Original Article Open Access

Protective effects of crocin against contrast induced acute kidney injury following angiography: A randomized controlled clinical trial

Arefe Khani[1], Javad Khalili Fard[2#], Arash Amin[3], Nasrollah Moradifar[4], Mehdi Birjandi[5], Fatemeh Ahmadpour[6], Amin Rakhshan[7], Seyyed Mohammad Mousavinia[7], Forouzan Ahmadpour[7*], Negin Monazzami Motlagh[8]

1- Pharmacy student, Razi Herbal Medicines Research Center, School of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran
2- Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
3- Lorestan Heart Center (Madani Hospital), Lorestan University of Medical Sciences, Khorramabad, Iran
4- Cardiovascular Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
5- Department of Biostatistics and Epidemiology, School of Health and Nutrition, Lorestan University of Medical Sciences, Khorramabad, Iran
6- Department of Clinical Laboratory Sciences, School of Allied Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
7- Razi Herbal Medicines Research Center, Shahid Madani Hospital, School of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran
8- General Physician, School of Medicine, Lorestan University of Medical Science, Khorramabad, Iran

Correspondence:

Forouzan Ahmadpour;
Razi Herbal Medicines Research Center, Shahid Madani Hospital, School of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran;
Email: ahmadpourforoz@yahoo.com

Received: 2025-02-20
Accepted: 2025-09-23

How to cite this article:

Khani A, Khalili Fard J, Amin A, Moradifar Nasrollah, Birjandi M, Ahmadpour F, Rakhshan A, Mousavinia SM, Ahmadpour F, Monazzami Motlagh N. **Protective effects of crocin against contrast induced acute kidney injury following angiography: A randomized controlled clinical trial.** ARYA Atheroscler. 2025; 21(6): 18-29.

DOI:
https://doi.org/10.48305/arya.2025.43490.3030

Abstract

BACKGROUND: The use of contrast media in angiography has risen alongside the increasing incidence of cardiovascular diseases. Contrast agents cause acute kidney injury due to increased oxidative stress. Antioxidants such as crocin may help prevent contrast-induced acute kidney injury (CI-AKI).

METHODS: A randomized controlled clinical trial involved 60 patients over 18 years old undergoing Percutaneous Coronary Intervention (PCI). Standard hydration therapy was administered to the patients in both groups. The intervention group received 30 mg crocin three consecutive times. Oxidative stress levels and antioxidant system activity were measured, including malondialdehyde (MDA), reactive oxygen species (ROS), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). The prevalence of CI-AKI was also examined by measuring serum creatinine (SCr), blood urea nitrogen (BUN), and the estimated glomerular filtration rate (eGFR).

RESULTS: The analysis found no statistically significant differences between the groups for the GPx, CAT, MDA, ROS, SOD, SCr, BUN, and eGFR indices ($P > 0.05$). The study found a significant decrease in the average SCr and BUN in the intervention group post-PCI ($P < 0.05$). There were two incidences of CIN in the control group and none in the intervention group; however, the two groups did not differ significantly ($P = 0.492$). Conclusion: Although oral administration of 30 mg of crocin did not lead to significant changes in oxidant biomarkers, the capacity of the antioxidant defense system tended to increase. Moreover, SCr, BUN, and the incidence of CI-AKI were lower in the intervention group.

Keywords: CI-AKI; Crocin; Angiography; Contrast Agents

Introduction

Coronary angiography is an invasive diagnostic procedure to visualize the coronary circulation[1,2]. Angioplasty and stent placement, which involve inflating a balloon into a coronary artery, are flexible and safe techniques known as percutaneous coronary intervention (PCI)[3–5]. PCI is a nonsurgical, invasive procedure that relieves coronary artery narrowing or blockage to treat stable ischemic heart disease[6]. The femoral artery has long been the preferred access point for PCI. However, radial vein access is widely used and recognized as the safest point[7–9].

A class of materials known as "radiography contrast agents" is used to enhance the visibility and contrast of internal organs, structures, and body fluids. Iodixanol is a nonionic iodinated contrast agent commonly used in coronary angiography[10]. Contrast agents can cause adverse reactions ranging from mild to severe. Among these side effects, contrast-induced acute kidney injury (CI-AKI) is an important dose-dependent response that can lead to iatrogenic renal injury[11,12]. CI-AKI is defined within 24 to 72 hours after iodinated contrast medium administration, involving an increase in blood urea nitrogen (BUN), serum creatinine (SCr), or a decrease in estimated glomerular filtration rate (eGFR)[13]. The most typical definition of CI-AKI is a rise in SCr ≥ 25% and/or 0.5 mg/dL and a reduction in the estimated glomerular filtration rate (eGFR) > 25% from baseline at 48 hours after contrast medium exposure[11,14].

CI-AKI is the third leading cause of acute kidney disease and tubular necrosis hospitalization. Although CI-AKI is reversible, up to 15% of patients may need short-term dialysis, which may increase morbidity for two years[11,15]. Early research suggests that the mortality rate of CI-AKI can range from 7 to 35 percent, depending on the patient's clinical state[16]. However, even mild renal failure might cause long-term kidney damage[17]. End-stage renal disease (ESRD) develops in 4% of severe CI-AKI cases due to kidney failure[15]. There is currently no proven treatment for CI-AKI, so prevention is the best approach. Despite fluid therapy, the high incidence after PCI requires additional treatment[18].

Due to renal failure and hypoxia, oxidative stress and increased reactive oxygen species (ROS) generation are the main causes of CI-AKI. High ROS levels disrupt the oxidant-antioxidant balance, leading to lipid peroxidation. Antioxidants may be effective in preventing CI-AKI[12,19,20].

Crocin, a hydrophilic carotenoid from Crocus sativus L., has been shown to have antioxidant and anti-inflammatory properties in both in vitro and in vivo studies. It acts as a hydrogen atom donor to glutathione peroxidase (GPx), glutathione S-transferase (GST), catalase (CAT), and superoxide dismutase (SOD), making it a potent antioxidant that protects against oxidative damage[21,22,23].

The study assessed the antioxidant effects of crocin on oxidative stress biomarkers after intravenous contrast agent administration during elective PCI.

Material and Methods

Study properties

The study is an open-labeled randomized controlled clinical trial on angiography candidates admitted to Shahid Ayatullah Madani Hospital in Lorestan, Iran, from December 2021 to March 2022. It was approved by the ethics committee of Lorestan University of Medical Sciences with the number IR.LUMS.REC.1400.122, and the study was registered in the Iranian clinical trial system with the code IRCT20200721048159N5. Participants were informed about the study's purpose before signing a consent form.

The following inclusion criteria were required: adults over 18 years old; patient consent to participate in the study; and identification by the cardiologist as a candidate for angiography. Exclusion criteria included withdrawal of the consent form, anaphylactic and anaphylactoid reactions, use of common antioxidant drugs, nephrotoxic drugs, warfarin therapy, unstable renal status, inability to receive intravenous hydration, participation in other clinical trials, history of hypersensitivity to contrast media, and pregnancy.

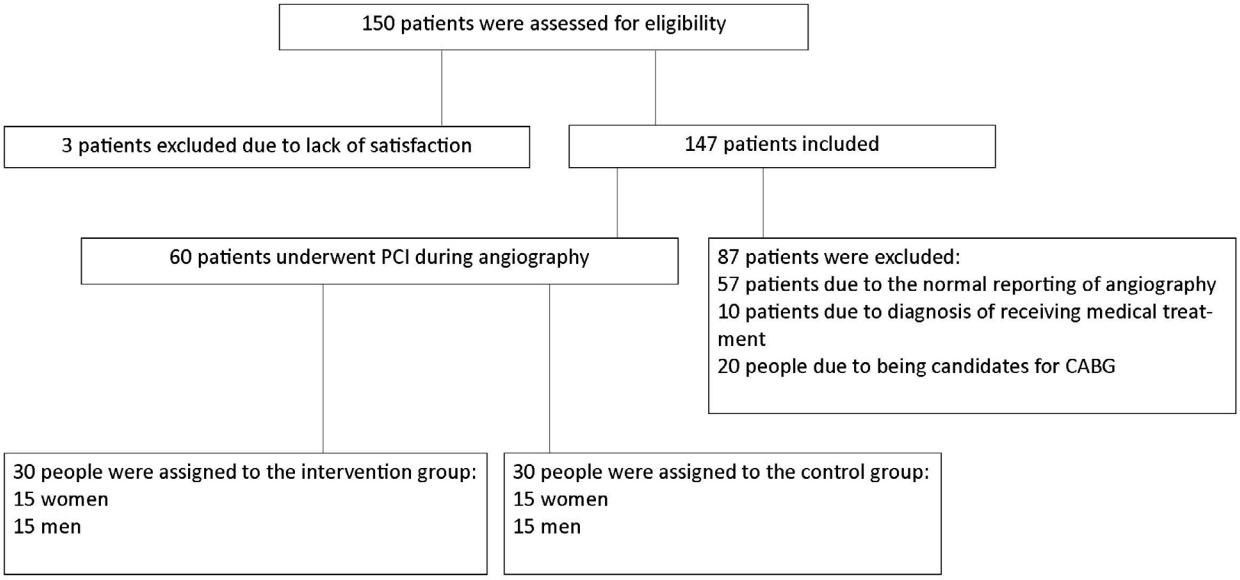

Figure 1. Flowchart of the study

Finally, 60 patients were selected and randomly divided into control and intervention groups using the blocked randomization method with the Excel function "RAND" (Figure 1).

Hydration Protocol

In the control group, 1 ml/kg/hr of normal saline was administered from six hours before to six hours after PCI, and in addition to hydration with 1 ml/kg/hr of normal saline from six hours before to six hours after PCI, the intervention group received 30 mg of crocin daily (two Krocina™ capsules from Samisaz Company containing 15 mg of purified crocin) in three consecutive doses: the night before angiography, and the first and second nights after angiography and PCI. It should be noted that in the case of patients with congestive heart failure and an ejection fraction below 45%, the dose of normal saline received by the patient was reduced to 0.5 ml/kg/hr. All patients received 300 mg of clopidogrel, 325 mg of aspirin, and 80 mg of atorvastatin (STAT, P.O.) the night before angiography and coronary intervention.

Study design

The control group received 1 ml/kg/hr of normal saline intravenously six hours before and after angiography, while the intervention group received 30 mg/day of crocin (Krocina™) orally in addition to hydration from the day before and after angiography. Additionally, patients in both groups received oral doses of 325 mg ASA, 80 mg atorvastatin, and 300 mg clopidogrel the day before angiography.

Blood samples were collected to assess oxidative stress biomarkers, including ROS, MDA, CAT, GPx, and SOD, four hours after contrast medium administration. SCr, BUN, and eGFR were also evaluated to estimate CI-AKI incidence 24 and 48 hours after contrast agent administration. Patients were followed up for one week to check for adverse reactions.

Calculation of Mehran score

The Mehran risk score is a scoring system used to predict the risk of CI-AKI incidence in patients undergoing elective PCI. It was developed in 2004 by studying 8,357 patients undergoing elective PCI with contrast. Hypotension, intra-aortic balloon pump, congestive heart failure, age > 75, amount of contrast material, and eGFR are risk factors considered in the Mehran scoring system. In this prediction criterion, the calculated risk scores are divided into four

classes, in which the risk of contrast-induced nephropathy (CIN) ranges from 7.5% (with a risk value ≤ 5) to 57.3% (with a risk value ≥ 16)[24,25]. We calculated the Mehran score to ensure that both control and intervention groups were fairly similar in terms of CI-AKI risk.

Sample preparation and biochemical tests
Fractionation and storage of samples
To obtain serum fractions, blood samples were centrifuged at 3000 rpm for five minutes. Serum from each sample was divided into six parts, labeled, and transferred to a −70°C freezer for later use.

Protein measurement method
Protein assay was performed via the Bradford method using a solution containing 0.05 g of Coomassie Brilliant Blue (CBB), 50 ml of 85% v/v phosphoric acid, 23.5 ml of 96% v/v ethanol, and distilled water up to 100 ml. Briefly, 200 µl of Bradford solution and 20 µl of serum were added to each tube. The color of the solutions changed from pale yellow to blue, and the absorbance was recorded on a Lambda 595 UV/Vis spectrophotometer[26].

ROS measurement
ROS production was measured using the Nitroblue Tetrazolium (NBT) assay. Briefly, 50 µl of serum sample was added to 50 µl of PBS buffer (containing NBT) in the test tube. After 60 minutes of incubation at room temperature, 100 µl of 50% acetic acid was added to each tube, and the absorbance of the samples was recorded on a Lambda 560 UV/Vis spectrophotometer[27].

MDA measurement
MDA concentration was measured using thiobarbituric acid reactive substances (TBARS). A total of 1500 µl of TBA solution was added to each tube, followed by 1000 µl of TCA solution. Then, 100 µl of each sample was added. After 30 minutes of incubation at 95°C, the sample color turned pink. Centrifugation was performed at 1000 rpm for 15 minutes, and absorbance was recorded with a UV/Vis Lambda 535 spectrophotometer. The MDA concentration of each sample was expressed in µmol/L/mg protein[28].

CAT activity
Briefly, each tube received 1000 µl of potassium phosphate buffer (50 µM). Ten µl of serum samples were added to test tubes. A Lambda 240 UV/Vis spectrophotometer was used to measure the absorbance of the samples after the addition of 50 µl of 2% hydrogen peroxide. Units per mg of protein were used to calculate enzyme activity[29].

GPx activity
The following solutions were used to measure GPx activity: 200 µl Tris HCl buffer, 200 µl glutathione, 100 µl sodium azide solution, 100 µl hydrogen peroxide, and 200 µl serum samples. The tubes were incubated for 15 minutes at 37°C, then 400 µl of 10% TCA solution was added. The tubes were centrifuged at 3000 rpm for three minutes, and 25 µl of supernatant was added to each well of a 64-well plate. The samples were then incubated at room temperature for 30 minutes. The absorbance of the samples was recorded on an ELISA microplate reader device, and enzyme activity was calculated as unit/mg protein[30].

SOD activity
The method for measuring SOD activity was performed using 230 µl of KH_2PO_4–EDTA buffer and serum samples. The plates were incubated for two minutes at room temperature, and then 10 µl of hematoxylin reagent was added. Absorbance was recorded on a Lambda 560 ELISA microplate reader device, and enzyme activity was calculated as unit/mg protein[31].

Statistical analysis
Data analysis was performed using SPSS version 26. Descriptive statistics (mean ± standard deviation) were calculated for all continuous variables. The normality of data distribution was assessed using the Kolmogorov-Smirnov test and visual inspection of histograms. For

Table 1. Comparison of clinical and demographic information of patients in control and intervention groups.

Variable			Control group n (%)	Intervention group n (%)	P value
Gender	Female		15 (%50.0)	15 (%50.0)	>0.99a
	Male		15 (%50.0)	15 (%50.0)	
Underlying disease	Hypertension	Yes	21 (%70.0)	17 (%56.7)	0.422 [a]
		No	9 (%30.0)	13 (%43.3)	
	Hyperlipidemia	Yes	14 (%46.7)	14 (%46.7)	>0.99 [a]
		No	16 (%53.3)	16 (%53.3)	
	Diabetes mellitus	Yes	9 (%30.0)	11 (%36.7)	0.785 [a]
		No	21 (%70.0)	19 (%63.7)	
	Anemia	Yes	3 (%10.0)	5 (%16.7)	0.706 [a]
		No	27 (%90.0)	25 (%83.3)	
	Cognitive Heart Failure	Yes	2 (%6.7)	0 (%0.0)	0.492 [a]
		No	28 (%93.3)	30 (%0.0)	
Mehran Score	<5		20 (%66.7)	19 (%63.7)	0.241[b]
	[5-10)		9 (%30.0)	9 (%30.0)	
	[10-16)		0 (%0.0)	1 (%3.3)	
	16≥		1 (%3.3)	1 (%3.3)	
Age (mean ± SD)	-		51.63±11.37	59.87±10.26	0.661[c]
Weight (mean ± SD)	-		68.80±10.25	73.57±11.28	0.492 [c]
Mehran Score (mean ± SD)	-		4.33±3.42	5.30±3.56	0.241 [b]
med (IQR)			4 (4)	5 (4.5)	

Note: SD: Standard Deviation.
[a] Chi-Square Test
[b] Mann-Whitney U test
[c] Independent t-test

between-group comparisons, independent samples t-tests were applied. Within-group (pre-post) comparisons were conducted using paired t-tests. For variables measured at three time points, repeated measures ANOVA was used to evaluate changes over time and interaction effects between groups. A p-value less than 0.05 was considered statistically significant.

Results

Demographic and clinical information of patients

There was no significant difference between the Mehran scores of the two groups (P = 0.241). Additionally, the age and average weight of the two groups did not significantly differ from one another (P > 0.05) (Table 1).

Laboratory findings

According to an independent t-test, baseline levels of ROS, MDA, CAT, GPx, and SOD did not change significantly between the control and intervention groups (P > 0.05) (Table 1). The intra-group changes were compared using a paired t-test. After four hours of PCI, the control group's ROS levels tended to rise while the intervention group's levels decreased, although this was not significant (P < 0.05) (Table 2). Both groups showed a declining mean MDA four hours post-PCI in comparison to baseline (P < 0.05), with no discernible difference in average MDA increases (P = 0.550) (Table 2). After PCI, CAT activity increased nonsignificantly in both the control and intervention groups. GPx activity

Table 2. Comparison of laboratory findings related to oxidative stress between control and intervention groups

Variable	Group	Time-baseline (mean ± SD)	Time- 4hrs. after PCI (mean ± SD)	Difference between baseline and 4 hrs. after PCI	P value (intragroup)	P value (intergroup)
ROS	Control	39.39±14.74	42.82±15.00	3.43±20.17	0.360 [a]	0.181 [b]
	Intervention	42.88±15.50	38.54±13.73	-4.57±24.09	0.332 [a]	
MDA	Control	0.68±0.41	0.52±0.25	-0.16±0.47	0.074 [a]	0.550 [b]
	Intervention	0.69±0.40	0.58±0.31	-0.90±0.43	0.258 [a]	
CAT	Control	138.83±40.59	148.74±47.05	9.92±54.74	0.329 [a]	0.851 [b]
	Intervention	138.03±10.25	145.28±40.47	7.24±54.76	0.457 [a]	
GPx	Control	3.39±0.76	3.35±1.06	-0.04±1.17	0.846 [a]	0.460 [b]
	intervention	3.18±1.13	3.42±1.15	0.25±1.78	0.453 [a]	
SOD	Control	36.05±7.92	36.84±8.43	0.79±9.17	0.642 [a]	0.565 [b]
	Intervention	36.04±10.20	35.36±9.14	-0.68±10.35	0.723 [a]	

Abbreviation: SD: Standard Deviation, ROS: Reactive oxygen species, MDA: Malondialdehyde, CAT: Catalase, GPx: Glutathione peroxidase, SOD: Superoxide dismutase.
[a] Paired t-test
[b] Independent t-test

tended to increase in the intervention group while it tended to decrease in the control group, but not significantly (P > 0.05) (Table 2). Data analysis revealed that there was an insignificant rise in the average SOD activity in the control group compared to baseline (P = 0.642). There was no significant change in mean SOD between the two groups (P = 0.565) (Table 2).

The results of repeated measures ANOVA showed that there was a significant decrease in the average SCr in the intervention group and in the BUN index over time in both groups (P < 0.05), but no significant difference between the two groups (P = 0.6) (Figure 2A, B; Table 3). Also, there was a nonsignificant increase in the average eGFR index over time in the control and intervention groups (P > 0.05). However, there was no significant difference between the average eGFR changes of the intervention and control groups (P = 0.741) (Figure 2C; Table 3).

Correlation of coronary artery access and oxidative stress level

The study found that 33.3% of the control group and 50% of the intervention group had access to the coronary arteries through the radial vein, while 66.7% and 50% of the control group had access through the femoral vein. The Chi-square statistical test revealed homogeneity in both groups' PCI access techniques (P = 0.295) (Table 4). Biomarkers for oxidative stress were compared between the control and intervention groups using the Wilcoxon rank test. No significant difference in oxidative stress markers was found between baseline and four hours after PCI. Additionally, the Mann-Whitney test revealed no discernible difference between the two groups' mean oxidative indices (P > 0.05) (Table 5).

Incidence of CI-AKI

The incidence rate of CI-AKI caused by iodixanol was 3.3%. In terms of the incidence of CI-AKI, there was no significant difference between the intervention and control groups, with the control group having two instances (6.7%) and the intervention group having none (P = 0.492) (Table 6).

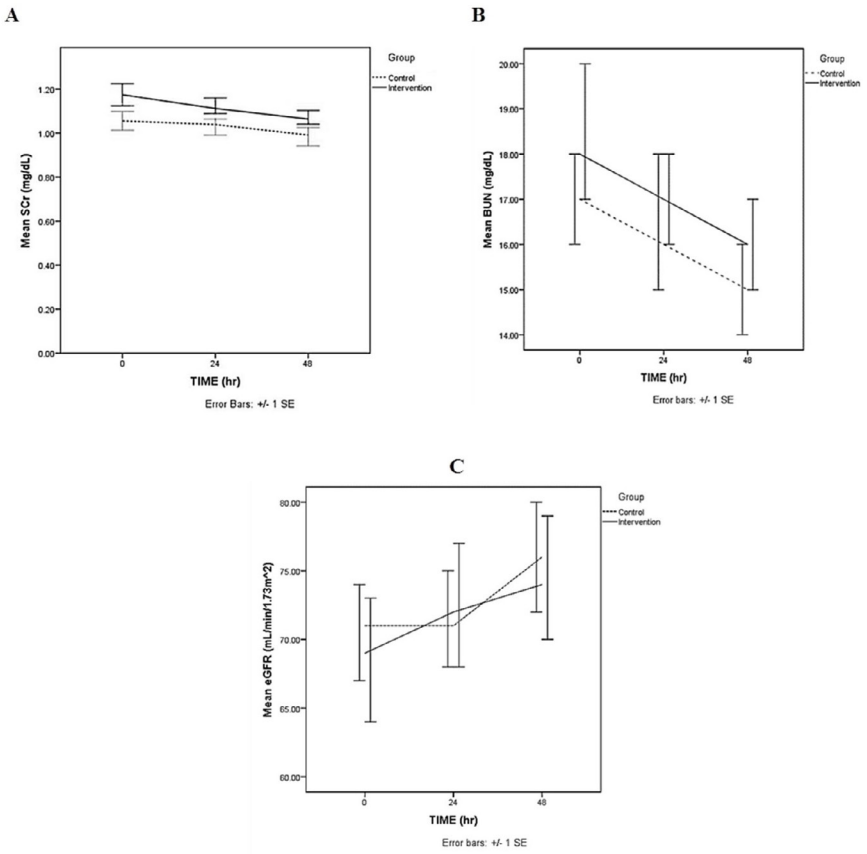

Figure 2. Comparison of A: SCr, B: BUN, and C: eGFR changes of two control and intervention groups. SCr: Serum Creatinine; BUN: Blood Urea Nitrogen; eGFR: estimated Glomerular Filtration Rate.

Table 3. Comparison of laboratory findings related to CI-AKI between control and intervention groups

Variable	Group	Time-baseline (mean ± SD)	Time- 4hrs. after PCI (mean ± SD)	Difference between baseline and 4 hrs. after PCI	P value (intragroup)	P value (intergroup)
ROS	Control	39.39±14.74	42.82±15.00	3.43±20.17	0.360 [a]	0.181 [b]
	Intervention	42.88±15.50	38.54±13.73	-4.57±24.09	0.332 [a]	
MDA	Control	0.68±0.41	0.52±0.25	-0.16±0.47	0.074 [a]	0.550 [b]
	Intervention	0.69±0.40	0.58±0.31	-0.90±0.43	0.258 [a]	
CAT	Control	138.83±40.59	148.74±47.05	9.92±54.74	0.329 [a]	0.851 [b]
	Intervention	138.03±10.25	145.28±40.47	7.24±54.76	0.457 [a]	
GPx	Control	3.39±0.76	3.35±1.06	-0.04±1.17	0.846 [a]	0.460 [b]
	intervention	3.18±1.13	3.42±1.15	0.25±1.78	0.453 [a]	
SOD	Control	36.05±7.92	36.84±8.43	0.79±9.17	0.642 [a]	0.565 [b]
	Intervention	36.04±10.20	35.36±9.14	-0.68±10.35	0.723 [a]	

Abbreviation: SD: Standard Deviation, ROS: Reactive oxygen species, MDA: Malondialdehyde, CAT: Catalase, GPx: Glutathione peroxidase, SOD: Superoxide dismutase.
[a] Paired t-test
[b] Independent t-test

Table 4. Consensus table of patients undergoing PCI according to the method of access to the coronary arteries during angiography and the studied groups

Method of access to coronary arteries	Control group n (%)	Intervention group n (%)	P value
Radial	10 (%33.3)	15 (%50.0)	0.295 [a]
Femoral	15 (%50.0)	15 (%50.0)	

[a] Chi-Square Test

Table 5. Comparison of the relationship between the method of access to coronary arteries and factors related to oxidative stress in both control and intervention groups.

Variable	Access to coronary arteries	Group	Time-baseline (mean ± SD)	Time- 4hrs. after PCI (mean ± SD)	Difference baseline and 4 hrs. after PCI	P value (intragroup)	P value (intergroup)
ROS (IU)	**Radial**	Control	40.23±14.84	38.41±10.88	-1.83±18.84	0.878 [a]	0.874 [b]
		Intervention	43.18±15.47	39.74±16.92	-3.44±27.83	0.733 [a]	
	Femoral	Control	38.97±15.06	45.03±17.86	6.06±20.75	0.370 [a]	0.120 [b]
		Intervention	42.58±16.07	37.34±16.07	-5.24±20.62	0.293 [a]	
MDA (umol/L)	**Radial**	Control	0.63±0.34	0.42±0.18	-0.21±0.23	0.370 [a]	0.297 [b]
		Intervention	0.68±0.48	0.64±0.37	-0.03±0.48	0.910 [a]	
	Femoral	Control	0.70±0.45	0.57±0.28	-0.13±0.56	0.292 [a]	0.937 [b]
		Intervention	0.66±0.32	0.51±0.24	-0.15±0.37	0.078 [a]	
CAT (unit/mg protein)	**Radial**	Control	122.00±43.71	146.82±34.73	24.82±43.06	0.139 [a]	0.5 [b]
		Intervention	141.05±34.69	154.02±35.91	12.97±41.91	0.156 [a]	
	Femoral	Control	147.24±37.23	149.70±52.96	2.47±59.32	0.911 [a]	0.965 [b]
		Intervention	135.03±57.92	136.55±44.04	1.52±66.22	0.910 [a]	
GPx (unit/mg protein)	**Radial**	Control	3.27±0.92	3.13±0.86	-0.15±1.02	0.799 [a]	0.484 [b]
		Intervention	3.30±1.22	3.65±1.21	0.35±2.04	0.496 [a]	
	Femoral	Control	3.46±0.70	3.47±1.15	0.01±1.25	0.681 [a]	0.781 [b]
		Intervention	3.05±1.07	3.19±1.09	0.14±1.55	0.394 [a]	
SOD (unit/mg protein)	**Radial**	Control	33.15±8.25	34.45±8.33	1.30±8.35	0.646 [a]	0.857 [b]
		Intervention	36.00±7.05	36.57±9.52	0.57±10.73	0.955 [a]	
	Femoral	Control	37.50±7.55	38.03±8.43	0.53±9.75	0.823 [a]	0.476 [b]
		Intervention	36.08±12.58	34.17±8.91	-1.92±10.17	0.693 [a]	

Abbreviation: SD: Standard Deviation, ROS: Reactive oxygen species, MDA: Malondialdehyde, CAT: Catalase, GPx: Glutathione peroxidase, SOD: Superoxide dismutase.
[a] Paired t-test
[b] Independent t-test

Side effects between intervention and control groups

Seventy-two hours after iodixanol administration, skin rashes manifested in two cases: one in the intervention group and the other in the control group.

Discussion

Coronary angiography commonly employs iodinated contrast agents. Acute kidney injury

Table 6. Comparison of the incidence of CI-AKI in two control and intervention groups

Variable		Control group n (%)	Intervention group n (%)	P value
Incidence of CI-AKI	Female	0 (%0.0)	0 (%0.0)	0.492 [a]
	Male	**2 (%6.7)**	0 (%0.0)	

Abbreviation: CI-AKI: Contrast-induced acute kidney injury.
[a] Chi-Square Test

is one of the harmful side effects of using these substances. Oxidative stress plays a crucial role in the pathology of CI-AKI. However, only a few clinical studies have investigated the extent of oxidative stress following the administration of contrast media[32]. A clinical study involving 27 non-diabetic patients found that giving a low-osmolarity non-ionic contrast agent before coronary angiography increased MDA levels and decreased SOD, CAT, and GPx activities over the first four hours. Additionally, the changes in eGFR were exactly the opposite of those in MDA[32]. A study of 5177 individuals with high-risk renal problems found no significant differences in antioxidant and free radical scavenger efficacy in preventing CI-AKI, despite N-acetylcysteine and sodium bicarbonate being known as antioxidants[12].

In accordance with recent in vitro and in vivo examinations, crocin is a potent antioxidant that can reduce ROS generation, lipid peroxidation, and activate mitochondrial protective antioxidant pathways[33,34]. According to research conducted on animals, crocin works as a nephroprotective drug against renal toxicity brought on by methotrexate, gentamicin, and cisplatin due to restoring oxidative equilibrium, increasing total antioxidant capacity, lowering MDA, and boosting GPx activity[35–37].

In the present clinical study, the effect of oral administration of crocin on oxidative stress indices in patients undergoing PCI was investigated. A tendency to increase the activity of the antioxidant defense system and reduce oxidative factors was observed with the consumption of 30 mg of crocin. However, these changes were not significant. The study identified no differences between the control and intervention groups in terms of coronary artery access methods on serum levels of oxidative stress biomarkers and antioxidant system activity. Our study assessed the incidence of CI-AKI caused by contrast agents following the administration of crocin. Two patients in the control group were found to have CI-AKI, but there were none in the intervention group.

Antioxidant treatment in various diseases can be ineffective, partially effective, or moderately effective due to factors such as short treatment duration, limited absorption, and low tissue specificity for the target tissue. Combining antioxidants may enhance clinical responses[38]. Therefore, the short study duration and administration interval may be responsible for the insufficient effectiveness of crocin in the current investigation. As we have shown, following crocin consumption, SCr and BUN decreased in the intervention group. In 2020, Behrouz and colleagues investigated the impact of crocin on inflammatory biomarkers in patients with type II diabetes. Fifty patients were divided into control and intervention groups. For 12 weeks, the intervention group took 15 mg of crocin twice daily, whereas the control group took a placebo. All inflammatory factors except MDA were significantly lower in the intervention group. However, MDA values did not differ significantly after 12 weeks[39].

Conclusion

The oral administration of 30 mg of crocin did not lead to significant changes in oxidant biomarkers. Moreover, SCr, BUN, and the incidence of CI-AKI were lower in the intervention group.

It is recommended that future studies include the following: using a larger sample size, increasing the duration of the intervention

and patient follow-up, employing multiple antioxidants and comparing them with each other, and evaluating additional serum markers.

Acknowledgements
We hereby thank Heart center department of Madani Hospital in Khorramabad, Lorestan University of Medical Sciences and patients. This work was financially supported by grant IR.LUMS.REC.1400.122 from the Department of pharmacotherapy, school of pharmacy. This paper is issued from the thesis of Arefe Khani.

Conflict of interests
The authors declare no conflict of interest.

Funding
This research was financially supported by a grant (PAIN-9906) from vice- chancellor for research affairs of Ahvaz Jundishapur University of Medical Sciences.

Author's Contributions
Study Conception or Design: AK, FA
Data Acquisition: AR
Data Analysis or Interpretation: AA, NM, MB, AR
Manuscript Drafting: JKF, MB, FA, SMM, NMM
Critical Manuscript Revision: FA

All authors have approved the final manuscript and are responsible for all aspects of the work.

References

1. Khan SU, Agarwal S, Arshad HB, Akbar UA, Mamas MA, Arora S, Baber U, Goel SS, Kleiman NS, Shah AR. Intravascular imaging guided versus coronary angiography guided percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2023 Nov 16;383:e077848. https://doi.org/10.1136/bmj-2023-077848
2. Emami M, Shafie D, Vakhshoori M, Eghbali-Babadi M, Ahmadipour E, Khosravi A. Evaluation of the efficiency of indirect blood pressure measurement methods in comparison to intra-arterial reading among Iranian individuals. Int Cardiovasc Res J. 2020;14(3).
3. Ahmad Y, Petrie MC, Jolicoeur EM, Madhavan MV, Velazquez EJ, Moses JW, et al. PCI in Patients With Heart Failure: Current Evidence, Impact of Complete Revascularization, and Contemporary Techniques to Improve Outcomes. J Soc Cardiovasc Angiogr Interv. 2022 Apr 11;1(2):100020. https://doi.org/10.1016/j.jscai.2022.100020
4. Health AS. Appropriate Use Criteria: Percutaneous Coronary Intervention. Cardiology. 2022:1–15.
5. Zadeh FJ, Ghasemi Y, Bagheri S, Maleknia M, Davari N, Rezaeeyan H. Do exosomes play role in cardiovascular disease development in hematological malignancy? Mol Biol Rep. 2020 Jul;47(7):5487-93. https://doi.org/10.1007/s11033-020-05453-z
6. Khan SQ, Ludman PF. Percutaneous coronary intervention. Medicine. 2022;50(7):437-44. https://doi.org/10.1016/j.mpmed.2022.04.008
7. Roczniak J, Koziołek W, Piechocki M, Tokarek T, Surdacki A, Bartuś S, et al. Comparison of Access Site-Related Complications and Quality of Life in Patients after Invasive Cardiology Procedures According to the Use of Radial, Femoral, or Brachial Approach. Int J Environ Res Public Health. 2021 Jun 7;18(11):6151. https://doi.org/10.3390/ijerph18116151
8. Senguttuvan NB, Reddy PM, Shankar P, Abdulkader RS, Yallanki HP, Kumar A, et al. Trans-radial approach versus trans-femoral approach in patients with acute coronary syndrome undergoing percutaneous coronary intervention: An updated meta-analysis of randomized controlled trials. PLoS One. 2022 Apr 28;17(4):e0266709. https://doi.org/10.1371/journal.pone.0266709
9. Samadzadeh Etehadi S. Determination of bacterial profiles in children with otitis media with effusion and adenoid hypertrophy. Afr J Biomed Res. 2025;28(2S):470-80. https://doi.org/10.53555/AJBR.v28i2S.6650
10. Alqallaf SM, Al-Jowder M, Abdulla S. Iodixanol induced allergy: a retrospective study at Mohammed Bin Khalifa Cardiac Centre, Kingdom of Bahrain. J Appl Pharm Sci. 2021;11(12):209-15. https://dx.doi.org/10.7324/JAPS.2021.1101221
11. Boozari M, Hosseinzadeh H. Preventing contrast-induced nephropathy (CIN) with herbal medicines: A review. Phytother Res. 2021 Mar;35(3):1130-1146. https://doi.org/10.1002/ptr.6880
12. Zhang F, Lu Z, Wang F. Advances in the pathogenesis and prevention of contrast-induced nephropathy. Life Sci. 2020 Oct 15;259:118379. https://doi.org/10.1016/j.lfs.2020.118379
13. Li Y, Wang J. Contrast-induced acute kidney injury: a review of definition, pathogenesis, risk factors, prevention and treatment. BMC Nephrol. 2024 Apr

22;25(1):140. https://doi.org/10.1186/s12882-024-03570-6
14. Chandiramani R, Cao D, Nicolas J, Mehran R. Contrast-induced acute kidney injury. Cardiovasc Interv Ther. 2020 Jul;35(3):209-17. https://doi.org/10.1007/s12928-020-00660-8
15. Kusirisin P, Chattipakorn SC, Chattipakorn N. Contrast-induced nephropathy and oxidative stress: mechanistic insights for better interventional approaches. J Transl Med. 2020 Oct 20;18(1):400. https://doi.org/10.1186/s12967-020-02574-8
16. Pistolesi V, Regolisti G, Morabito S, Gandolfini I, Corrado S, Piotti G, et al. Contrast medium induced acute kidney injury: a narrative review. J Nephrol. 2018 Dec;31(6):797-812. https://doi.org/10.1007/s40620-018-0498-y
17. Sabaghian T, Gheydari ME, Divani F. Evaluation of Curcumin (Turmeric Extract) Effect on Prevention of CIN in Patient Under Elective Coronary Angiography, a Randomized Double Blind Placebocontrolled Clinical Trial. Iran J Kidney Dis. 2020 May;14(3):198-205.
18. Zhao J, Liu H, Xu B, Peng J, Xing Y, Tang W, et al. The Role of Xuefu Zhuyu Decoction in Prevention of Contrast-Induced Nephropathy after Percutaneous Coronary Intervention. Evid Based Complement Alternat Med. 2020 Apr 27;2020:5419016. https://doi.org/10.1155/2020/5419016
19. Aksoy F, Aydın Baş H, Bağcı A, Basri Savaş H. Predictive value of oxidant and antioxidant status for contrast-induced nephropathy after percutaneous coronary intervention for ST-segment elevation myocardial infarction. Rev Port Cardiol (Engl Ed). 2021 Jul;40(7):489-97. https://doi.org/10.1016/j.repce.2021.07.018
20. Cervantes-Gracia K, Raja K, Llanas-Cornejo D, Cobley JN, Megson IL, Chahwan R, Husi H. Oxidative stress and inflammation in the development of cardiovascular disease and contrast induced nephropathy. Vessel Plus. 2020;4:27. http://dx.doi.org/10.20517/2574-1209.2020.22
21. Boozari M, Hosseinzadeh H. Natural medicines for acute renal failure: A review. Phytother Res. 2017 Dec;31(12):1824-35. https://doi.org/10.1002/ptr.5943
22. Ghiasian M, Khamisabadi F, Kheiripour N, Karami M, Haddadi R, Ghaleiha A, et al. Effects of crocin in reducing DNA damage, inflammation, and oxidative stress in multiple sclerosis patients: A double-blind, randomized, and placebo-controlled trial. J Biochem Mol Toxicol. 2019 Dec;33(12):e22410. https://doi.org/10.1002/jbt.22410
23. Korani S, Korani M, Sathyapalan T, Sahebkar A. Therapeutic effects of Crocin in autoimmune diseases: A review. Biofactors. 2019 Nov;45(6):835-43. https://doi.org/10.1002/biof.1557
24. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004 Oct 6;44(7):1393-9. https://doi.org/10.1016/j.jacc.2004.06.068
25. Sgura FA, Bertelli L, Monopoli D, Leuzzi C, Guerri E, Spartà I, et al. Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. Circ Cardiovasc Interv. 2010 Oct;3(5):491-8. https://doi.org/10.1161/circinterventions.110.955310
26. Kielkopf CL, Bauer W, Urbatsch IL. Bradford Assay for Determining Protein Concentration. Cold Spring Harb Protoc. 2020 Apr 1;2020(4):102269. https://doi.org/10.1101/pdb.prot102269
27. Esfandiari N, Sharma RK, Saleh RA, Thomas AJ Jr, Agarwal A. Utility of the nitroblue tetrazolium reduction test for assessment of reactive oxygen species production by seminal leukocytes and spermatozoa. J Androl. 2003 Nov-Dec;24(6):862-70. https://doi.org/10.1002/j.1939-4640.2003.tb03137.x
28. Ahmadvand H, Dehnoo MG, Cheraghi R, Rasoulian B, Ezatpour B, Azadpour M, et al. Amelioration of altered serum, liver, and kidney antioxidant enzymes activities by sodium selenite in alloxan-induced diabetic rats. Rep Biochem Mol Biol. 2014 Oct;3(1):14-20.
29. Nasiry D, Khalatbary AR, Ahmadvand H, Talebpour Amiri FB. Effects of Juglans regia L. leaf extract supplementation on testicular functions in diabetic rats. Biotech Histochem. 2021 Jan;96(1):41-7. https://doi.org/10.1080/10520295.2020.1755893
30. Nasri M, Adibhesami G, Mahdavifard S, Babaeenezhad E, Ahmadvand H. Exogenous glutamine ameliorates diabetic nephropathy in a rat model of type 2 diabetes mellitus through its antioxidant and anti-inflammatory activities. Arch Physiol Biochem. 2023 Apr;129(2):363-72. https://doi.org/10.1080/13813455.2020.1828478
31. Martin JP Jr, Dailey M, Sugarman E. Negative and positive assays of superoxide dismutase based on hematoxylin autoxidation. Arch Biochem Biophys. 1987 Jun;255(2):329-36. https://doi.org/10.1016/0003-9861(87)90400-0
32. Manda P, Rao PS, Bitla AR, Vinapamula KS,

Jeyaseelan L, Rajasekhar D, et al. Study of contrast-induced oxidative stress in nondiabetic patients undergoing coronary angiography. Saudi J Kidney Dis Transpl. 2019 Jan-Feb;30(1):45-52.
33. Rahiman N, Akaberi M, Sahebkar A, Emami SA, Tayarani-Najaran Z. Protective effects of saffron and its active components against oxidative stress and apoptosis in endothelial cells. Microvasc Res. 2018 Jul;118:82-9. https://doi.org/10.1016/j.mvr.2018.03.003
34. Yousefsani BS, Pourahmad J, Hosseinzadeh H. The mechanism of protective effect of crocin against liver mitochondrial toxicity caused by arsenic III. Toxicol Mech Methods. 2018 Feb;28(2):105-14. https://doi.org/10.1080/15376516.2017.1368054
35. Jalili C, Ghanbari A, Roshankhah S, Salahshoor MR. Toxic Effects of Methotrexate on Rat Kidney Recovered by Crocin as a Consequence of Antioxidant Activity and Lipid Peroxidation Prevention. Iran Biomed J. 2020 Jan;24(1):39-46. https://doi.org/10.29252/ibj.24.1.39
36. Naghizadeh B, Mansouri SM, Mashhadian NV. Crocin attenuates cisplatin-induced renal oxidative stress in rats. Food Chem Toxicol. 2010 Oct;48(10):2650-5. https://doi.org/10.1016/j.fct.2010.06.035
37. Yarijani ZM, Najafi H, Hamid Madani S. Protective effect of crocin on gentamicin-induced nephrotoxicity in rats. Iran J Basic Med Sci. 2016 Mar;19(3):337-43.
38. Firuzi O, Miri R, Tavakkoli M, Saso L. Antioxidant therapy: current status and future prospects. Curr Med Chem. 2011;18(25):3871-88. https://doi.org/10.2174/092986711803414368
39. Behrouz V, Sohrab G, Hedayati M, Sedaghat M. Inflammatory markers response to crocin supplementation in patients with type 2 diabetes mellitus: A randomized controlled trial. Phytother Res. 2021 Jul;35(7):4022-31. https://doi.org/10.1002/ptr.7124