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The combination effects of sodium selenite and vitamin E on renal ischemia-reperfusion injury in rats

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ABSTRACT

Introduction: Renal ischemia-reperfusion (RIR) injury is one of the main causes of acute kidney failure.
Objectives: The purpose of this study was to assess the effects of vitamin E, as well as a combination of vitamin E and sodium selenite (Se), on a rat model of RIR injury.
Materials and Methods: Current study was a laboratory experimental investigation using a post-test only control group desgin. A total of thirty-two adult male Sprague Dawley rats were divided into four equal groups: group 1 (control), group 2 [(IR; ischemia-reperfusion) + 0.25 mL saline)], group 3 (IR+1 mg/kg sodium Se and 100 mg/kg vitamin E), and group 4 (IR+100 mg/kg vitamin E). RIR injury was initiated by clamping the right and left pedicles for a duration of 45 minutes, followed by a 24-hour period of reperfusion. The intraperitoneal administration of daily therapy commenced 12 days prior to the development of RIR.
Results: Ischemia-reperfusion injury resulted in a considerable elevation in serum levels of urea, creatinine, and malondialdehyde (MDA), as well as enhanced serum myeloperoxidase (MPO) activity and renal MDA levels. Nevertheless, RIR markedly reduced the concentration of glutathione (GSH) in the serum, as well as the enzymatic activities of glutathione peroxidase (GPX) and paraoxonase 1 (PON1) in the serum. Additionally, RIR decreased the enzymatic activities of GPX and catalase (CAT) in the kidneys. In RIR animals, sodium Se plus vitamin E significantly improved renal function parameters, MDA content, GSH, and GPX activity in the kidneys.
Conclusion: Our findings showed that the effects of sodium Se and vitamin E on reducing oxidative stress and inflammatory markers and improving renal function biomarkers were comparable to those of vitamin E alone.

Implication for health policy/practice/research/medical education:
Our study indicated that the combination of sodium selenite (Se) and vitamin E could ameliorate renal and liver functional markers, lipid peroxidation, the activities of antioxidant enzymes, and the levels of glutathione in the renal ischemia-reperfusion-treated group. The findings of this study will contribute to the enhancement of outcomes associated with renal ischemia-reperfusion complications in patients.
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Introduction

Renal ischemia-reperfusion (RIR) injury increases mortality and morbidity by causing acute kidney failure. Common surgical procedures in urology and vascular medicine, such as renal transplantation, bypass surgery, renal angioplasty, and renal pedicle occlusion, can temporarily interrupt or reduce blood flow to the kidneys (1). Restoring blood flow to ischemic kidneys increases the risk of early ischemic injury due to increased reactive oxygen species (ROS) and the accumulation of activated neutrophils (2,3). Inflammation is recognized to have a significant impact on the development of ischemia-reperfusion (IR) injury (4). The IR state culminates in the adhesion of neutrophils to vascular endothelial cells,

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allowing them to invade the extravascular space (5-7). The activated neutrophils secrete ROS, lactoferrin, proteases, and myeloperoxidase (MPO) in the extracellular fluid (8). Myeloperoxidase contributes to the formation of hypochlorous acid (HOCl), an agent that is thought to be cytotoxic and cause oxidative damage (9). Reactive nitrogen species and ROS have been demonstrated to have a significant impact on renal damage during IR injury (10). ROS cause cytotoxic effects, which include lipid peroxidation, DNA damage, protein oxidation and nitrosylation, and the induction of apoptosis (11). The reperfusion phase leads to a stimulation of nitric oxide (NO) synthetase and a reduction of endogenous antioxidant enzymes (12). Selenium is advocated as a vital trace element in the diet that protects cells from free radicals and oxidative stress (4). Additionally, it contributes to maintaining the structure of antioxidant enzymes such as glutathione peroxidase (GPX) and binds to the catalyzing site (5). The function of selenium as an antioxidant is related to its direct action or its role as a cofactor for antioxidant enzymes (6). Vitamin E is found in the structure of cell membranes and is involved in their consistency. The membrane lipids are protected from oxidative stress by vitamin E (7,8). As a powerful antioxidant, vitamin E scavenges peroxyl radicals and interrupts the chain reaction that leads to lipid peroxidation (9). The beneficial effects of vitamin E on IR injury by reducing lipid peroxidation and supporting antioxidant defenses have been demonstrated in published data (10-12).

Objectives

Due to the role of ROS in the pathogenesis of RIR, we used sodium selenite (Se) and vitamin E as antioxidants to investigate the effect of their combination on RIR injury in rats using biochemical parameters. No detailed study has yet been conducted on this topic.

Materials and Methods

Animals and study design

Thirty-two male Sprague Dawley rats weighing 200–180 were purchased from the Pasteur institute in Tehran and kept in a special environment with a humidity of 50±10% and a temperature of 22 °C for ten days to adapt to the environment. A 12-hour period of both light and darkness was seen at the animal laboratory of the Razi herbal medicines research center. The rats were fed with laboratory pellet diets and had unrestricted access to water. The procedures for our investigation were authorized by the animal ethics board of the Lorestan university of medical sciences. Furthermore, this research agreed to the rules set by the public health and medical research commission.

On April 27, 2021, the animals were divided randomly into four equal groups; group 1 as control, which received daily 0.25 mL saline (n = 8); group 2 as IR, which received daily 0.25 mL saline (n = 8); group 3 as IR, which received daily 1 mg/kg sodium Se and 100 mg/kg vitamin E (n = 8); and group 4 as IR, which received daily 100 mg/kg vitamin E (n = 8). For the random selection design, the rats were numbered from 1 to 32. Small and large odd numbers were placed in group 1 and 3, respectively, and even numbers took action in the same way in group 2 and 4. The weights of the rats were measured after dividing them into groups. The average weight of the rats in different groups was close to each other, and weight equalization was performed if necessary. According to the claims of the selling company, the rats were almost the same age. The daily treatments was initiated intraperitoneally 12 days prior to the development of RIR. The dosage of sodium Se and vitamin E employed in our investigation is in line with that of earlier studies, which demonstrated the antioxidant properties of sodium Se and vitamin E (10,13).

Surgery procedure

The animal was anesthetized with ketamine (75 mg/kg, intraperitoneally) and xylazine (8 mg/kg, intraperitoneally). The abdominal surface was then shaved and sterilized with povidone-iodine. A midline cut was made to reveal the abdominal cavity in order to create ischemia. Then, the left and right pedicles were separated clamped for 45 minutes using safe clamps, respectively. Next, we removed the clamps and assessed the kidneys for five minutes to ensure that renal blood flow had returned. The reperfusion phase was considered to last 24 hours. Sterile gauze protected the viscera during the surgery. Saline (1 mL, 37 °C) was intraperitoneally poured before suturing the abdominal incision, and a 4-0 silk suture was used to close the abdomen. The control group was subjected to the surgery method similar to the IR groups; however, the renal pedicles were not clamped. The surgical team was unaware of the intervention method for the groups, and blinding of the surgical team was easily performed.

Biochemical analysis

After a 24-hour period of reperfusion, the rats were anesthetized with xylazine and ketamine on May 10, 2021. After that, we took blood samples from their hearts and let them coagulate at 25 °C for 20 minutes in the lab. Next, kidneys were removed, and renal biochemical markers were assayable on the right kidney. In order to prepare serum samples for biochemical analysis, we centrifuged the blood for 15 minutes at 3000×g. Then, we stored the samples at -70 °C. Using a homogenizer, renal samples were homogenized in a Tris-HCL buffer with a pH of 7.4, 50 mmol/L of Tris-HCL, and 1.15 percent KCl. Following that, the samples were centrifuged for 30 minutes at a temperature of 4 °C at 18000 g. Renal tissue was biochemically evaluated using the supernatant solution. This study included the blinding of the evaluators; the names of the samples were written with numbers and

English letters, and the evaluators did not know about the intervention in different groups.

Measurement of renal functional markers

Serum concentrations of renal function indicators, such as urea and creatinine, were determined using commercial kits and a biochemical autoanalyzer (Olympus AU-600, Tokyo, Japan). Since obtaining sufficient urine samples was one of the limitations of our study, the examination of kidney function parameters in the urine was not performed. Before conducting the main study, for the pilot study, a number of healthy rats that were purchased from the same company were evaluated by measuring the renal function parameters in the serum, and the healthy functioning of the kidneys of these rats was ensured.

Evaluation of inflammatory and oxidative stress biomarkers

The levels of NO, malondialdehyde (MDA), and glutathione (GSH) as well as the activities of GPX, catalase (CAT), and MPO in the kidney, serum, and liver of rats, were evaluated using colorimetric commercial biochemical kits (Asan, Khorramabad, Iran).

Paraoxonase 1

The activity of serum paraoxonase 1 (PON1) was measured using paraoxon as a substrate. This was conducted by measuring the increase in absorption at 412 nm, which is caused by the production of 4-nitrophenol. We added 50 mL of serum to 1 mL of 100 mM Tris-HCl buffer (pH = 8.0), which included 2 mM $CaCl_2$ and 5 mM paraoxon, to determine the enzymatic activity at 25 °C. We also measured the 4-nitrophenol formation rate at 412 nm. A molar extinction coefficient of 17 100/Mcm was utilized for calculating enzymatic activity (14).

Statistical analysis

The results were expressed as mean values ± standard error (SE). The study used the least significant difference (LSD) test for data comparison between groups. Statistical analysis were performed using version 26 of a software package, with a *P* value of less than 0.05 as the threshold for statistical significance.

Results

Effect of sodium Se plus vitamin E and vitamin E alone on renal function markers in RIR animals

The urea level in the serum of rats in the IR group was significantly increased (1.46-fold) compared to the control group. Administration of sodium Se plus vitamin E or vitamin E alone in RIR rats was not effective in preventing the increase in urea levels compared to the IR group (Figure 1). Serum creatinine levels in the IR group showed a significant increase of 2.78-fold compared to the control animals. The combination of sodium Se with vitamin E or vitamin E alone effectively prevented the

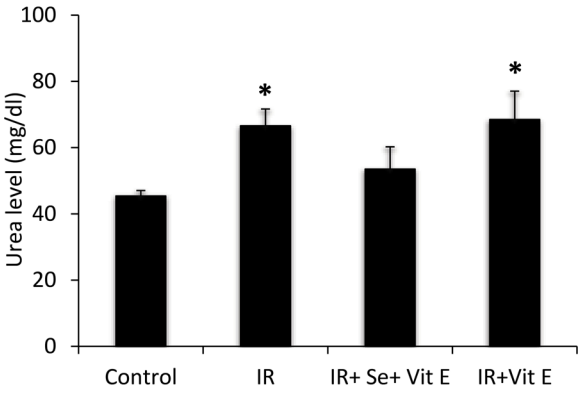

Figure 1. Effect of sodium selenite (Se) plus vitamin E (Vit E) and vitamin E alone on serum urea level in rats with renal ischemia-reperfusion. Bars indicate the mean ± standard error (SE). * $P < 0.05$ compared with the control group.

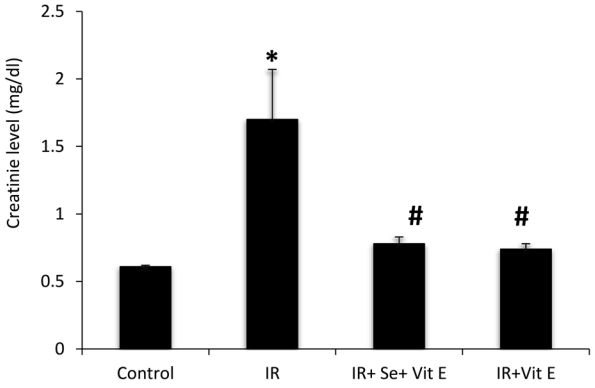

Figure 2. Effect of sodium selenite (Se) plus vitamin E (Vit E) and vitamin E alone on serum creatinine level in rats with renal ischemia-reperfusion. Bars indicate the mean ± standard error (SE). * $P < 0.05$ compared with the control group. # $P < 0.05$ compared with the IR group.

increase in creatinine in the RIR rats compared to the IR group (Figure 2).

Effect of sodium Se plus vitamin E and vitamin E alone on oxidative stress and inflammatory biomarkers in RIR animals

Serum and renal GSH levels significantly (1.51-fold and 2.43-fold, respectively) decreased in the IR group compared to the control group. In comparison to the IR group, sodium Se plus vitamin E significantly (100.61%) increased GSH levels in the renals of RIR rats but not GSH levels in the serum (Tables 1 and 2). Vitamin E was able to increase serum and renal GSH levels in RIR rats by 39.20% and 104.60%, respectively, compared to control group (Tables 1 and 2).

Renal CAT activity decreased significantly by 8.00-fold in the IR group compared to control group, while there was no significant change in serum CAT activity. In the RIR animals, the combination of sodium Se and vitamin E resulted in a great (91.60%) increase in serum CAT levels but had no effect on renal function compared to the IR

Table 1. Effects of sodium selenite (Se) and vitamin E (Vit E) co-administration and vitamin E alone on serum MDA and GSH levels and serum activities of CAT, GPX, and PON1 in rats with renal ischemia-reperfusion

Groups	MDA (nmol/mg protein)	GSH (nmol/mg protein)	CAT (U/mg protein)	GPX (U/mg protein)	PON1 (U/min)
Control	37.82±4.20	12.12±1.11	76.31±9.93	2233.0±386.23	23.63±5.87
IR	101.05±7.91*	8.01±0.44*	54.31 ±6.07	1299.3±77.71*	9.55±2.06*
IR + Se + Vit E	43.31±2.10#	10.57±0.34	104.06±4.61#	2326.9±126.91#	35.69±1.99#
IR + Vit E	59.57±9.68*#	11.15±0.15#	74.76±11.54	2471.7±194.00#	25.04±1.91#

Abbreviations: MDA, Malondialdehyde; GSH, Glutathione; GPX, Glutathione peroxidase; PON1, Paraoxonase 1; CAT, Catalase; IR, ischemia-reperfusion. Values are expressed as mean ± standard error (SE). * $P < 0.05$ compared with the control group. # P < 0.05 compared with the IR group.

Table 2. Effects of sodium selenite (Se) and vitamin E (Vit E) co-administration and Vit E alone on renal MDA and GSH levels and renal activities of CAT and GPX in rats with renal ischemia-reperfusion

Groups	MDA (nmol/mg protein)	GSH (nmol/mg protein)	CAT (U/mg protein)	GPX (U/mg protein)
Control	78.65±12.54	15.88±2.47	418.76±135.56	1078.6±105.40
IR	283.32±56.13*	6.52±0.65*	52.34±5.91*	346.22±23.92*
IR + Se + Vit E	130.22±20.71#	13.08±0.86#	159.56±25.72*	803.16±40.80*#
IR + Vit E	201.19±38.36*	13.34±2.31#	157.71±38.65*	701.48±47.28*#

Abbreviations: MDA, Malondialdehyde; GSH, Glutathione; GPX, Glutathione peroxidase; PON1, Paraoxonase 1; CAT, Catalase; IR, ischemia-reperfusion. Values are expressed as mean ± standard error (SE). * $P < 0.05$ compared with the control group. # P < 0.05 compared with the IR group.

group (Tables 1 and 2). The administration of vitamin E in RIR animals did not result in a significant increase in serum and renal CAT activity, as shown in Tables 1 and 2.

GPX activity in the serum and kidneys decreased significantly in the IR group compared to the control group (1.71-fold and 3.11-fold, respectively). Furthermore, compared to the IR group, sodium Se plus vitamin E was able to significantly increase the level of serum and renal GPX activity in the RIR animals (79.08% and 131.97%, respectively) (Tables 1 and 2). Vitamin E was able to increase the serum and renal GPX levels significantly more in RIR animals compared to control group (90.23% and 102.61%, respectively) (Tables 1 and 2).

Serum PON1 activity decreased significantly in the IR group compared to the control group (2.47-fold). In the RIR animals, administration of sodium Se plus vitamin E or vitamin E alone resulted in a significant increase in serum PON1 activity compared to the IR group (the increase was 273.71% and 162.19%, respectively) (Table 1).

Figure 3 shows that MPO activity in the serum increased significantly (2.33-fold) in the IR group compared to the control animals. In the RIR animals, the simultaneous administration of sodium Se and vitamin E, but not vitamin E alone, significantly (64.62%) prevented the increase in serum MPO activity compared to the IR group (Figure 3).

Serum NO levels were slightly (1.05-fold) increased in the IR group compared to the control group, but not statistically significant. Treatment of the RIR animals with sodium Se plus vitamin E or vitamin E alone significantly (17.15% and 12.74%, respectively) prevented the increase in serum NO levels compared to the IR group (Figure 4).

Discussion

Though various mechanisms have been suggested to elucidate the development of RIR injury, the majority of research has concentrated on the involvement of ROS and inflammatory factors. On the other hand, antioxidant drugs are known to have a significant impact on acute inflammatory responses and the regulation of oxidative stress. In this study, administrations of sodium Se plus vitamin E and vitamin E alone have beneficial effects on RIR-induced damages.

The effect of vitamin E and sodium Se on serum urea and creatinine in the studied groups

According to our findings, untreated RIR animals' serum levels of urea and creatinine increased significantly in

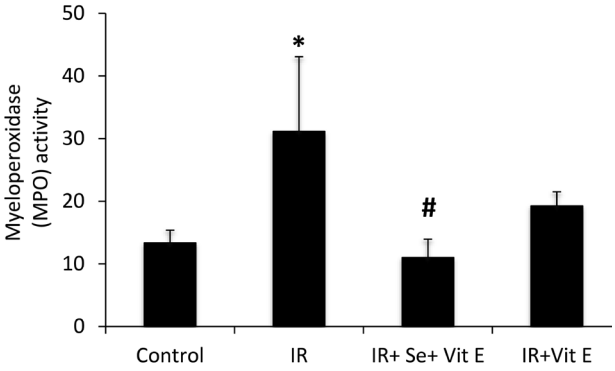

Figure 3. Effect of sodium selenite (Se) plus vitamin E (Vit E) and Vit E alone on serum myeloperoxidase (MPO) activity in rats with renal ischemia-reperfusion. Bars indicate the mean ± standard error (SE). * $P < 0.05$ compared with the control group. # $P < 0.05$ compared with the IR group.

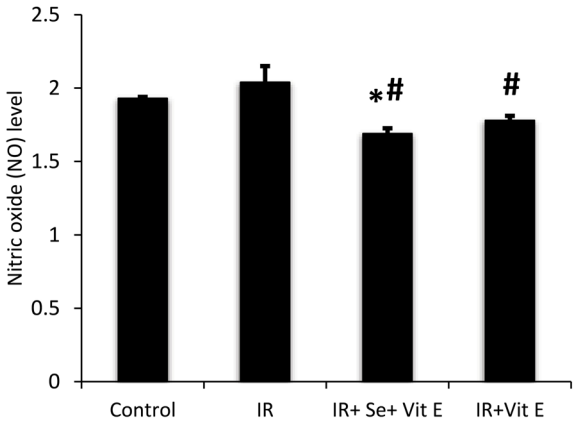

Figure 4. Effect of sodium selenite (Se) plus vitamin E (Vit E) and Vit E alone on serum nitric oxide (NO) level in rats with renal ischemia-reperfusion. Bars indicate the mean ± standard error (SE). * $P < 0.05$ compared with the control group. # $P < 0.05$ compared with the IR group.

comparison to the control group. Treatment of RIR animals with sodium Se plus vitamin E and vitamin E alone improved creatinine levels. It was shown that the group receiving sodium Se with vitamin E did not significantly differ in their urea levels from the control group ($P > 0.05$). Based on similar studies, curcumin (15, 16), garlic oil (17), ascorbic acid (18), and pycnogenol (19) had a protective effect on kidney function parameters and reduced urea and creatinine levels. Moreover, according to other research, the antioxidants α-tocopherol (20,21) and oxytocin (22,23) had similar effects on the levels of urea and creatinine parameters. Thus, the use of antioxidants with protective effects on renal function, such as those containing vitamin E and selenium, may prevent or substantially reduce the damages to renal function caused by RIR.

The effect of vitamin E and sodium Se on the antioxidant enzymes GSH, GPX, CAT, and PON1 activity in the groups under study

The activity of GPX and GSH in the serum and renal levels, as well as CAT activity in the kidneys and PON1 activity in the serum, were shown to be lower in the IR group than the control group. Treatment of RIR animals with sodium Se plus vitamin E significantly improved renal GSH levels, serum and renal GPX activities, serum CAT, and PON1 activities in comparison with the IR group. In comparison to the IR group, administration of vitamin E in RIR animals significantly improved serum and renal GSH levels, as well as GPX and PON1 activities. Vitamin E alone did not improve antioxidant biomarkers as much as sodium Se plus vitamin E did, except for GSH level and serum GPX activity. Antioxidant agents, including GPX, SOD, CAT, and GSH, are markers for the evaluation of oxidative stress status. Natural antioxidants such as coenzyme Q10 (24), sitagliptin (25), silymarin (26), and vitamin C (27) could improve antioxidant status. In a previous study, selenium can reduce IRI by reducing the level of NO activity and increasing the activity of GPX and PON (28). Our study supports previous studies indicating that natural antioxidants can enhance the functioning of the antioxidant defense system and increase levels of GSH. This may result in a reduction of problems related to RIR injury caused by oxidative stress.

The effect of vitamin E and sodium Se on MPO and NO levels in the studied groups

Renal ischemia-reperfusion significantly increased serum MPO activity in IR animals compared with the control group. Administration of sodium Se in combination with vitamin E, but not vitamin E alone, resulted in a substantial reduction in MPO activity in RIR animals compared to the IR group.

MPO plays a part in catalyzing the generation of HOCl, which is considered a cytotoxic agent and causes oxidative damage (29). It has been demonstrated that natural antioxidants could reduce MPO activity in RIR conditions (30,31). Furthermore, Tirosh et al showed that selenium inhibited MPO function in septic rats (32). In another study, vitamin E indicated an anti-inflammatory effect by improving the levels of inflammatory cytokines and MPO activity in acetic acid-induced ulcerative colitis in rats (33). Our results are in accordance with other research, showing the anti-inflammatory effects of selenium and vitamin E. We also found that the effect of sodium Se plus vitamin E on the reduction of MPO activities in RIR animals was higher than that of vitamin E alone.

Compared to control animals, the serum NO concentration in the IR group increased, although the difference was not statistically significant. Treatment of RIR animals with sodium Se plus vitamin E and vitamin E alone significantly decreased NO levels in comparison with the IR group. IR increases inducible nitric oxide synthase (iNOS) activity, which produces NO (34). The reaction of NO with the superoxide anion results in peroxynitrite formation, a powerful and offensive cellular oxidant (34). This study is in accordance with other research showing that selenium plus vitamin E improved the level of NO in streptozotocin-induced diabetic rats (35). Our results show that the effect of sodium Se and vitamin E on lowering NO levels in RIR animals was stronger than that of vitamin E alone.

The effect of vitamin E and sodium Se on MDA levels in the studied groups

Our research showed that sodium Se plus vitamin E can help protect against renal and liver function markers (MDA) in RIR injury in rats. Moreover, we found that the combined protective impact of sodium Se and vitamin E is higher than that of vitamin E alone in reducing oxidative stress and inflammatory markers. Therefore, a combination of sodium Se and vitamin E as antioxidants with many protective effects can be recommended to

patients who suffer from RIR complications. Additionally, there is a report that selenium could enhance antioxidant enzymes and reduce lipid peroxidation (LPO) in sciatic nerve IR in rats (28). Kabay et al showed that vitamin E reduced LPO and increased antioxidant activities in the central nervous system in streptozotocin-induced diabetic rats (36). Our findings support previous research by demonstrating the beneficial impacts of vitamin E and selenium on MDA and antioxidant enzyme activity. Therefore, reducing the consequences of RIR-induced oxidative damage may be accomplished by using natural antioxidants that have positive effects on oxidative stress indicators. Our study and previous research revealed the protective effect of natural antioxidants on RIR-induced complications. Hence, the use of antioxidants is one of the substantial treatment programs for patients who suffer from RIR complications. However, the detailed mechanisms of the anti-inflammatory and antioxidant actions of sodium Se and vitamin E cannot be fully expressed in our study, but other studies have indicated the anti-inflammatory and antioxidant mechanisms of selenium and vitamin E. For instance, Dhalla et al showed vitamin E directly scavenges peroxyl radicals and breaks the chain reaction, leading to LPO (9). In addition, it has been shown that selenium inorganic compounds inhibit iron-induced DNA injuries through the metal binding mechanism (37). Moreover, alpha-tocopherol reduced the extrication of pro-inflammatory cytokines, chemokine interleukin-8, and decreased monocyte adhesion to the endothelium (38).

Conclusion

According to our study, sodium Se with vitamin E relieved LPO, MPO, NO, and biomarkers of kidney function, and has beneficial effects on antioxidant enzymes and GSH in rats with RIR injury. In addition, we found that sodium Se and vitamin E operate more effectively together to protect against oxidative stress and inflammatory indicators than does vitamin E lonely. Therefore, a combination of sodium Se and vitamin E as antioxidants with many protective effects can be recommended to patients who suffer from RIR complications. Amelioration of renal function, LPO, inflammatory markers, and antioxidant status by sodium Se and vitamin E can improve RIR complications.

Authors' contribution

Conceptualization: Hassan Ahmadvand and Esmaeel Babaeenezhad.
Data curation: Sahar Yarahmadi, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Formal analysis: Hassan Ahmadvand.
Investigation: Sahar Yarahmadi, Mohsen Mehrjoo, Sahar Asgharzadeh, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Methodology: Sahar Yarahmadi, Mohsen Mehrjoo, Sahar Asgharzadeh, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Project administration: Hassan Ahmadvand and Esmaeel Babaeenezhad.
Resources: Sahar Yarahmadi, Mohsen Mehrjoo, Sahar Asgharzadeh, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Software: Hassan Ahmadvand and Esmaeel Babaeenezhad.
Supervision: Hassan Ahmadvand and Esmaeel Babaeenezhad.
Validation: Sahar Yarahmadi, Mohsen Mehrjoo, Sahar Asgharzadeh, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Visualization: Sahar Yarahmadi, Mohsen Mehrjoo, Sahar Asgharzadeh, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Writing–original draft: Esmaeel Babaeenezhad.
Writing–review & editing: Sahar Yarahmadi, Mohsen Mehrjoo, Sahar Asgharzadeh, Samaneh Pakravan, Hassan Ahmadvand, Esmaeel Babaeenezhad.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research and protocol for this study adhered to the guidelines for animal studies and received approval from the Ethics Committee of Lorestan University of Medical Sciences (Ethical code #IR.LUMS.REC.1400.033). Additionally, we followed the animal experiment guidelines established by the United States National Institutes of Health (NIH, 1978). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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