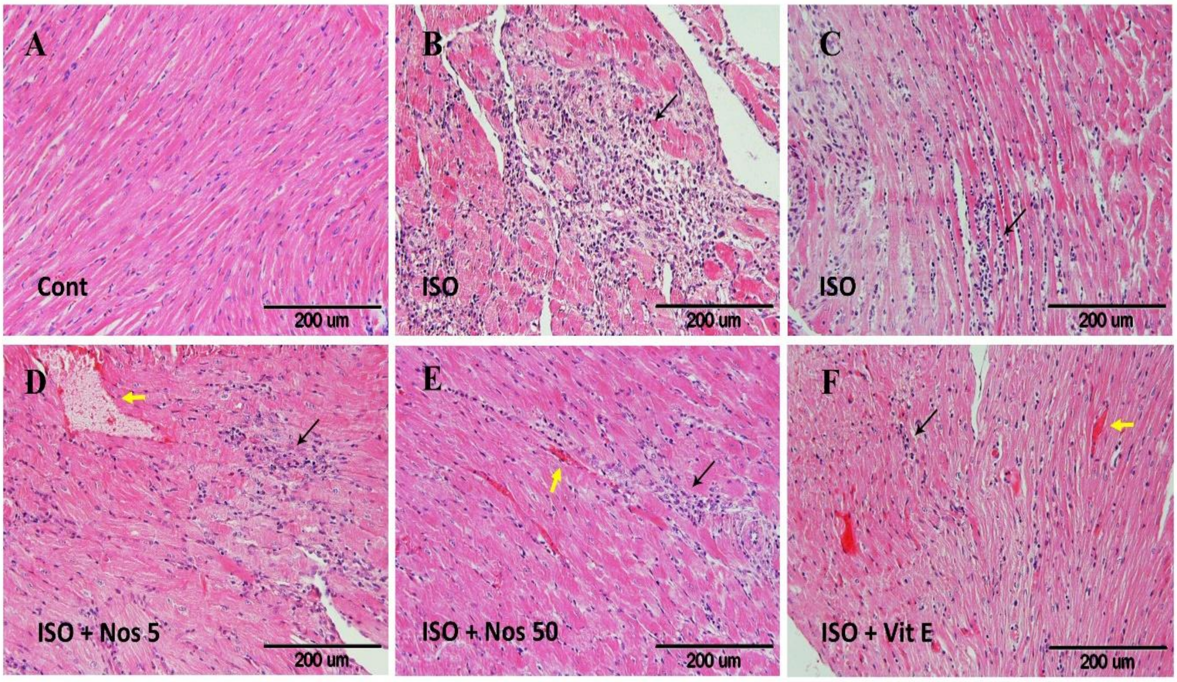

Figure 12. Effect of noscapine on histological changes of heart tissue in the co-treatment experiment. Control group (A), Isoprenaline group (B and C), widespread myocardial structure disorder, and sub-endocardial necrosis with inflammatory infiltration (black arrow). In the group of ISO + Nos 5 mg/kg (D), Moderate inflammatory infiltrates (black arrow) and vascular congestion (yellow arrow). ISO + Nos 50 mg/kg and ISO + Vit E groups (E and F) showed minimal inflammatory infiltration and vascular congestion (black and yellow arrows). (H&E × 200). Abbreviation: Cont: control; Vit E: vitamin E; Nos: noscapine; ISO: Isoprenaline.

Discussion

Our findings showed that isoprenaline administration leads to the elevation of lipid peroxidation, oxidative stress, liver enzymes, cardiac markers, TG, cholesterol, and LDL and a decrease in antioxidant enzymes and HDL. Importantly, either noscapine administered as a pre-treatment or co-treatment significantly mitigated these alterations, indicating a protective effect likely driven by its ability to modulate oxidative stress.

Isoprenaline is a well-established non-selective β-adrenergic agonist that produces myocardial degeneration through excessive catecholamine stimulation and subsequent oxidative stress. Because repeated or high-dose isoprenaline reliably induces biochemical and structural changes resembling human MI, it is widely employed as an experimental model for evaluating cardioprotective agents (Brooks and Conrad 2009; Shukla, Sharma and Singh 2015).

In the isoprenaline model, oxidative stress is evidenced by increased lipid peroxidation and elevated MDA levels, along with reduced activities of catalase, SOD, andthiol. This well-established imbalance between oxidants and antioxidants is a key mechanism contributing to isoprenaline-induced myocardial injury (Lobo Filho et al. 2011; Shukla, Sharma and Singh 2015; Ulla et al. 2017). Isoprenaline also promotes myocardial necrosis which is reflected by increased inflammatory mediators such as interlukin (IL-6) and tumor necrosis factor (TNF-α), as well as elevated leakage markers including LDH, CK-MB, and AST (Shukla, Sharma and Singh 2015). These studies are in confirmation of our findings, which showed that isoprenaline increased MDA, lipid profile, cardiac markers, and liver enzymes, while reducing anti-oxidant enzymes.

Several recent studies have demonstrated the beneficial effects of natural products in attenuation of isoprenaline-induced cardiac toxicity via modulation of oxidative stress (Hosseini et al. 2023; Hosseini et al. 2022). In agreement with these findings, noscapine in the present study, markedly reduced MDA levels, consistent with earlier reports showing its ability to limit lipid peroxidation in models of cerebral ischemia (Kawadkar et al. 2021), ethanol-induced hepatic injury (Aneja, Katyal and Chandra 2004), and rotenone-related neurotoxicity (Jayaraj et al. 2021b).

GSH is responsible for scavenging and neutralizing superoxide radicals which are generated in the myocardium; also, catalase (CAT) and SOD regulate the generation of free radicals by the conversion of superoxide radicals to hydrogen peroxide (Lobo Filho et al. 2011; Shukla, Sharma and Singh 2015).

Noscapine antioxidant effect appears to extend to restoration of endogenous defenses, as we observed significant increases in GSH, SOD, and CAT activities, results that align with previous work demonstrating similar enzyme upregulation following noscapine treatment (Gupta et al. 2023; Jayaraj et al. 2021b).

Isoprenaline-induced membrane necrosis disrupts cellular integrity and increases membrane permeability, resulting in leakage of cardiac injury markers such as CK-MB, LDH, AST, and ALT (Shukla, Sharma and Singh 2015). In the present study, noscapine significantly attenuated the rise in CK-MB and LDH, indicating preservation of membrane stability and reduced myocardial damage. Whereas there are few studies about noscapine cardiovascular properties, our information about of noscapine on LDH and CK-MB is low.

In addition to enzyme leakage, isoprenaline produced marked dyslipidemia, characterized by elevated TG, cholesterol, and LDL, accompanied by reduced HDL, consistent with earlier reports (Manjula et al. 1992). This lipid disturbance is commonly attributed to β-adrenergic-induced increases in cAMP and mobilization of lipids from adipose tissue

(Ithayarasi and Devi 1997). Pre or co-treatment by noscapine effectively reversed these changes, restoring lipid parameters toward normal levels. Similar lipid-lowering and antioxidant effects have been described in diabetic rats treated with noscapine (Wei and Zheng 2025), supporting the compound broader metabolic and redox-modulating potential.

Additionally, noscapine has demonstrated anti-inflammatory properties through suppression of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α in Human (THP-1) and murine (RAW 264.7) macrophages (Zughaier et al. 2010). Noscapine significantly reduced the paw volume, arthritic scoring, and reversed the body mass in rheumatic rats (Akhter et al. 2022).

Beyond its antioxidant activity, noscapine cardioprotective effects may also involve opioid and sigma-1 receptor pathways (Headrick et al. 2015). Recent studies have reported the presence of κ and δ opioid receptors in the myocardium and protective effects in ischemic preconditioning (Lotz and Kehl 2015). In other research, the cardioprotective effect of morphine has been reported via activation of central opioid receptors (He et al. 2018; Wong, Ling and Irwin 2010). Also, deltorphin-II reduces infarct size by activation of δ-2 receptor in cardiac (Maslov et al. 2010). Co-administration of morphine with verapamil has a cardio-protective effect against isoprenaline-induced toxicity (Joukar et al. 2011).

The presence of sigma receptors in the heart has been reported, and it was shown that 75% of them are sigma-1 receptors (Dumont and Lemaire 1991; Novakova et al. 1995). PRE-084, as a sigma-1 receptor agonist, reduced injury in the heart following ischemia-reperfusion through activation of Akt and endothelial nitric oxide synthase (eNOS) (Gao et al. 2018). Different studies have shown that sigma-1 receptors are expressed in ventricular, arterial, and intracardiac neurons in guinea pigs and rats (Stracina et al. 2015; Zhang and Cuevas 2005). Therefore, these receptors can have pharmacological effects in some cardiovascular diseases (Kaur, Muthuraman and Gautam 2021; Stracina and Nováková 2018).

Although direct evidence in cardiac tissue remains limited, noscapine has been shown to preserve mitochondrial integrity and modulate intrinsic apoptotic pathways in cardiomyocyte models. In H9c2 cells, noscapine reduced nitric oxide production and normalized the Bax/Bcl-2 ratio following oxygen-glucose deprivation/reperfusion (OGD/R), consistent with reduced cytochrome-c release and caspase activation reported in other cellular systems. Mechanistic studies in cancer models further demonstrate that noscapine disrupts mitochondrial membrane potential, induces cytochrome-c release, and alters Bax and Bcl-2 expression, which is probably related to modulation of sigma-1 receptors (Vahabzadeh et al. 2020).

According to our findings, both the reduction of oxidative stress and the activation of sigma-1 receptors appear to contribute to the cardioprotective effects of noscapine against isoprenaline-induced toxicity. However, further investigations are required to clarify the precise mechanisms underlying noscapine protective actions.

This study has some limitations. First, the absence of a noscapine-only group prevents us from determining whether noscapine has intrinsic cardiovascular effects independent of isoprenaline. Second, no direct molecular analyses (such as Bax/Bcl-2, cytochrome-c, Akt/eNOS, or sigma-1 receptor expression) were performed, so the proposed mechanisms remain indirect. Finally, the evaluation was limited to an acute model with all measurements taken on day 10; long-term outcomes such as remodeling, fibrosis, and recovery were not assessed.

Noscapine reduced isoprenaline-induced cardiotoxicity by attenuation of oxidative stress and lipid peroxidation. This protective mechanism may be mediated by the modulation of sigma-1 receptors, which are known to play a role in the regulation of certain cardiovascular diseases. More studies are needed to understand the accurate mechanism.

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Conflicts of interest

The authors had no competing interests.

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Authors' Contributions

A.H. designed the study, MS.A., F.T., MM.D., AH.M. performed the experiment and wrote the first draft of the manuscript. All authors contributed to writing the project and read and approved the final manuscript submission. This study has been done by the authors mentioned in this article, and the authors will bear all responsibilities related to the contents of this article.

Abbreviations

LDH, Lactate dehydrogenase; CK-MB, Creatine kinase muscle-brain; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; SOD, Superoxide dismutase; MDA, Malondialdehyde; HDL, High density lipoprotein; CVD, Cardiovascular diseases; WHO, World Health Organization; MI, Myocardial infarction; ACE, Angiotensin-converting enzyme; CNS, Central nervous system; S.C., Subcutaneously; NIH, National Institutes of Health; TBA, Thiobarbituric acid; TG, Triglyceride; Chol, Cholesterol; LDL, Low density lipoprotein; DTNB, 5,5′-Dithiobis-(2-nitrobenzoic) acid; CAT, Catalase; IL-6, Interlukin-6; TNF-α, Tumor necrosis factor-α; eNOS, Endothelial nitric oxide synthase

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