Ilam University of Medical Sciences

Plant Biotechnology Persa

Online ISSN: 2676-7414

Homepage: https://pbp.medilam.ac.ir

Nanoparticle-Based Drug Delivery in Renal Ischemia-Reperfusion Injury: Insights into Molecular Signaling Pathways: A Systematic Review

Maryam Kheiry[1,2], Mohammad Reza Kaffashian[1,2], Alireza Aliboroni[1,2], Maryam Maleki[1,2] ✉

[1]Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran
[2]Department of Physiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran

Article Info

Article type:
Review Article

Article History:
Received: 31 Jan 2026
Revised: 03 May 2026
Accepted: 19 May 2026
Published Online:

✉ ***Correspondence to:***
Maryam Maleki

Email:
maryammaleki777@yahoo.com

A B S T R A C T

Objective: Renal ischemia-reperfusion injury (RIRI) is a major cause of acute kidney damage following surgery, trauma, organ transplantation, and thrombotic events, primarily due to oxidative stress and cellular injury. Nanoparticles (NPs) have emerged as promising therapeutic tools by enabling targeted drug delivery, controlled release, and reduced systemic toxicity. This systematic review evaluates the effects of NP-based therapies on IRIR, with a focus on their modulation of key molecular signaling pathways.

Methods: A systematic search was performed in PubMed, Scopus, and Web of Science for studies published between 1990 and 2024. After applying predefined inclusion and exclusion criteria, 14 studies were included in the final analysis.

Results: NP-based interventions consistently improved experimental RIRI outcomes by reducing oxidative stress, preserving renal function markers, attenuating inflammation and fibrosis, and modulating immune and gene-expression responses. These effects were observed across different nanoformulations and therapeutic cargos.

Conclusion: Current evidence supports nanoparticles as promising candidates for the prevention and treatment of renal IRIR, with clear potential for translation into advanced renal drug-delivery and renoprotective strategies.

Keywords: Nanoparticle exposure, Renal ischemia-reperfusion injury, Signaling pathways

➢ **How to cite this paper**
Kheiry M, Kaffashian MR, Aliboroni A, Maleki M. Nanoparticle-Based Drug Delivery in Renal Ischemia-Reperfusion Injury: Insights into Molecular Signaling Pathways. Plant Biotechnology Persa. 2026; 8(3): Proof.

DOI: 10.61882/pbp.7.4.4
Publisher: Ilam University of Medical Sciences

Introduction

Renal ischemia-reperfusion injury (RIRI) is a leading cause of acute kidney injury, particularly during kidney transplantation, major vascular surgeries, and resuscitation after severe hypotension. Despite advances in supportive care, current therapies are unable to adequately suppress the intense oxidative stress, inflammation, and cell death triggered during ischemia and reperfusion. This therapeutic gap highlights an urgent need for novel strategies capable of neutralizing reactive oxygen species (ROS) and modulating dysregulated molecular pathways in RIRI [1, 2].

Nanoparticles have recently emerged as promising candidates due to their ability to deliver therapeutic agents directly to injured renal tissue, enhance drug stability, and reduce systemic toxicity. In addition, several nanomaterials exhibit intrinsic antioxidant or "nanozyme-like'' activity, enabling direct scavenging of ROS and attenuation of inflammatory responses [3-5]. Metal-oxide and polymer-based nanoparticles have demonstrated strong biological activities relevant to renal protection, including antioxidative, anti-inflammatory, and anti-fibrotic effects [6] including antioxidant, antimicrobial, anti-cancer, anti-diabetic, anti-inflammatory, and wound-healing effects [7].

Considering the limited effectiveness of current treatments and the growing evidence supporting nanoscale therapeutics, this review examines how nanoparticle-based interventions modulate key signaling pathways associated with RIRI and highlights their potential for future clinical application.

Study design

Systematic review

This systematic review was developed in alignment with widely accepted guidelines for reporting systematic reviews [8]. The methodology employed in this work builds upon protocols established in earlier publications by our research team [9, 10].

Databases and search strategy

An extensive search was performed across multiple English-language academic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, to identify studies relevant to the topic. A detailed search strategy was initially designed in PubMed using a combination of carefully selected keywords, Boolean operators, and search fields. This search syntax was subsequently tailored for compatibility with the other databases. The literature search was conducted comprehensively and without temporal limitations, covering studies published up to the end of 2024. A concise overview of the individual search approaches used across each database is presented in Table 1.

Table 1: Search Syntax

Database	Search strategy	Records retrieved (n)
PubMed	(("Nanoparticles"[Mesh] OR nanoparticle*[Title/Abstract] OR "Titanium dioxide nanoparticle*"[Title/Abstract] OR "Gold nanoparticle*"[Title/Abstract] OR "Zinc oxide nanoparticle*"[Title/Abstract] OR "Iron nanoparticle*"[Title/Abstract] OR nanocapsule*[Title/Abstract] OR "Metal nanoparticle*"[Title/Abstract]) AND ("Renal ischemia-reperfusion injury"[Title/Abstract] OR "Kidney ischemia-reperfusion injury"[Title/Abstract] OR ((renal OR kidney)[Title/Abstract] AND ("ischemia-reperfusion"[Title/Abstract] OR "I/R injury"[Title/Abstract]))))	22
Scopus	TITLE-ABS (nanoparticle* OR "Titanium dioxide nanoparticle*" OR "Gold nanoparticle*" OR "Zinc oxide nanoparticle*" OR "Iron nanoparticle*" OR nanocapsule* OR "Metal nanoparticle*") AND TITLE-ABS ("Renal ischemia-reperfusion injury" OR "Kidney ischemia-reperfusion injury" OR ((renal OR kidney) AND ("ischemia-reperfusion" OR "I/R injury")))	28
Web of Science Core Collection	TS=(nanoparticle* OR "Titanium dioxide nanoparticle*" OR "Gold nanoparticle*" OR "Zinc oxide nanoparticle*" OR "Iron nanoparticle*" OR nanocapsule* OR "Metal nanoparticle*") AND TS=("Renal ischemia-reperfusion injury" OR "Kidney ischemia-reperfusion injury" OR ((renal OR kidney) AND ("ischemia-reperfusion" OR "I/R injury")))	32

Study selection

Figure 1. illustrated the Summary of a standard four-step protocol for literature review based on legitimate keywords. we manually examined the references list of the included studies to gather any additional pertinent papers in order to collect all potentially relevant research. The inclusion criteria were on the association of nanoparticle with Renal ischemia/reperfusion injury (RIRI) in English. Studies were excluded if they were Review articles, duplicate articles, editorials, brief communications, rules, theses, oral presentations, book chapters, conference abstracts, comments, white papers, and technical reports.

Data extraction

Data were independently collected by two reviewers (MM, MKh) on the following aspects: author names, research model, publication year, type of disease, types of nanoparticles used, results obtained, agents involved, exposure duration, receptors/pathways studied, assessment periods, therapeutic interventions related to

nanoparticle exposure and ischemia/reperfusion injury, protective effects observed, and molecular pathways involved. Any disagreements between the two reviewers during this process were resolved with the assistance of a third researcher.

Results

After literature search in the data resources, 87 articles were found. Then, 74 articles were discarded because some were unrelated to the association of nanoparticle exposure with RIRI, duplicate articles, review articles, letters to the editor, and progress articles. Finally, after reviewing the full texts of the articles, 14 articles published between 2016 and 2024 that met the inclusion/exclusion criteria were selected for this SR (Figure. 1).

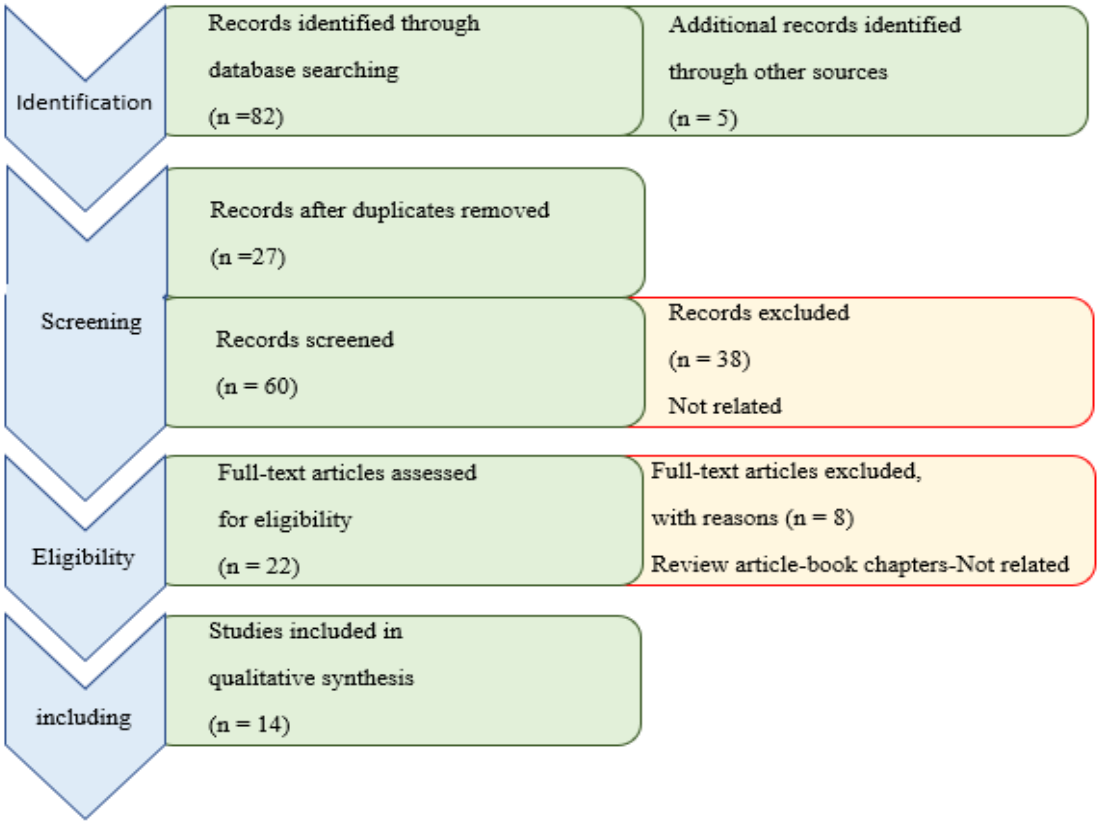

Figure 1: Summary of a standard four-step protocol for literature review

Table 2 displays the 14 articles' complete descriptions and a summary of their characteristics.

Table 2: Characteristics of studies conducted on the relationship between nanoparticles and renal ischemia-reperfusion injury (RIRI)

Year	Ref.	Model (Animal/Human) In vivo/ In vitro	Injury/disease	Nanoparticle(s)	Investigation	Brief Results
2021	Awadalla et al [1]	Male Sprague Dawley rats	RIRI	ZnO-NPs	Effects of FA and ZnO-NPs and a combination of both on RIRI	FA and ZnO-NPs showed protective effects on cells against RIRI, with their combination offering enhanced kidney protection.
2022	Zhou et al. [11]	In vivo (mouse)	In vivo RIRI	CNPs	Effects of CNPs prophylactic in RIRI	CNPs show promise as a treatment or preventive approach for RIRI and kidney fibrosis.
		In vitro (HK2, RTEC cells)	In vitro hypoxia			

2023	Embaby et al. [12]	Male Sprague Dawley albino rats	RIRI	ZnO-NPs	Efficacy of ZnO-NPs and/or MIL on RIRI	ZnO-NPs and MIL also provided cellular protection in acute RIRI cases, and their combination proved even more effective.
2021	Liu et al. [13]	In vivo (C57BL/6 male mice)	RIRI	T-NPCoQ10	Efficacy of mitochondria-targeted nanocarrier to delivery of CoQ10 for RIRI	Delivering CoQ10 directly to mitochondria presents a highly effective strategy for controlling inflammation and oxidative damage in RIRI.
		In vitro (HK-2 cells)	(In vitro) oxygen-glucose deprivation			
2021	Xie et al. [14]	Male mice	RIRI	PHD2 siRNA G5-FA	Effects of PHD2 siRNA G5-FA on RIRI	G5-FA functions as a reliable carrier for delivering siRNA to the kidney. Suppressing PHD2 in renal tissues may help manage RIRI.
2022	Hou et al. [15]	In vivo mice)	In vivo: RIRI			

				LSKL/NPs	Effects of NPs targeting TSP-1 on RIRI	LSKL/NPs can reduce and deactivate TSP-1, presenting a viable therapeutic method for RIRI.
		In vitro (HK-2 cells)	In vitro TSP-1 induced human renal tubular epithelial cell apoptosis			
2020	Liu et.al. [16]	In vivo (mice)	RIRI	N-NP CoQ10	Efficacy of a N-NP CoQ10 strategy for RIRI treatment.	Administering N-NP CoQ10 may represent a promising approach in RIRI treatment.
		In vitro (human, HK-2 cells)				
2022	Xu et al [17]	In vivo (male BALB/c mice)	RIRI	NP-IGF-1C	Effects of NP-IGF-1C on preventing RIRI	NP-IGF-1C have demonstrated a protective effect during RIRI progression.
		In vitro (HEK293 cells)	In vitro Oxygen-glucose deprivation/reperfusion			
2016	Xu et al [18]	In vitro (HK-2 cells)	HK-2 cells IRI	Cur-NPs	Effect of Cur-NPs on HK-2 cells exposed to IRI	Cur-NPs helped safeguard HK-2 cells exposed to IRI.

2017	Xie et al [19]	Sprague-Dawley rats	RIRI	BBR-NPs	Effects of BBR-NP on the IRI renal cells	BBR-NP were more effective than berberine alone in preventing kidney injury caused by IRI.
2022	Saleh et al [20]	Male diabetic mice	RIRI induced AKI	PEG-AuNPs	Effect of PEG-AuNPs on RIRI induced AKI	PEG-AuNPs are a potential treatment for diabetic AKI triggered by IRI.
2024	Karimi et al [21]	Sprague–Dawley rats	RIRI induced AKI	Chitosan - NPs	Effects of a combination (TNG and chitosan – NPs) on RIRI induced AKI	A combination of TNG and Chitosan – NPs offered kidney protection from RIRI-induced AKI.
2024	Saiz et al [22]	In vivo Mice	In vivo Bilateral ischemia reperfusion injury(clamping both renal pedicles)	JQ1- NPs	Effects of BET inhibitor nanotherapy on kidney damage and CKD progression after RIRI	BET inhibitor-based nanotherapy showed protective effects against kidney damage and slowed the progression of CKD following RIRI.

		In vitro HK-2 cell	In vitro -			
2024	Guo et al [23]	In vivo (Male C57/B6 mice)	In vivo (RIRI)	Albumin - NPs	Effects of the Albumin -NPs on RIRI	Prolonged retention of albumin - NPs alleviates RIRI
		In vitro (TCMK-1 cells)	In vitro Hypoxia-Reoxygenation Model			

Nanoparticles(NPs), Renal ischemia/reperfusion injury (RIRI), Ischemia/reperfusion injury (IRI) ,Acute kidney injuri (AKI) Ferulic acid (FA) ,Zinc oxide nanoparticles (ZnO-NPs), Human kidney tubular epithelial cells (HK2), Renal tubular epithelial cells (RTEC), Thrombospondin-1(TSP-1), Ceria-NPs(CNPs), Milrinone (MIL), Mitochondria-targeted TPP CoQ10

nanoparticles (T-NPCoQ10), Small interfering RNA (siRNA), Folic acid (FA)-decorated polyamidoamine dendrimer generation 5 (G5-FA), Prolyl Hydroxylase Domain Protein 2(PHD2), Thrombospondin-1(TSP-1), Peptide which inhibits TSP-1 activation (LSKL), Neutrophil membrane-enveloped Coenzyme Q (N-NP CoQ10), IGF-1C nanoparticles (NP-IGF-1C), curcumin-carrying distearoy lphosphatidylethanolamine -polyethylene glycol nanoparticles (Cur-NPs), Berberine nanoparticles (BBR-NP), Polyethylene glycol capped gold nanoparticles (PEG-AuNPs), Adenosine5′ monophosphate–activated protein kinase nuclear factor erythroid-2-related factor- 2 (AMPK-Nrf2), Acute kidney injury (AKI), trinitroglycerine (TNG), Human Embryonic Kidney (HEK) 293, Mouse proximal tubular epithelial cells (TCMK-1), Chronic kidney disease (CKD), Extra-Terminal motif (BET).

Characteristics of studies conducted on the relationship between NPs utilization and IRRI are indicated in Table 3.

Table3: Characteristics of studies that show the positive point of treatment by nanoparticles for renal ischemia-reperfusion injury (RIRI)

Year	Ref.	Model of ischemia	Time of ischemia	Nanoparticle (dose or size)	Effective size/dose	Treatment duration by Nanoparticle	Measurement/ assayed factor(s)	Final Results	(Probable) Physiological/ pharmacological route(s) of action
2021	Awadalla et al [1]	Occlusion of left renal pedicle and Right nephrectomy 5 min before removal of the clamp	45 min	ZnO-NP 5 mg/Kg, i.p.	5 mg/Kg i.p.	2 hrs before ischemia	Cr, BUN, MDA, TNF-α, Bax, caspase-3, CAT, SOD, Expression of Nrf2, HO-1, HIF-1α genes and ki67	↓Cr and BUN	↑ Cell proliferation, ↓ Oxidative stress, ↑ (ki67), upregulation of antioxidant genes and downregulation of inflammatory cytokine and apoptotic genes upregulation of (Nrf2, HO-1 and HIF-1α) and downregulation of (TNF-α and caspase-3 and Bax).
2022	Zhou et al. [11]	Unilateral nephrectomy and contralateral	40 min	In vivo Ceria -NP		In vivo: 2 h before surgery	Cr, BUN, Histological analysis, Cytochrome c	↓Cr , BUN and MDA	In vivo: ↓Oxidative stress,

		renal vascular clamping		10 mg/kg i.v.	NP118 nm		quantification, Flow cytometry, MDA, Nrf2, macrophage infiltration	Improvement in Histological change. ↑Cytochrome c quantification	↓ RIRI induced inflammatory response, ↓ macrophage infiltration and polarization to M1 phenotype, Regulating the Nrf2 pathway, ↓ pro-inflammatory cytokine and chemokine production.
		In vitro serum-free condition followed by 2 h of standard condition (IR mimicking condition)		In vitro Ceria -NP 20 µg/mL		In vitro: 12 h			In vitro: ↓ Intracellular ROS production, ↓ lipopolysaccharide-induced inflammation in RAW264.7 cells
2023	Embaby et al. [12]	Unilateral RIRI and right nephrectomy	45 min	ZnO-NP (5, 7.5, and 10 mg/kg b.wt. i.p.)	10 mg/kg i.p.	2 h before RIRI induction	Cr, urea, GPx, CAT, and SOD activities, MDA and NO concentrations. TNF-α, NF-κB, KIM-1, NGAL, and caspase-3 Nrf2. renal lesions and fibrosis, vascular permeability	↓Cr and urea, Improvement in Histopathological change, Improvement in vascular permeability,	↓Oxidative stress, apoptosis ↑Antioxidant activity, ↑ GPx, CAT, and SOD activities, ↓ MDA and NO concentrations. ↓Renal expressions of TNF-α, NF-κB, KIM-1, NGAL, and caspase-3, ↑ Gene expressionNrf2 mRNA

								renal lesions and fibrosis.	
2021	Liu et al. [13]	bilaterally Renal hilum clamping	40 min	T-NPCoQ10	In vivo: 50 mg/kg	In vivo: 24 h before I/R surgery	In vivo: Plasma Cr, BUN, tubular injury score Protein carbonyl content, mtDNA damage, BAX, Caspase- 3, Bcl-2, and IL-1β, TNF-α, and IL-6,	↓Cr, BUN and tubular injury score ↓Protein carbonyl content	In vivo: ↓Oxidative injury in both cell and animal models, ↓ mtDNA damage, ↓ inflammatory and apoptotic responses, ↓BAX, Caspase- 3, Bcl-2, and IL-1β, TNF-α, and IL-6
		In vitro Oxygen-glucose deprivation	8-h		In vitro 5 μM	In vitro: incubation with T-NPCoQ10 for 2 h (according to methods)			In vitro: ↓ROS generation
							In vitro: ROS generation		
2021	Xie et al. [14]	Right kidney was removed, and the renal pedicle of left kidney was clipped by microvascular clamp	30 min	PHD2 siRNA G5-FA	7 mg siRNA/1 7.5 mg G5-FA per 10 g b.wt.	24 hours prior to I/R surgery.	PHD2 and GLUT1 mRNA, PHD2 protein, Cr /BUN Kidney Injury Molecule-1,	Improved Renal Function in RIRI, Mice. ↓ BUN and Cr in RIRI with PHD2 siRNA G5-FA group	G5-FA is a vector to deliver siRNA for local gene knock-down in kidney. ↓Majority of PHD2 expression in the kidney by G5-FA–mediated siRNA delivery due to selective targeting to the proximal tubules (↓ PHD2 mRNA and protein)

							Neutrophil Gelatinase-Associated Lipocalin, Histologic study, Hypoxia	↓Ttubular dilation, ↓loss of brush border, ↓vacuolar degeneration, ↓tubular necrosis, ↓cast formation in RIRI with PHD2 siRNA G5-FA group	↑mRNA Expression of HIF-1(Target Gene GLUT1) by silencing of PHD2 in Kidney ↓NGAL, KIM-1, and IL-1b levels in RIRI 1 PHD2 siRNA G5-FA group
2022	Hou et al. [15]	Left renal pedicle clamping for 28 min immediately following surgical removal of the right kidney	28 min Invitro	LSKL/NP	In vivo: 0.12 g/kg /bw In vitro:	In vivo: 3h after RIRI In vitro: 72 h	In vivo: renal lesion scoring, histology, IL-6 concentration, Cr	In vivo: ↓serum Cr, ↓Renal histologic lesions ↓Renal pathological scores	↓TSP-1production in the kidneys by LSKL/NPs (probably TSP-1 protein adsorbed on LSKL/NPs were rapidly taken up, and it failed to induce tubular epithelial cell death. TSP-1 adsorbed on LSKL/NPs and neutralized was incapable of signaling through CD47. ↓ TSP-1proteins out of the tissue, ↓TSP-1 concentration in IR kidneys by LSKL/NP recirculation

									↓Renal cell apoptosis ↓ IL-6
		Invitro: TSP-1 induced human renal tubular epithelial cell apoptosis					In vitro: Apoptosis	In vitro: ↓Apoptosis	In vitro ↓Total apoptotic cell
2020	Liu et.al. [16]	Bilaterally renal hilum clamping	40 min	N-NP CoQ10	In vivo: 50 mg/kg	In vivo: 24 h before I/R surgery	In vivo: Cr, BUN, IL-1 β, TNF- α, IL-6, BAX, Bcl-2, Caspase-3, SOD, GSH and MDA	In vivo: Improve renal function, ↓ Cr, BUN	In vivo: ↓Oxidative damage, ↓ Renal cell apoptosis, ↓ Inflammatory response, ↓IL-1 β, TNF- α, IL-6, MDA and BAX, Caspase-3, ↑ SOD, GSH, Bcl-2 protein
		Oxygen-glucose deprivation/reperfusion	In vitro 8 h.		In vitro:5 µM	In vitro: 24 h	In vitro: Apoptosis, mtDNA damage, Protein carbonyl content	In vitro: ↓Protein carbonyl content	In vitro: ↓Oxidative damage, ↓Cell apoptosis

								and mtDNA damage	
2022	Xu et al [17]	Both renal arteries clamping	45 min	NP-IGF-1C	In vivo: 200 µl	In vivo: 2 h before the operation and 24 h and 48 h after the operation	In vivo: serum Cr, BUN, KIM-1 and NAGL, CAT, MDA, GSH-Px, IL-6 and IL-10, Histopathological evaluation, Bax and Bcl-2	In vivo: ↑renal function, ↓serum Cr, BUN, Improved Histopathological evaluation,	In vivo: ↓ Inflammatory factors, oxidative stress, apoptosis and biomarkers of renal injury, ↓KIM-1 and NAGL, MDA, IL-6 and IL-10, ↑Antioxidant enzyme levels, ↑ CAT, GSH-Px, ↓Bax and ↑Bcl-2
		Oxygen-glucose deprivation/reperfusion	8 h						
					In vitro: …	In vitro: 24 h	In vitro: oxidative damage	In vitro: ↑Cell viability	In vitro: ↑Live-dead %
2016	Xu et al [18]	Cell cultured under ischemia and hypoxia	24 h	Cur-NP (81.93 ± 0.5 nm)	50 µM	24 h	Cell viability, caspase-3 and Bax, Bcl-2, increased SOD, apoptotic rate, reactive	Improved cell viability	Downregulated protein expression levels of caspase-3 and Bax, upregulated expression of Bcl-2 protein,

							oxygen species level, and MDA		↑ Antioxidant enzyme (↑SOD level), ↓ Apoptotic rate, ↓Reactive oxygen species level, and MDA
2017	Xie et al [19]	Right nephrectomy and left renal artery occlusion	In vivo 45 min	BBR-NP	4mg/kg	Six and 24 hours before RIRI	BUN and Cr, neutrophil infiltrations and tubular necrosis, MDA, cytoplasm Cyt-C, mitochondria Cyt-C, Caspase-3 and MMP,	↓BUN and Cr levels and neutrophil infiltrations and tubular necrosis	↓ Oxidative stress and apoptosis, Caspase-3 and MMP, MDA, cytoplasm Cyt-C, ↑ mitochondria Cyt- C
2022	Saleh et al [20]	Bilateral vascular pedicles clamping	30 min	PEG-AuNP 40 µg/kg 150 µg/kg 400 µg/kg	40 µg/kg 150 µg/kg 400 µg/kg	30 min earlier to ischemia and 5 min prior to reperfusion for 3 consecutive days	BUN, Cr, MDA, GSH, GPx, SOD, AMPK, PI3K, AKT, Nrf2, HO-1, IL-1β, and TNF-α	↓BUN, Cr and histological damage. ↓renal fibrosis ↑recovering of damaged renal cells, ↓Renal tubular atrophy, glomerular damage, mitochondrial	↓ Inflammatory cytokines, ↑ antioxidant system. ↓ Apoptosis ↓ MDA, TNF-α and IL-1β, upregulated the AMPK-Nrf2 pathway.

								damage, and necrotic area.	
2024	Karimi et al. [21]	Bilateral renal pedicles occlusion	60 min	Chitosan nanoparticles	60 (mg/kg)	30 min before renal ischemia	Oxidative stress, TAC, histopathological examination, Cr and BUN, GFR, urine flow rate	↑TAC ↓BUN and Cr ↓urine flow rate	Attenuated oxidative stress ↑GFR Corrected the renal histopathological changes
2024	Saiz et al. [22]	In vivo Bilateral IRI (clamping both renal pedicles)	In vivo 45 or 30 min (depending on the experimental set)	In vivo JQ1- NPs 10, 20, 30, and 40 mg/kg	In vivo 40 mg/kg	In vivo 1 h after surgery	In vivo BUN and Cr, Lcn2 and NGAL gene, KIM-1 Immune cells (neutrophils and monocytes) infiltration, Expression of proinflammatory cytokines genes	In vivo ↓BUN and Cr ↓neutrophils and monocytes	In vivo ↓Lcn2 and NGAL gene, ↓KIM-1 ↓Immune cells infiltration ↓Expression of proinflammatory cytokines genes

				In vitro JQ1- NPs 10,50, 250 and 500 nm				In vitro ↓IL6 and CCL2	In vitro ↓ Pro-inflammatory genes
							In vitro IL6 and CCL2		
		In vitro -	In vitro -		In vitro 500 nm	In vitro 1, 3, 6, 18, and 24 h			
2024	Guo et al. [23]	In vivo: Bilateral Ischemia-Reperfusion Surgery(pedicle was clamped with an artery clamp)	In vivo: 35 min	Albumin - NPs	In vivo: 10 mg/kg	In vivo: NP injection:1h After ischemia-reperfusion surgery Sampling: At 48 h postreperfusion	In vivo: BUN Cytokine Levels (IL-1β, IL-18) and LDH levels Pyroptosis effector molecule GSDMD and KIM-1	↓BUN ↓Cytokine Levels (IL-1β, IL-18) ↓LDH levels	↓Pyroptosis effector molecule GSDMD ↓KIM-1 Corrected the renal histopathological changes
		In vitro:	In vitro: 12 h.						

		Hypoxia-Reoxygenation Model					Histopathological examination		
					In vitro: (BSA@ DSF NPs) (1 μM)	In vitro: 2h	In vitro: Oxidative Stress GSDMD IL-1β and IL-18	In vitro: ↓IL-1β, IL-18	In vitro: ↓Pyroptosis cells ↓ GSDMD ↓Oxidative Stress

Nanoparticles (NPs), 46 nm (NP46), 81 nm (NP81), and 118 nm (NP118), Intravenous injection (i.v), Malondialdehyde (MDA), Total superoxide dismutase (T-SOD), Catalase (CAT) , Proliferation marker (ki67), Glutathione peroxidase (GSH-Px), kidney injury molecule-1 (KIM-1), Neutrophil gelatinase-associated lipocalin (NAGL), Blood Urea Nitrogen (BUN), Creatinine(Cr), Thrombospondin-1 (TSP-1), Peptide which inhibits TSP-1 activation (LSKL), Blood urea nitrogen (BUN), Creatinine (Cr), BAX (Apoptosis Regulator), glutathione(GSH), interleukin-1-beta (IL-1β), Tumor necrosis factor alpha (TNF-α), interleukin-6(IL-6), Nitric oxide(NO), Nuclear factor κ B (NF-κB), Hypoxia-inducible factor 1(HIF-1α), nuclear factor erythroid 2–related factor 2(Nrf2), Heme oxygenase 1(HO-1), hypoxia-inducible factor 1(HIF-1α), Mitochondrial DNA (mtDNA), Total antioxidative capacity (TAC), Neutrophil membrane-enveloped Coenzyme Q (N-NP CoQ10), Bovine serum albumin (BSA), Disulfiram (DSF). Folic acid (FA)-decorated polyamidoamine dendrimer generation 5 (G5-FA), Ischemia reperfusion injury (IRI).

DISCUSSION

Renal ischemia-reperfusion injury (RIRI) has increasingly been recognized as a major complication in various clinical scenarios. Despite its clinical relevance, therapeutic options to prevent or manage this condition remain inadequate. Recent comprehensive analyses have pointed to the promise of nanoparticle (NP)-mediated drug delivery systems, which provide numerous advantages such as targeted delivery, controlled drug release, chemical stability, and reduced toxicity [24, 25]. This review analyzed a range of nanoparticles including ZnO-NPs, Ceria-NPs, T-NPCoQ10, LSKL/NP, N-NP CoQ10, NP-IGF-1C, Cur-NPs, BBR-NPs, PEG-AuNPs, Albumin-NPs, Chitosan-NPs, JQ1-NPs, and G5-FA nanoparticles carrying PHD2 siRNA that have been studied in the context of RIRI.

Due to their unique physicochemical characteristics, nanomaterials exhibit enhanced biological interactions compared to their bulk counterparts. Properties like high surface area-to-volume ratios (e.g., in ZnO-NPs) [26, 27], good solubility, and sustained drug release (as observed in Cur-NPs) make them ideal for biomedical applications. Certain nanoparticles, such as Ceria-NPs, also exhibit enzyme-mimicking behavior, and their efficacy in immune modulation can be influenced by particle size highlighting the need to fine-tune NP dimensions for optimal therapeutic outcomes [11, 28]. Nanoparticles serve as effective carriers for delivering otherwise unstable therapeutic agents such as small molecule drugs and peptides, which are often rapidly degraded or cleared from the system. By encapsulating these agents, NPs enhance their bioavailability, reduce systemic toxicity, and improve drug targeting [29] demonstrated in formulations like G5-FA/PHD2 siRNA, LSKL/NPs, and NPCoQ10 [13-15].

Another factor that changes in renal ischemia is plasma urea and creatinine levels. Furthermore, RIRI often leads to elevated plasma creatinine and urea levels. Studies show that treatment with LSKL/NPs, BBR-NPs, ZnO-NPs, Albumin-NPs, JQ1-NPs, and Chitosan-NPs can significantly reduce these markers, indicating potential for renal protection [1, 12, 15, 19, 21, 22].

RIRI contributes significantly to illness and death by impacting several biological mechanisms, including oxidative stress, antioxidant defenses, inflammation, fibrosis, immune regulation, apoptosis, and gene expression.

Ischemia-reperfusion (I/R) events lead to a marked rise in malondialdehyde (MDA), an indicator of lipid peroxidation, while significantly lowering the activities of antioxidant defenses like TAC, GPx, CAT, and SOD in kidney tissues, compared to healthy controls and sham groups [12]. Research has shown that treatments with various nanoparticles such as ZnO-NPs, CNPs, T-NPCoQ10, BBR-NPs, PEG-AuNPs, NP-IGF-1C, Albumin-NPs, and Chitosan-NPs [1, 11-13, 17, 20, 21, 23] enhance antioxidant defenses by boosting Nrf2 and HO-1 levels, scavenging reactive oxygen species (ROS), and reducing MDA levels, thus offering renal protection from RIRI. Specifically, BBR-NPs inhibit the MMP-9 pathway, helping to counter oxidative and mitochondrial stress [19]. Moreover, pretreatment with these nanoparticles helps mitigate oxidative stress and enhance renal protection by promoting Nrf2 activation and improving antioxidant enzyme activity.

RIRI triggers a heightened expression of inflammatory markers such as TNF-α, NF-kB, IL-1β, and IL-18 in renal tissues.

Various nanoparticle treatments including PEG-AuNPs, NP-IGF-1C, LSKL/NPs, T-NPCoQ10, Albumin-NPs, JQ1-NPs, and ZnO-NPs have demonstrated anti-inflammatory properties in managing RIRI [1, 12, 13, 15, 17, 22, 23]. These nanoparticles reduce inflammation by decreasing macrophage infiltration, limiting the shift of macrophages to the M1 pro-inflammatory type, and lowering the production of inflammatory cytokines

and chemokines, leading to functional kidney recovery [11]. Additionally, certain NPs selectively target neutrophil-associated molecules to effectively reduce inflammation and improve kidney function during RIRI.

Several studies have reported elevated levels of apoptotic markers like caspase-3 and Bax as well as kidney injury indicators (KIM-1 and NGAL) in tissues affected by RIRI.

Treatments with T-NPCoQ10, BBR-NPs, NP-IGF-1C, N-NP CoQ10, Cur-NPs, and ZnO-NPs show anti-apoptotic effects by suppressing pro-apoptotic genes (Caspase-3 and Bax), enhancing anti-apoptotic gene Bcl-2 expression, and reducing cellular apoptosis in kidney tissues [1, 12-14, 16-18]. Moreover, JQ1-NPs and ZnO-NPs significantly lower NGAL and KIM-1 levels [12, 22]. Pretreatment with PEG-AuNPs also helps mitigate severe tissue damage, including necrosis and apoptosis, by activating phosphorylated AMPK, which plays a key role in preventing mitochondrial dysfunction and limiting excessive mitochondrial ROS production after RIRI [20].

limitations and future directions

The use of nanoparticles in the treatment of RIRI requires a thorough safety assessment. There are concerns about the potential toxicity, metabolism, and long-term effects of nanoparticles in the kidney. Nanoparticle toxicity can result from oxidative stress, inflammation, and cellular damage, which are influenced by their type, size, and structure. How these nanoparticles are metabolized and cleared from the body, particularly by the kidneys, is critical to preventing accumulation and chronic renal toxicity. The long-term outcomes of RIRI treatment with nanoparticles are not yet fully understood, and further research is needed to ensure their long-term safety and efficacy.

Conclussion

This systematic review investigated the role of nanoparticles (NPs) in relation to RIRI. The reviewed studies consistently showed that RIRI is associated with increased inflammatory cytokines, heightened oxidative stress, elevated levels of serum creatinine and urea nitrogen, and suppressed antioxidant defense mechanisms. Various types of nanoparticles have demonstrated the ability to influence these pathological pathways, highlighting their potential therapeutic impact. These findings are crucial for informing policymakers about the benefits of integrating nanoparticle-based interventions in managing RIRI.

Acknowledgment

We acknowledge the assistance of Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran during the process of this study.

Author Contribution

planned conducting the study, methodology, investigation, supervision, writing– review & editing were performed by MKh and MM. writing – review & editing were performed by AA and MRK. All authors read and approved the final manuscript.

Ethical approval

This study was a systematic review and did not use laboratory animals or human data in a laboratory manner and has an ethical code (Ethics ID: IR. MEDILAM.REC.1402./240) from Ilam University of Medical Sciences**.**

Funding

Grant NO: IR. MEDILAM.REC. 1402./240 from Ilam University of Medical Sciences**.**

Informed consent

Not applicable.

Competing interest

The authors declare no conflict of interests in this study.

References

1. Awadalla A, Hussein AM, Yousra M, Barakat N, Hamam ET, El-Sherbiny M, et al. Effect of zinc oxide nanoparticles and ferulic acid on renal ischemia/reperfusion injury: possible underlying mechanisms. Biomed Pharmacother. 2021;140:111686. doi: 10.1016/j.biopha.2021.111686
2. AA S. Pathophysiology of ischemic acute kidney injury. Nat Rev Nephrol. 2011;7:189-200. doi: 10.1038/nrneph.2011.16
3. Ali ES, Sharker SM, Islam MT, Khan IN, Shaw S, Rahman MA, et al., editors. Targeting cancer cells with nanotherapeutics and nanodiagnostics: Current status and future perspectives. Semin Cancer Biol. 2021: Elsevier. doi: 10.1016/j.semcancer.2020.01.011
4. Gupta RB, Kompella UB. Nanoparticle technology for drug delivery: CRC Press; 2006.
5. Li F, Qiu Y, Xia F, Sun H, Liao H, Xie A, et al. Dual detoxification and inflammatory regulation by ceria nanozymes for drug-induced liver injury therapy. Nano Today. 2020;35:100925. doi:10.1016/j.nantod.2020.100925
6. Liang C, Fang J, Hu J, Geng X, Liu H, Feng Y, et al. Toxicokinetics of zinc oxide nanoparticles and food grade bulk-sized zinc oxide in rats after oral dosages. NanoImpact. 2022;25:100368. do: 10.1016/j.impact.2021.100368
7. Mishra PK, Mishra H, Ekielski A, Talegaonkar S, Vaidya B. Zinc oxide nanoparticles: a promising nanomaterial for biomedical applications. Drug discover today. 2017;22(12):1825-34. doi: 10.1016/j.drudis.2017.08.006
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1-9. doi: 10.1186/2046-4053-4-1
9. Maleki M, Noorimotlagh Z, Mirzaee SA, Jaafarzadeh N, Martinez SS, Rahim F, et al. An updated systematic review on the maternal exposure to environmental pesticides and involved mechanisms of autism spectrum disorder (ASD) progression risk in children. Rev Environ Health. 2023;38(4):727-40. doi: 10.1515/reveh-2022-0092
10. Maleki M, Aliboroni A, Kheiri A, Kaffashian MR, Kheiry M. Association of the ACE2-Angiotensin1-7–Mas axis with lung damage caused by cigarette smoke exposure: a systematic review. Rev Environ Health. 2024;39(4):755-63. Doi: 10.1515/reveh-2023-0028
11. Zhou L, Tang S, Li F, Wu Y, Li S, Cui L, et al. Ceria nanoparticles prophylactic used for renal ischemia-reperfusion injury treatment by attenuating oxidative stress and inflammatory response. Biomater. 2022;287:121686. doi: 10.1016/j.biomaterials.2022.121686
12. Embaby EM, Saleh RM, Marghani BH, Barakat N, Awadin W, Elshal MF, et al. The combined effect of zinc oxide nanoparticles and milrinone on acute renal ischemia/reperfusion injury in rats: Potential underlying mechanisms. Life Sci. 2023;323:121435. doi: 10.1016/j.lfs.2023.121435
13. Liu Z, Li Y, Li C, Yu L, Chang Y, Qu M. Delivery of coenzyme Q10 with mitochondria-targeted nanocarrier attenuates renal ischemia-reperfusion injury in mice. Mater Sci Eng C. 2021;131:112536. doi: 10.1016/j.msec.2021.112536
14. Xie D, Wang J, Hu G, Chen C, Yang H, Ritter JK, et al. Kidney-targeted delivery of prolyl hydroxylase domain protein 2 small interfering RNA with nanoparticles alleviated renal ischemia/reperfusion injury. J Pharmacol Exp Ther. 2021;378(3):235-43. doi: 10.1124/jpet.121.000667
15. Hou Y, Xin Y, Liu S, Li Y, Meng X, Wang J, et al. A biocompatible nanoparticle-based approach to inhibiting renal ischemia reperfusion injury in mice by blocking thrombospondin-1 activity. Am J Transplant. 2022;22(9):2246-53. doi: 10.1111/ajt.17052
16. Liu Z, Liu X, Yang Q, Yu L, Chang Y, Qu M. Neutrophil membrane-enveloped nanoparticles for the amelioration of renal ischemia-reperfusion injury in mice. Acta Biomater. 2020;104:158-66. doi: 10.1016/j.actbio.2020.01.018
17. Xu M, Zhao M, Zheng D. Effect of IGF-1C domain-modified nanoparticles on renal ischemia–reperfusion injury in mice. Renal Fail. 2022;44(1):1377-88. doi: 10.1080/0886022X.2022.2098773
18. Xu Y, Hu N, Jiang W, Yuan H-F, Zheng D-H. Curcumin-carrying nanoparticles prevent ischemia-reperfusion injury in human renal cells. Onco target. 2016;7(52):87390. doi. 10.18632/oncotarget.13626
19. Xie D, Xu Y, Jing W, Juxiang Z, Hailun L, Yu H, et al. Berberine nanoparticles protects tubular epithelial cells from renal ischemia-reperfusion injury. Onco target. 2017;8(15):24154. doi: 10.18632/oncotarget.16530
20. Saleh H, Salama M, Hussein RM. Polyethylene glycol capped gold nanoparticles ameliorate renal ischemia–reperfusion injury in diabetic mice through AMPK-Nrf2 signaling pathway. Environ Sci Pollut Res Int. 2022;29(51):77884-907. doi :10.1007/s11356-022-21235-5
21. Karimi Z, Asadi K, Ghahramani P, Gholami A. Trinitroglycerine-loaded chitosan nanoparticles attenuate renal ischemia-reperfusion injury by modulating oxidative stress. Sci Rep. 2024;14(1):32112.
22. Saiz ML, Lozano-Chamizo L, Florez AB, Marciello M, Diaz-Bulnes P, Corte-Iglesias V, et al. BET inhibitor nanotherapy halts kidney damage and reduces chronic kidney disease progression after ischemia-reperfusion injury. Biomed Pharmacother. 2024;174:116492. doi: 10.1016/j.biopha.2024.116492
23. Guo L, Wang H, Liu X, Liu Q, Zhang J, Ding D, et al. Prolonged Retention of Albumin Nanoparticles Alleviates Renal Ischemia-Reperfusion Injury through Targeted Pyroptosis. ACS Appl Mater Interfaces.2024;16(44):59921-33. doi: 10.1021/acsami.4c13481

24. Mou X, Ali Z, Li S, He N. Applications of magnetic nanoparticles in targeted drug delivery system. J Nanosci Nanotechnol. 2015;15(1):54-62. Doi: 10.1166/jnn.2015.9585
25. Sahoo N, Sahoo RK, Biswas N, Guha A, Kuotsu K. Recent advancement of gelatin nanoparticles in drug and vaccine delivery. Int J Biol Macromol. 2015;81:317-31. doi: 10.1016/j.ijbiomac.2015.08.006
26. Heng BC, Zhao X, Tan EC, Khamis N, Assodani A, Xiong S, et al. Evaluation of the cytotoxic and inflammatory potential of differentially shaped zinc oxide nanoparticles. Arch Toxicol. 2011;85:1517-28. doi: 10.1007/s00204-011-0722-1
27. Patil RM, Thorat ND, Shete PB, Bedge PA, Gavde S, Joshi MG, et al. Comprehensive cytotoxicity studies of superparamagnetic iron oxide nanoparticles. Biochem Biophys Rep. 2018;13:63-72.doi: 10.1016/j.bbrep.2017.12.002
28. Niikura K, Matsunaga T, Suzuki T, Kobayashi S, Yamaguchi H, Orba Y, et al. Gold nanoparticles as a vaccine platform: influence of size and shape on immunological responses in vitro and in vivo. ACS nano. 2013;7(5):3926-38. doi:10.1021/nn3057005
29. Spicer CD, Jumeaux C, Gupta B, Stevens MM. Peptide and protein nanoparticle conjugates: versatile platforms for biomedical applications. Chem Soc Rev. 2018;47(10):3574-620.