

Protective effects of simvastatin-loaded nano-niosomes against myocardial ischemia/reperfusion-induced acute kidney injury

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ABSTRACT

Introduction: Although simvastatin attenuates renal injury in several ways, its poor solubility and bioavailability may reduce its efficiency. This study evaluated the effect of simvastatin-loaded nano-niosomes against myocardial ischemia/reperfusion (MI/R)-induced kidney failure and compared its efficiency with simvastatin.

Methods: Nano-niosomes were prepared using the surface-active agent film hydration method. For inducing MI/R, the left anterior descending artery (LAD) was ligated, and then recirculation was established. Drug formulations at a concentration of 3 mg/kg were administered into the myocardial tissue. Western blot assay was applied to measure protein levels. An ELISA assay was used to evaluate the expression of inflammatory cytokines, oxidative stress markers, and markers of renal function. H&E staining was done to determine tissue damage.

Results: The induction of MI/R in rats increased serum levels of creatinine, BUN, and uric acid; elevated levels of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, and IL-11), NF- κ B, BAX, and caspase-3 in renal tissue; and decreased the activities of antioxidant enzymes SOD, GPX, and catalase, as well as Bcl-2 protein in renal tissue. Although all of these changes were neutralized by medication with simvastatin and simvastatin-loaded nano-niosomes, simvastatin-loaded nano-niosomes had a more powerful impact on reducing MI/R-induced renal injury compared to simvastatin.

Conclusion: The outcomes conclude that nano-niosomes can be considered a good candidate to improve the efficiency of simvastatin against MI/R-induced renal injury. Simvastatin-loaded nano-niosomes are capable of reducing MI/R-induced renal injury and improving renal function by reducing inflammation, suppressing oxidative stress, targeting NF- κ B protein, and attenuating apoptotic cell death.

Keywords:

Simvastatin
Inflammation
Oxidative stress
Apoptosis

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Introduction

There is a bidirectional correlation between chronic renal disorder disease and cardiovascular condition that is defined as cardiorenal syndrome (Rangaswami et al., 2019). Acute kidney injury (AKI) is a syndrome and one of the substantial complications of cardiac surgery. It is characterized by loss of renal function in patients and is associated with long hospital stays and high mortality (Gallagher et al., 2015). Coronary revascularization, shock, and cardiopulmonary bypass (a surgery for the replacement of a heart valve) are linked with a high prevalence of AKI (Choi et al., 2011). Development of AKI has been reported in almost 50% of subjects after exposure to cardiopulmonary bypass, which is associated with shorter survival (Pickering et al., 2015). The incidence of AKI following cardiopulmonary bypass and coronary revascularization is correlated with several factors, such as reduction in relative perfusion pressure, loss of pulsatile blood flow during surgery, and initiation of oxidative stress and inflammatory responses owing to foreign body reaction (Tang et al., 2020). Among these factors, perioperative renal hypoperfusion results in kidney ischemia-reperfusion injury (I/R), excessive generation of reactive oxygen species (ROS), and hence aggravation of injury because of the elevation of oxidative stress and acute inflammatory reactions (Chen et al., 2014; Ozer et al., 2005). After an acute myocardial infarction, acute inflammatory reactions may confer adverse cardiac remodelling, and circulating inflammatory cytokines may mediate leukocyte infiltration in the kidney, which in turn causes renal injury (Ernandez and Mayadas 2016).

Some investigations have suggested that the residual inflammatory risk of myocardial infarction (MI) patients is connected to renal dysfunction. For example, Fu BS et al. found that elevated high-sensitivity C-reactive protein, an indicator of inflammation in the body, in post-MI patients is associated with an increased risk for AKI in these patients (Fu et al., 2019). Another study indicated that there is a close inflammatory interplay between the cardiac and the renal tissue early after MI that is relevant to CXCR4 and its ligand (Werner et al., 2021).

Statins, as competitive and selective inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are usually employed to reduce dyslipidemia and plasma cholesterol as well as prevent coronary artery disorders (Pang et al., 2020; Tokgozoglu and Zamo-

rano, 2020). Several studies have indicated that the use of statins contributes to reducing renal ischemia/reperfusion injury by enhancing angiogenesis (Chade et al., 2006), inhibiting oxidative stress (Zhang et al., 2017), and inhibiting inflammation (Zhao et al., 2014). Currently, nano-niosomes have gained much attention from the research community owing to their unique properties like biocompatibility, biodegradability, stability, non-toxicity, and their capacity for loading both lipophilic and hydrophilic compounds (Bahrololoumi and Nikazar 2023; Izhar et al., 2023). No previous investigation has assessed simvastatin-loaded nano-niosomes specifically for MI/R-induced cardiorenal disorder, with simultaneous assessment of inflammation, oxidative stress, apoptosis, and NF- κ B signaling. Owing to the poor solubility and bioavailability of simvastatin (Ullah et al., 2022), in this study, we designed a nanocarrier system using simvastatin-loaded nano-niosomes to improve the poor solubility and bioavailability of the drug and explore whether this nano-formulation is capable of improving myocardial ischemia/reperfusion-induced acute kidney injury in rats by targeting inflammation.

Material and Methods

Synthesis of nano-niosomes

Preparation of nano-niosomes was based on our previous investigation and the surface-active agent film hydration method (Naseroleslami et al., 2022). After dissolution of polyethylene glycol (PEG), cholesterol, and nonionic surface-active Span-60 in 100% ethanol under stirring for 5 min at 60°C (150 rpm), the solvent was evaporated using a rotary evaporator, and a thin layer was formed on the wall of the bottom flask. After adding the dissolved drug to the surface-active and cholesterol film, it was hydrated for 10 min at 60°.

Characterization of particles

Transmission electron microscopy (TEM) analysis was used to assess the shape and size of particles. To this end, the samples were deposited onto the copper grid covered with carbon at an increasing voltage of 80 kV.

Animal models and consideration of ethics

Male Wistar rats (250–350 g) were procured from the Animal Center of Iran University of Medical Sciences. The rats were placed in a pathogen-free room on a natural 12 h light/dark schedule, with $60 \pm 5\%$ humidity, at a

temperature of 20–22°C with free accessibility to water ad libitum and meals. All steps were performed according to the approval of the Ethics Committee of Iran University of Medical Sciences. Moreover, all experimental procedures were based on the principles outlined in the Guide for the Care and Use of Laboratory Animals created by the US National Institutes of Health.

Study design

The animals were accidentally divided into Five groups (5 rats per category): 1) Sham group (Sham): The animals were exposed to surgical shock without ligation of the left anterior descending artery (LAD); 2) myocardial ischemia/reperfusion (MI/R) group: the animals were exposed to LAD for 45 min and then recirculation was established for 24 h; 3) MI/R + nano-niosomes group: the animals were exposed to LAD for 45 min and then they intramyocardially received a dose of 3 mg/kg nano-niosomes 10 min prior to the end of LAD ligation; 4) MI/R + simvastatin: the animals were exposed to LAD for 45 min and afterward they intramyocardially received a dose of 3 mg/kg simvastatin 10 min prior to the end of LAD ligation; 5) MI/R + nano-simvastatin: The animals were exposed to LAD for 45 min and then a dose of 3 mg/kg nano-niosomes containing simvastatin was intramyocardially injected prior to the end of LAD ligation. The intramyocardial drug administration allows us to evaluate the direct delivery of the target drug to the heart tissue by avoiding the systemic effects of intravenous injection.

MI/R model

In order to establish an MI/R model in rats, a mixture of ketamine (60 mg/kg) and xylazine (5 µg/kg) was intraperitoneally administered to animals. After anaesthesia, the rats were fixed in a supine sleeping position and endotracheal intubation was performed through a vein puncture needle and its connection to a small-animal ventilator (tidal volume 2–3 mL, respiratory rate 65–70 per min). To induce MI/R, a left thoracotomy at the fourth intercostal space was performed, and the pericardium was opened to reveal the heart. Then, a ligation was established by passing a 5–0 silk suture under the LAD. The regional cyanosis of the myocardial surface, QRS widening, and ST-segment changes were monitored to assess the successful establishment of the model. The rats' body temperature was monitored and

maintained at 37°C throughout the procedure via a rectal probe.

Assessment of serum creatinine, BUN, and uric acid

At the end of reperfusion, blood samples were obtained and centrifuged at $1,000 \times g$ for 10 min at 4°C. Next, serum was collected and kept at –20°C. The serum amounts of creatinine, BUN, and uric acid were assessed by commercial products according to the producer's guidelines.

Assessment of pro-inflammatory cytokines and oxidative stress factors

After reperfusion, the animals were sacrificed and the left kidney was dissected and collected on ice. After washing the tissue with cold saline solution and weighing, 150 mg of the tissue was separated and homogenized within 1.5 mL phosphate buffer using a homogenizer (IKA T18, Basic ULTRA TURRAX, USA) at 5000 rpm for 3 min. Whole steps were performed at 4°C to minimize the destruction of cytokines and enzymes. Afterwards, the samples were centrifuged at $1,200 \times g$ for 10 min, and the supernatant was collected. Measurement of pro-inflammatory cytokines and oxidative stress factors was done using commercial products based on the manufacturer's instructions.

Western blot test

The proteins were isolated from frozen renal samples after homogenization using RIPA buffer (protease and phosphatase inhibitor) (Sigma-Aldrich). The protein concentration was evaluated using a BCA protein assay product. The 12% SDS-PAGE was used to separate equal amounts of protein (30 µg) at 100 V for 3 h. Proteins were transferred onto polyvinylidene Difluoride membranes at 200 mA for 2 h, and then the membranes were incubated with primary antibodies overnight at 4°C. The samples were washed three times and incubated with secondary antibody at a dilution of 1:2,000 in TBS-T containing 5% skimmed milk for 60 min at 25°C. Enhanced chemiluminescence (PerkinElmer, Inc., Waltham, MA, USA) was used as a detector of the immunoreactive bands on X-ray film. The Alpha Ease® FC Imaging System was applied to measure the optical density of the bands. β-Actin was used as a loading control.

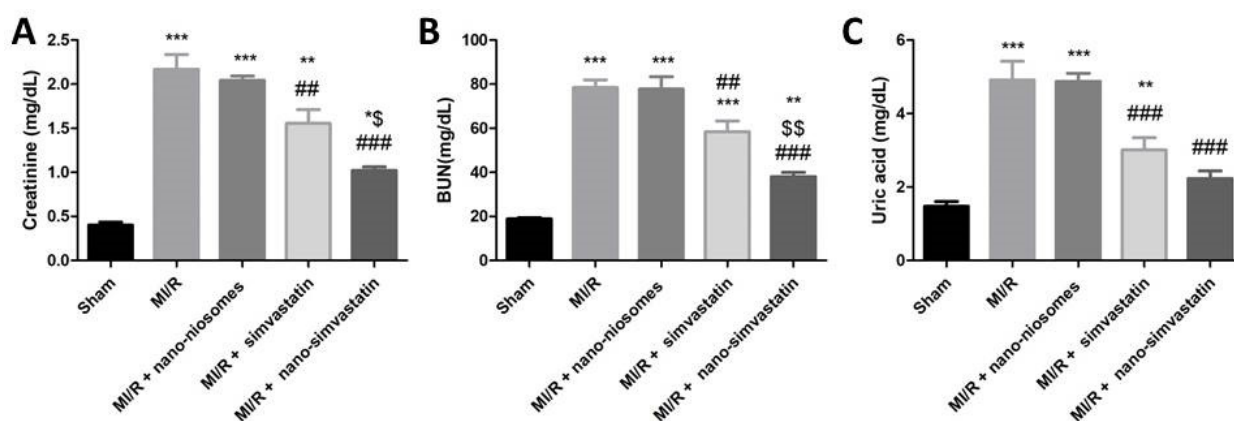


FIGURE 1. Impact of simvastatin-loaded nano-niosomes on renal function. (A) Creatinine, (B) BUN, and (C) Uric acid (*** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$ vs. sham; ## $p < 0.01$ and ### $p < 0.001$ vs. MI/R; \$ $p < 0.05$ and \$\$ $p < 0.01$ vs. MI/R + simvastatin).

Renal histopathological evaluation

After the experimental period was terminated, the animals were sacrificed under deep anaesthesia. The left kidney tissue was dissected and fixed in 10% Formalin overnight. Then, they were cut into 5 μm thick sections, embedded in paraffin, and stained with hematoxylin at 37°C for 3 min and eosin at 37°C for 10 sec. Photographed sections were examined using a light microscope (Nikon Eclipse 80i; Tokyo, Japan). A renal pathologist, unaware of the study structure, performed a morphological assessment.

Statistical analysis

Results are presented as mean $\pm$ SD. GraphPad Prism software version 5 was used to perform statistical assessments. Comparison between categories was done by a one-way test of variance and then the Tukey post hoc test for multiple comparisons. A p -value less than 0.05 was considered statistically significant.

Results

Evaluation of nano-formulation

Following setting the specimens onto the carbon-coated copper grid at an increasing voltage of 80 kV, the shape and size of nano-carriers were evaluated by transmission electron microscopy (TEM). Dynamic light scattering (DLS) with He-Ne laser at a wavelength of 632.8 nm (Malvern, Zetasizer Nano ZSE, Worcestershire, UK) was applied to assess the hydrodynamic size of nano-niosomes with SIM or without SIM. Fourier transform infrared (FTIR) spectrum with a Nicolet Ava-

tar 360 FT-IR spectrometer (USA) was used to calculate loading SIM into the form of nano-niosomes. FTIR was done with a scanning spectrum in the range of 4000–400 cm^{-1} (19).

Serum concentrations of creatinine, BUN, and uric acid

As shown in Figure 1 A-C, significantly elevated serum concentrations of creatinine ($p < 0.001$), BUN ($p < 0.001$), and uric acid ($p < 0.001$) were seen in MI/R versus the sham category. Following the induction of MI/R, administration of both SIM ($p < 0.01$ and $p < 0.001$) and SIM-loaded niosomes ($p < 0.001$) markedly reduced serum concentrations of creatinine, BUN, and uric acid versus the MI/R category, whereas only nano-niosomes failed to produce substantial changes in serum levels of creatinine, BUN, and uric acid versus the MI/R cohort. SIM-loaded niosomes exhibited more efficacy in reducing serum levels of creatinine, BUN, and uric acid versus SIM alone.

Tissue levels of Oxidative stress factors

The occurrence of MI/R in rats significantly decreased the function of antioxidant enzymes SOD ($p < 0.001$), GPX ($p < 0.001$), and catalase ($p < 0.001$) in renal tissue in comparison with the sham animals. However, treatment of MI/R animals with both SIM ($p < 0.05$ and $p < 0.01$) and SIM-loaded niosomes ($p < 0.01$ and $p < 0.001$) markedly improved the function of antioxidant enzymes SOD, GPX, and catalase in renal tissue versus the MI/R cohort. There were no substantial differences between

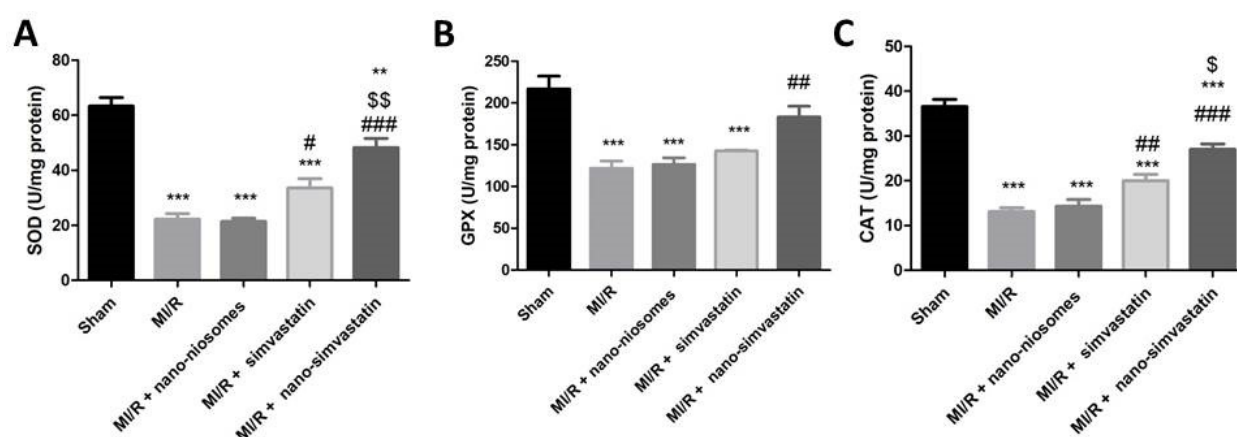


FIGURE 2. Impact of simvastatin-loaded nano-niosomes on antioxidant enzymes. (A) SOD, (B) GPX, and (C) CAT (**p < 0.001 and **p < 0.01 vs. sham; ## p < 0.01 and ###p < 0.001 vs. MI/R; \$ p < 0.05 and \$\$p < 0.01 vs. MI/R + simvastatin).

the MI/R cohort and the MI/R + nano-niosomes cohort. SIM-loaded nano-niosomes displayed a more powerful effect in restoring the function of antioxidant enzymes (Figure 2 A-C).

Tissue levels of pro-inflammatory factors

To assess renal injury caused by MI/R, we measured amounts of inflammation factors such as TNF- α , IL-1 β , IL-6, and IL-11 (Figure 3 A-D). Following MI/R-induction in rats, tissue contents of pro-inflammatory factors TNF- α (p < 0.001), IL-1 β (p < 0.001), IL-6 (p < 0.001), and IL-11 (p < 0.001) were markedly increased versus sham rats. Although significantly reduced concentrations of pro-inflammatory factors were seen in renal tissue following treatment with both SIM (p < 0.05 and p < 0.01) and SIM-loaded niosomes (p < 0.001), encapsulating the drug in nanocarriers resulted in more efficacy in reducing TNF- α , IL-1 β , IL-6, and IL-11.

Tissue levels of BAX, Bcl-2, and Caspase-3

To provide greater insights into the mechanism behind the protective impact of SIM-loaded niosomes against MI/R-induced AKI in rats, we measured tissue amounts of BAX, Bcl-2, and Caspase-3 (Figure 4 A-C). Based on analysis, MI/R in rats was correlated with significantly elevated concentrations of BAX (p < 0.01) and Caspase-3 (p < 0.01) and decreased levels of Bcl-2 protein (p < 0.01) in comparison with those in the sham cohort. The SIM-loaded niosomes treatment cohorts exhibited markedly suppressed induction of BAX and Caspase-3 and Bcl-2 upregulation in comparison with

the MI/R cohort (p < 0.05 and p < 0.01). SIM-loaded niosomes had stronger effects on the inhibition of apoptosis, and only simvastatin failed to create significant differences.

Tissue levels of NF- κ B protein

Tissue levels of NF- κ B protein (p < 0.001) were considerably elevated in the kidney samples of the MI/R cohort in comparison with those in the sham cohort (Figure 4D). NF- κ B was markedly underexpressed in the renal tissue of MI/R animals treated with both SIM (p < 0.05) and SIM-loaded niosomes (p < 0.001). SIM-loaded niosomes exhibited more efficacy in the suppression of sample amounts of NF- κ B protein.

Tissue damage

Compared to the sham, haemorrhage and cell degeneration were seen in MI/R and MI/R + nano-niosomes. Both SIM and SIM-loaded niosomes were able to reduce injury more than MI/R and MI/R + nano-niosomes (Figure 5).

Discussion

The newly identified findings of the current investigation are that the encapsulation of SIM-loaded nano-niosomes resulted in more efficient and protective effects against MI/R-induced renal injury. Moreover, we found that the protective effects of SIM-loaded nano-niosomes against MI/R-induced renal failure are associated with the attenuation of inflammation, OS, and targeting of the ERK/NF- κ B signaling pathway. MI/R-induced re-

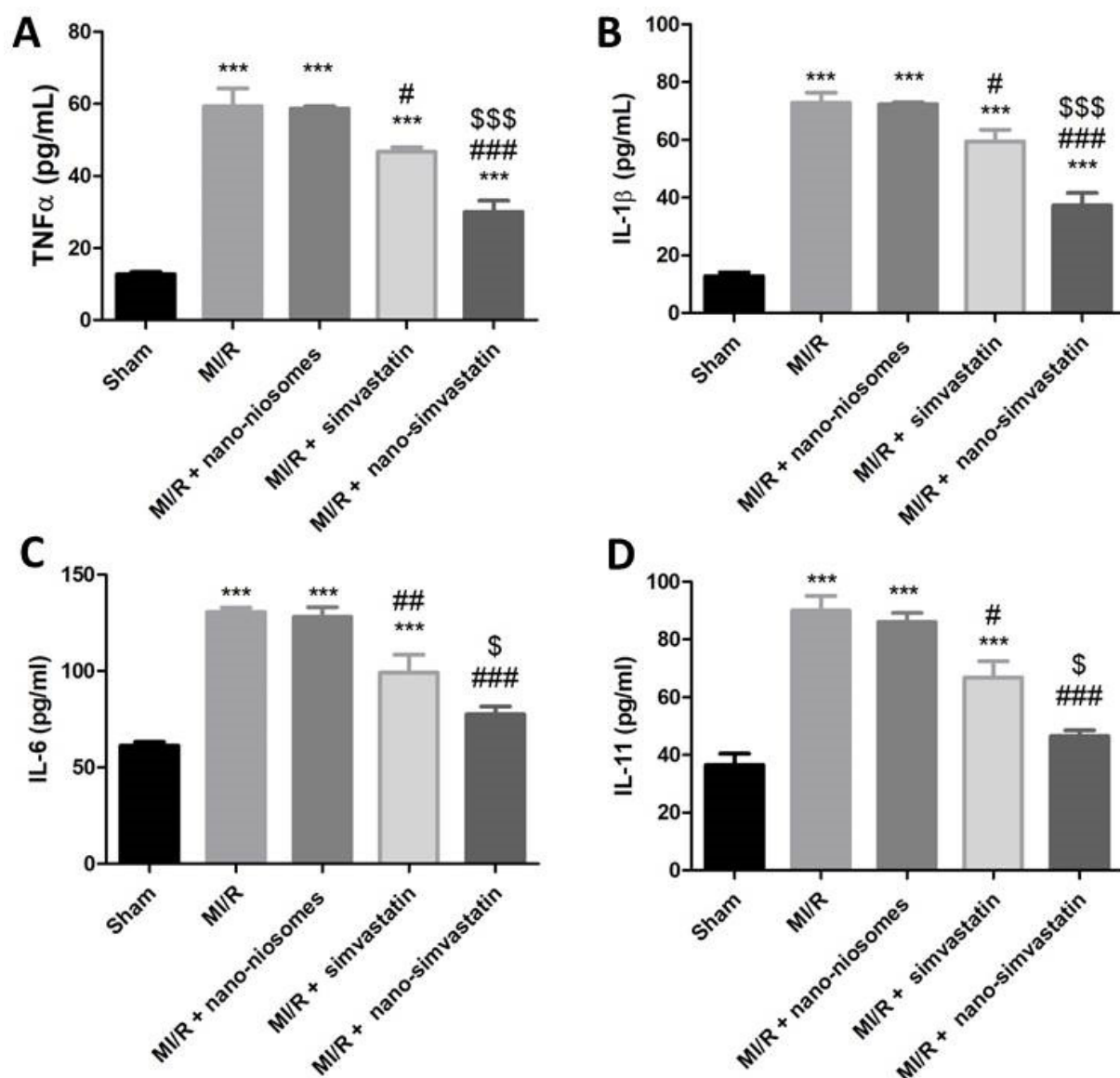


FIGURE 3. Impact of simvastatin-loaded nano-niosomes on pro-inflammatory factors. (A) TNF- α , (B) IL-1 β , (C) IL-6, and (D) IL-11 (**p < 0.01 vs. sham; # p < 0.05, ## p < 0.01 and ### p < 0.001 vs. MI/R; \$ p < 0.05 and \$\$\$ p < 0.001 vs. MI/R + simvastatin).

nal injury is a common complication after MI and cardiopulmonary bypass, which in turn increases the economic burden. MI/R-induced renal injury may increase the mortality of all cardiac surgery subjects up to 60% and gives rise to a 25-fold increase in deaths relevant to valve surgeries (Borthwick and Ferguson 2010; Englberger et al., 2011). The abnormal physiological reperfusion caused by MI and cardiac surgery initiates OS, inflammation, and hence apoptotic cell death in the renal tissue (Grayson et al., 2003). There is a close relationship between mortality risk in patients with acute MI and declining estimated glomerular filtration rate (GFR)

(Anavekar et al., 2004). The most commonly used biomarker to determine renal function is serum creatinine. BUN is another determinant of early renal dysfunction that occurs post-MI (Wen et al., 2020). Likewise, elevated serum uric acid levels in subjects with congestive heart failure are associated with a derangement in renal function (Tian et al., 2012). These results are compatible with our results that the introduction of MI/R gave rise to elevated concentrations of creatinine, BUN, and uric acid, indicating renal dysfunction caused by MI/R, and such changes were reversed by both SIM and SIM-loaded niosomes. Supporting our data, Zhang et al. showed

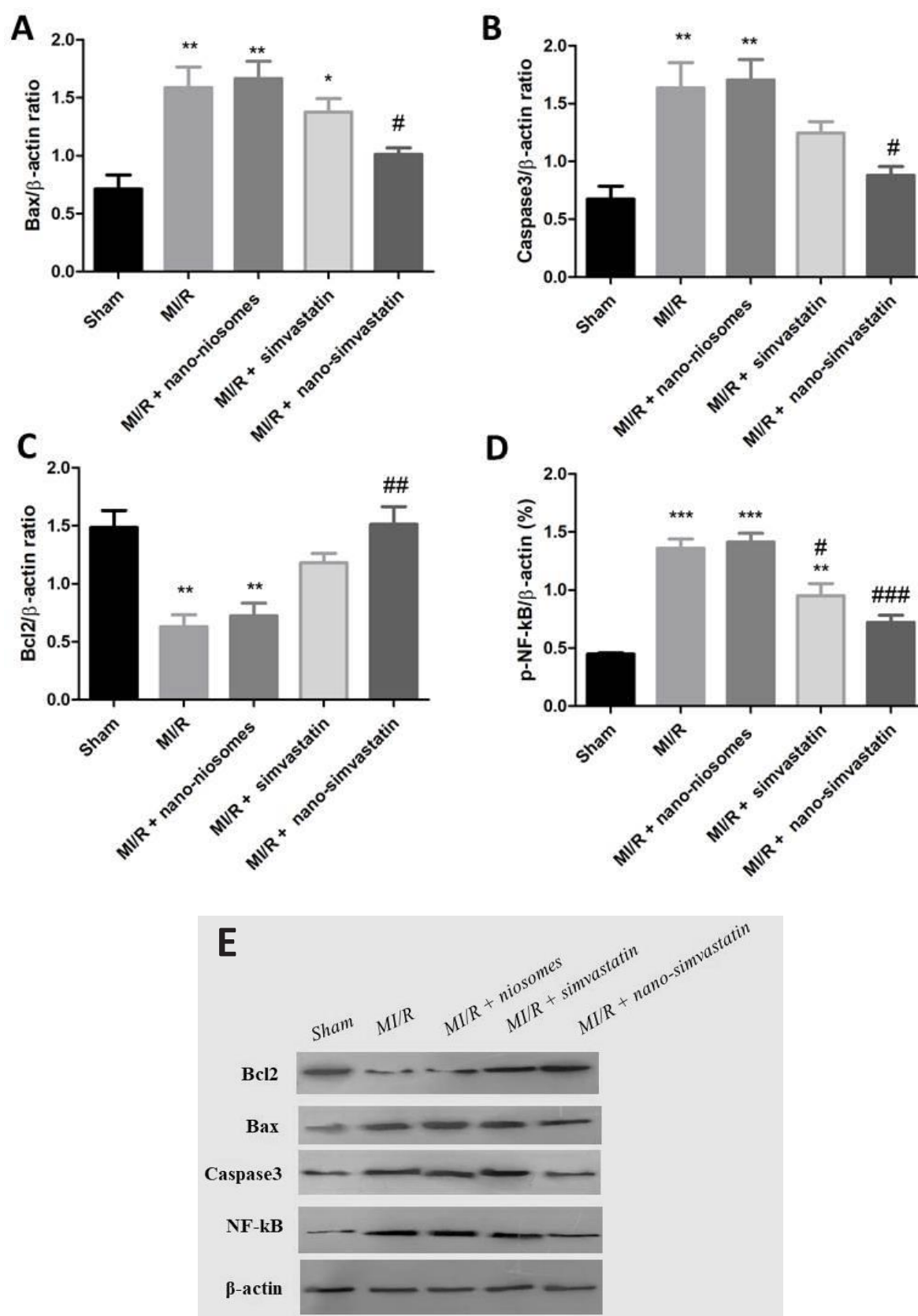


FIGURE 4. Impact of simvastatin-loaded nano-niosomes on apoptotic factors and NF- κ B. (A) BAX, (B) Caspase-3, (C) Bcl-2, and (D) NF- κ B (**p < 0.01, ***p < 0.001, and *p < 0.05 vs. sham; # p < 0.05, ## p < 0.01, and ###p < 0.001 vs. MI/R). (E) western blot analysis of Bcl-2, BAX, Caspase-3, and β -actin in different treatment and control groups.

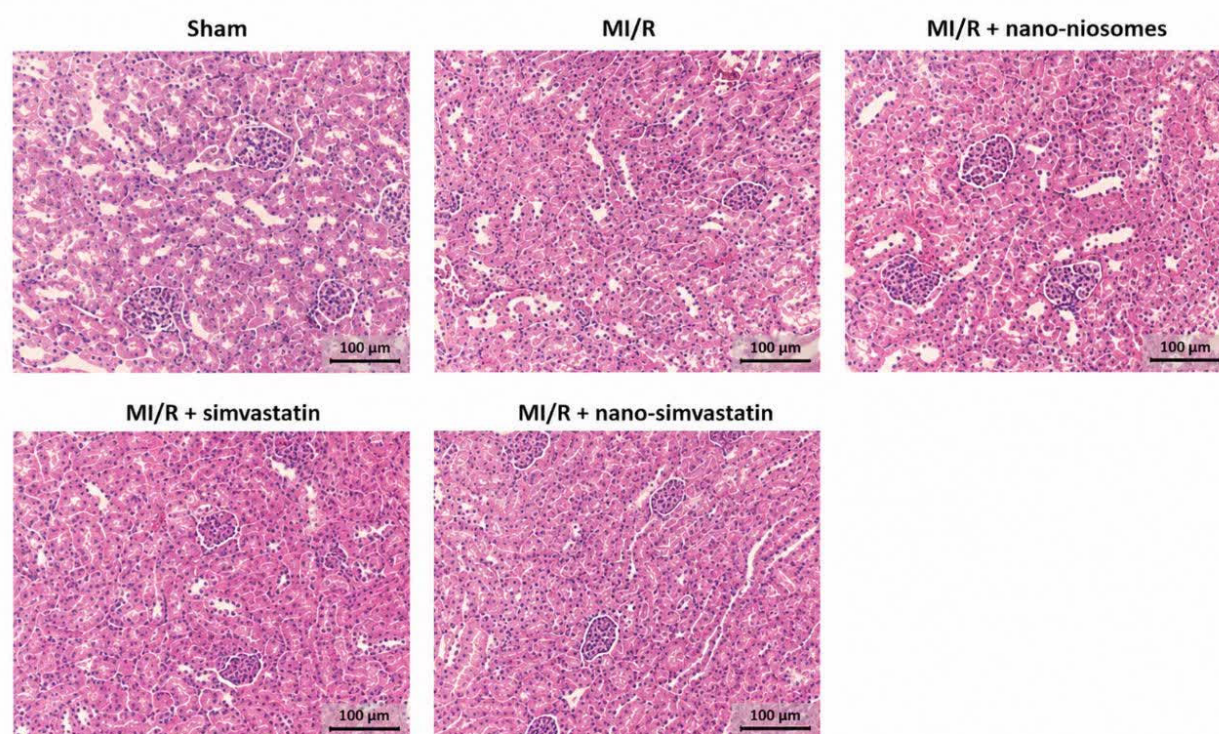


FIGURE 5. H&E staining of renal tissues in the experimental groups. Hemorrhage and cellular degeneration were observed in MI/R animals, which were ameliorated following treatment with both simvastatin and simvastatin-loaded nano-niosomes. Images were obtained at 100 $\times$ magnification, and the scale bar represents 100 μ m.

that SIM pretreatment improved renal impairment in rats with kidney I/R by reducing levels of creatinine and BUN (Zhang et al., 2017).

Several investigations have indicated that reduced renal function following MI/R is linked to excessive production of ROS (Tong et al., 2020). Excessive generation of ROS triggers lipid peroxidation, along with DNA and protein impairment, and apoptotic and necrotic cell death in several ways (Piko et al., 2023; Zhou et al., 2022). Moreover, excessive generation of ROS is associated with decreased function of antioxidant enzymes (SOD, CAT, and GPX) involved in the neutralization of ROS-mediated injury (Ighodaro and Akinloye 2018). Lee et al. found that cardiac arrest-induced OS is associated with decreased function of antioxidant enzymes (SOD, CAT, and GPX) in renal tissue (Lee et al., 2023). Consistent with previous reports, our results showed reduced function of antioxidant enzymes (SOD, CAT, and GPX) in renal tissue after MI/R, indicating elevation of OS in the kidney tissue in post-MI/R rats that was restored by both SIM and SIM-loaded nano-niosomes.

Corresponding to our reports, Kafkasli et al. reported that prolonged SIM treatment reduced damage in the I/R–I/R-induced acute kidney failure model of rats by reinforcing the anti-oxidative defence system (Kafkasli and Ozkorkmaz 2021).

NF- κ B is an OS-dependent factor that is activated in MI/R-induced renal injury. Fujii et al. found that activation of NF- κ B is associated with increased OS in renal tissue after MI in rats (Fujii et al., 2016). In normal conditions, NF- κ B forms a complex with the inhibitor of κ B (I κ B) proteins and remains inactive in the cytoplasm. During pathological conditions, exposure to ROS and other stimulators confers substantial changes, such as rapid phosphorylation, site-specific ubiquitination, separation of I κ B, translocation to the nucleus, and hence modulation of genes involved in inflammation and apoptotic cell death (Henke et al., 2007; Li et al., 2021; Zhang and Sun, 2015). These previous reports are compatible with our findings that demonstrated increased levels of NF- κ B, BAX, and Caspase-3 and downregulation of Bcl-2 protein in renal tissue after MI in rats,

which were reversed by both SIM and SIM-loaded niosomes. Consistent with what we found, a previous study showed that SIM is capable of ameliorating apoptosis in renal tissue by reducing caspase-3 and upregulating cell-survival molecules (Nežić et al., 2020). NF- κ B activation is associated with overproduction of pro-inflammatory cytokines (Zhang et al., 2020). In addition to OS, MI/R is associated with elevated mRNA levels of inflammatory cytokines, overexpression of VCAM-1 in renal glomeruli, and leukocyte infiltration in the renal tissue (Ruparelia et al., 2013). In line with these previous reports, our study indicates that tissue amounts of pro-inflammatory markers TNF- α , IL-1 β , IL-6, and IL-11 were markedly increased after MI/R, which were reduced by both SIM and SIM-loaded nano-niosomes.

Collectively, the findings of the current study suggest that SIM-loaded niosomes probably reduce MI/R-induced renal injury and improve renal function by reducing inflammation, suppressing OS, and targeting NF- κ B protein. Moreover, our results revealed that encapsulating SIM into niosomes enhanced its efficiency and protective effects in coping with MI/R-induced renal damage.

This study has several limitations that should be considered when interpreting the findings. First, the use of a rat model restricts the direct translation of results to clinical settings, as human physiological responses to MI/R injury and to SIM-loaded niosomes may be different. In addition, this investigation focused only on short-term outcomes, and hence the long-term effects of treatment, such as potential chronic renal changes, fibrosis development, or sustained inflammatory responses, remain undiscovered. The study also used just one dose of SIM and SIM-loaded niosomes, without dose–response or time-course assessments, which hampers understanding of the optimal therapeutic window. Furthermore, although the study examined OS and the ERK/NF- κ B signaling axis, other key pathways involved in MI/R-induced renal injury remained unexamined, potentially narrowing the mechanistic insight gained. Another limitation is the lack of pharmacokinetic or biodistribution analysis to determine how SIM-loaded nano-niosomes are processed in vivo. Potential toxicities or off-target effects of the formulation were also not assessed. Finally, a reduced sample size may restrict statistical power and decrease the ability to generalize the results. The use of intramyocardial injection for delivering drugs

may introduce variability in drug distribution, potentially leading to inconsistent therapeutic effects across the heart and complicating the evaluation of myocardial repair. Additionally, the short reperfusion time after MI may not properly mimic the chronic effects of I/R injury, limiting the ability to examine long-term kidney dysfunction or remodelling in the post-MI setting. Finally, the absence of a standardized kidney histological scoring system hinders the interpretation of renal damage. These factors collectively undermine the reliability and clinical applicability of the findings, indicating the need for more refined methodologies to improve the accuracy and generalizability of outcomes.

Acknowledgement

There was no external grant for this project.

Conflict of interest

There was no conflict of interest.

Ethics

Animal experiments have been performed in accordance with the Guide for the Care and Use of Laboratory Animals according to the ARRIVE Guidelines of Research Ethics Committee, Faculty of Pharmacy and Pharmaceutical Sciences, Tehran Islamic Azad University of Medical Sciences with code of IR.IAU.PS.REC.1403.020. Conceptualization, M.N., M.M., and N.A.; writing—original draft preparation, K.B. and Z.B.; editing and review, M.M. and M.N. All authors have read and agreed to the published version of the manuscript. This research received no external funding.

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