DOI: 10.15825/1995-1191-2026-1-181-196

CURRENT ISSUES IN THE PREVENTION AND MANAGEMENT OF OXIDATIVE STRESS IN ACUTE RENAL ISCHEMIC-REPERFUSION INJURY

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Renal ischemia–reperfusion injury (IRI), which develops during organ-preserving kidney surgery and particularly during kidney transplantation (KT), remains a major challenge in urology and transplantology, as it can lead to progression of acute kidney injury and chronic graft dysfunction. Conservative strategies aimed at minimizing oxidative stress are especially important in situations where surgical options are limited. In transplantology, IRI is of particular relevance, as KT is the treatment of choice for patients with end-stage renal disease, significantly improving both quality of life and survival compared with renal replacement therapy. A critical stage of the transplantation procedure involves donor organ ischemia (warm and cold), followed by reperfusion after restoration of blood flow in the recipient. The severity of IRI directly influences graft function and is a key risk factor for delayed graft function and acute rejection [1, 2]. Therefore, the search for effective the search for to prevent and correct IRI is critical to improving kidney transplant outcomes. **Objective** to systematize current knowledge on the potential of conservative methods for correcting renal IRI caused by excessive reactive oxygen species (ROS) during organ-preserving kidney surgery and KT under conditions of warm ischemia. **Methods.** A systematic analysis of literature published over the past 10 years was conducted using the PubMed search engine, the Cochrane Library database of evidence-based medicine, and the Scopus unified bibliographic and abstract database of peer-reviewed scientific literature. Particular emphasis was placed on randomized studies evaluating drugs or newly synthesized compounds that suppress ROS formation and restore or enhance the body's antioxidant capacity. **Conclusion.** At the current stage of medical science, considerable attention is focused on substances capable of blocking the molecular mechanisms involved in mitochondrial membrane pore opening, as well as on agents that suppress ROS formation through inhibition of NADPH oxidase and xanthine oxidase. The therapeutic potential of exogenous enzyme preparations (such as superoxide dismutase and catalase), low-molecular-weight catalytic ROS scavengers, and non-enzymatic antioxidants – including supraphysiological doses of ascorbic acid and mitochondria-targeted agents such as mitoquinone and elamipretide – is actively being investigated. In the future, the results of these studies may form the basis for the development of effective antioxidant strategies for the prevention and treatment of renal IRI during organ-preserving kidney surgery and transplantation.

Keywords: renal ischemia–reperfusion injury, reactive oxygen species, oxidative stress, antioxidant protection, kidney transplantation.

1. INTRODUCTION

In urological surgery, acute renal ischemia–reperfusion injury (IRI) is an anticipated consequence of organ-preserving kidney procedures. Such injury may occur during surgical management of benign renal tumors, selected cystic kidney lesions, renal echinococcosis, nephrolithiasis refractory to conservative treatment, nephrotuberculosis, traumatic injury to the renal parenchyma, and, most commonly, localized renal cell carcinoma [3–7].

The issue of renal IRI is equally significant in transplantology. Kidney transplantation (KT) remains the treatment of choice for patients with end-stage chronic kidney disease, offering substantial improvements in both quality of life and survival compared with long-term renal replacement therapy [8, 9]. A critical phase of transplantation involves ischemia of the donor organ – both warm and cold – followed by reperfusion after restoration of blood flow in the recipient. The severity of renal IRI has a direct impact on graft function and represents a major risk factor for delayed graft function and acute rejection [1, 2, 10].

Therefore, the search for effective strategies for prevention and mitigation of renal IRI is critical to impro-

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ving outcomes in both kidney resection and transplantation.

The immediate cause of IRI is the restoration of renal blood flow after a period of suspension. Temporary cessation of perfusion is required during surgery to prevent intraoperative parenchymal bleeding when resecting the affected renal segment or constructing vascular anastomoses. Thus, reperfusion is preceded by warm ischemia induced by clamping the renal artery. Although both ischemia and subsequent reperfusion are essential steps in the surgical procedure – first minimizing blood loss and then restoring organ perfusion – they also initiate a cascade of mechanisms leading to renal tissue injury.

During ischemia, the primary injurious factor is hypoxia (or anoxia), whereas reperfusion introduces normoxic conditions that paradoxically exacerbate tissue injury. The consequences of primary injury and the principal mechanisms of secondary cellular alteration include: 1) Under hypoxic conditions – cellular hypoergia due to impaired ATP production, dysfunction of ATP-dependent ion pumps, and increased generation of reactive oxygen species (ROS), activating free radical–mediated damage to proteins, lipids, carbohydrates, nucleic acids, mitochondria, and cell membranes; 2) Upon reperfusion – an even more pronounced, "avalanche-like" overproduction of ROS.

Subsequent downstream injury mechanisms involve increased permeability of cellular and organelle membranes (including lysosomal membrane destabilization with release of proteolytic enzymes), alterations in redox balance, mitochondrial structural and functional impairment, disturbances in ionic homeostasis (particularly potassium and calcium), metabolic acidosis, and cellular swelling. Edematous cells may compress adjacent microvessels, leading to microcirculatory disorders.

These changes represent a universal, nonspecific cellular response to injury and occur in virtually all cell types, including renal parenchymal cells (nephrocytes), regardless of whether the initiating insult is ischemia or reperfusion [11–13].

2. PATHOGENESIS OF RENAL ISCHEMIC-REPERFUSION INJURY

Ischemia and subsequent reperfusion during organ-preserving renal surgery and KT represents one of the leading causes of acute kidney injury in the early postoperative period [14–16]. The predominant structural damage affects the nephron, particularly the tubular epithelial cells [17]. Over time, this injury may contribute to progression of chronic kidney disease and ultimately chronic renal failure [18–22].

The principal mediators of tissue injury during ischemia and reperfusion are ROS – electrically unstable and highly reactive molecules capable of damaging cellular structures. The primary sources of ROS include the mitochondrial electron transport chain (ETC), as well as enzymatic reactions catalyzed by xanthine oxidase (XO), nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), myeloperoxidase (MPO), and others.

Under conditions of excessive ROS generation – particularly during reperfusion – the imbalance between prooxidant production and antioxidant defense leads to oxidative stress, which plays a central role in cellular and tissue injury. Accordingly, two principal pharmacological strategies are distinguished in the prevention and correction of IRI: 1) Reduction or suppression of ROS production by targeting the mitochondrial ETC and inhibiting ROS-generating oxidases; 2) Neutralization and elimination of ROS by restoring or enhancing the endogenous antioxidant defense system of the cell and extracellular environment [23].

3. MAIN TARGETS FOR PHARMACOLOGICAL CORRECTION OF OXIDATIVE STRESS IN RENAL IRI

3.1. Suppression of the formation of reactive oxygen species

3.1.1. Inhibition of mitochondrial permeability transition pore (mPTP) opening

Under physiological conditions, ETC is responsible for generating up to 90% of all reactive oxygen species (ROS) as metabolic by-products [23, 24]. During ischemia – and particularly upon reperfusion – ROS production increases dramatically. This surge, combined with ischemia–reperfusion–induced disorders in ATP biosynthesis and intracellular calcium homeostasis, promotes the formation of pores at contact sites between the inner and outer mitochondrial membranes. These pores, known as mitochondrial permeability transition pores (mPTP), alter mitochondrial membrane permeability [25–30].

The formation of mPTP leads to further disruption of ionic homeostasis, especially calcium balance, and impairs the energy-synthesizing function of mitochondria. At the same time, it sustains and amplifies ROS generation, thereby perpetuating a vicious cycle of mitochondrial dysfunction. Persistent and uncontrolled mPTP opening can ultimately trigger mitochondrial-dependent apoptotic pathways, contributing to irreversible cell injury.

As defined by Zhou et al. (2023), the opening of mPTP "is a major determinant of mitochondrial dysfunction to induce cellular damage or death" [31]. In light of current evidence, pharmacological inhibition of mPTP opening represents one of the most promising therapeutic strategies for the prevention and mitigation of IRI [32–34].

MPTP is a multiprotein complex that includes the voltage-dependent anion channel (VDAC, also known as porin), the adenine nucleotide translocator (ANT), the peripheral benzodiazepine receptor, and the chaperone protein cyclophilin-D (CypD), one of the 18 known human cyclophilins. Among these components, CypD –

also referred to as peptidyl-prolyl cis-trans isomerase F – plays a central regulatory role in controlling mPTP opening from the inner mitochondrial membrane [35].

Fayaz et al. (2015) metaphorically described cyclophilin-D as "the key to the death door" [36]. Accordingly, pharmacological inhibition of CypD activity is a rational strategy for preventing mPTP opening in pathological conditions associated with mitochondrial dysfunction [37], including renal IRI [38].

One of the earliest agents identified as a CypD inhibitor was cyclosporin A (CsA), a calcineurin inhibitor. CsA is a neutral, lipophilic cyclic undecapeptide composed of 11 amino acids, with a molecular weight of 1202.6 Da, and exhibits high affinity for cyclophilins. Since the early 1980s, it has been widely used as an immunosuppressive and immunomodulatory agent in immunology, transplantology, and oncology [39, 40].

Preclinical studies are currently underway to investigate the potential role of CsA in the treatment of renal IRI. In experimental models of renal IRI in small laboratory animals – typically involving unilateral nephrectomy followed by 30 minutes of occlusion of the renal artery supplying the contralateral kidney and subsequent reperfusion for 60–90 minutes – several protective effects of CsA have been reported. Postconditioning with CsA has been shown to attenuate renal damage caused by IRI [41]. Specifically, CsA administration enhances the calcium retention capacity of renal mitochondria and improves oxidative phosphorylation following reperfusion, although these effects appear to be dose- and time-dependent [42]. In rat models, CsA treatment has also been associated with reduced apoptotic cell counts, decreased severity of microstructural alterations in renal tissue, preservation of tubular epithelial cell viability, and maintenance of overall renal function [43, 44].

However, these findings are not universally supported. For example, Lee et al. (2015) reported evidence of CsA-associated nephrotoxicity, including cytoplasmic vacuolization in glomerular endothelial cells, reduced glomerular size, and a marked decrease in renal blood flow during reperfusion [45]. Similarly, Oliveira et al. (2019), assessing serum creatinine, urea, sodium levels, and histopathological changes in a rat model of 30-minute renal ischemia followed by reperfusion, concluded that "CsA was incapable of preventing the deleterious effects of ischemia-reperfusion injury in rat kidneys" [46].

Briston et al. (2019) attributed the inconsistent and often negative outcomes of preclinical evaluations of CsA to its narrow therapeutic window and the challenges associated with precise dosing, in addition to its inherent nephrotoxic and immunosuppressive properties. This limitation was also highlighted in studies investigating the cardioprotective activity of CsA in myocardial IRI, where the difference between concentrations yielding beneficial effects and those producing adverse outcomes did not exceed 0.2 μM.

Furthermore, it was found that inactivation of CypD does not completely prevent the opening of mPTP but rather delays it until more severe disturbances in intracellular calcium homeostasis develop.

Despite these limitations, inhibition of mPTP opening remains a therapeutically relevant and promising strategy, necessitating the development of alternative approaches [47]. Current research in this area is progressing along two main directions. The first involves the development of novel CypD inhibitors, including derivatives of CsA and sanglifehrin A, as well as small-molecule, non-peptide, low-molecular-weight cyclophilin inhibitors. The second focuses on identification and development of compounds capable of inactivating mPTP through CypD-independent mechanisms [47, 48].

As noted by Briston et al. (2019), advances in these areas could significantly reshape therapeutic strategies not only for IRI but also for a broad spectrum of diseases in which mPTP opening plays a central role in pathogenesis [47].

3.1.2. Inhibition of NADPH oxidases (NOX)

NOX are a family of enzymes that catalyze the formation of the coenzyme NADP+ from NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) in the reaction of NADPH with molecular oxygen. The products of the reaction, in addition to NADP+, are atomic hydrogen and the superoxide anion radical $O_2^{\cdot -}$. The generated superoxide in turn, induces the formation of other ROS.

NOX are expressed and localized in all cells capable of phagocytosis (monocytes and macrophages, neutrophils, eosinophils, labrocytes), their biological role is associated with the ability to generate $O_2^{\cdot -}$ and consists in the implementation of phagocytic defense as such.

In addition, these enzymes may be present in non-phagocytic cells – the so-called non-phagocytic constitutively active NOX, which are always present in the cell, constantly forming $O_2^{\cdot -}$ and, thereby participating in the regulation of cell proliferation and differentiation, as well as the processes of expression of certain genes at the transcription stage.

NOX exist in the form of several isoforms, among which there are 5 multiprotein NOX complexes (NOX-1–NOX-5) and 2 DUOX dual oxidase complexes (DUOX 1 and 2). NOX consists of four cytosolic and two membrane subunits. Phagocytic NOX are activated through the fusion of membrane and cytosolic components after the latter are translocated to the plasma membrane. The membrane subunits (gp91phox and p22phox) determine the catalytic properties of the activated enzyme, whereas the cytosolic subunits (p47phox, p67phox, p40phox, Rac) perform mainly regulatory functions [49–55].

In the ischemic region, phagocytosis of molecular and cellular structures altered and/or destroyed as a result of oxygen deprivation naturally triggers the activation of

phagocytic NOX, leading to the formation of $O_2^{\cdot-}$ and other ROS. Under conditions of subsequent reperfusion, the generation of ROS increases exponentially, accompanied by intensified free radical damage to nucleic acids, proteins, and lipids, formation of new phlogogens, recruitment of additional phagocytic cells, and further amplification of ROS production. These processes ultimately result in the establishment of a vicious cycle underlying the mechanisms of IRI [56, 57].

Consequently, suppression of ROS formation through NOX inhibition may be a relevant strategy for the prevention and treatment of diseases associated with oxidative stress, including various forms of IRI [58–61].

Apocynin (acetovanillin, 4-hydroxy-3-methoxyacetophenone), an aromatic compound of plant origin, first described in 1883 by German pharmacologist Oswald Schmiedeberg, and diphenylenedione chloride, an aromatic halogen-containing compound, were among the first substances for which NOX inhibitory properties were confirmed. The mechanism of action of apocynin is associated with its ability to inhibit NOX activation by blocking the translocation of the cytosolic subunits p47phox and p67phox to the membrane, whereas diphenylenedione chloride limits the electron transfer function of NOX enzymes.

However, as noted in the review by Wu et al. (2018), both substances possess additional biological activities, including antioxidant effects and can inhibit nitric oxide synthesis, xanthine oxidase, cytochrome P450 reductase, and mitochondrial enzymes. Consequently, it is difficult to unequivocally attribute the protective effects of apocynin and diphenylenedione chloride against IRI solely to inhibition of the NOX enzyme [62].

According to Chokri et al. (2020), over the past decade, several thousand molecules with presumed NOX-inhibitory activity have been screened. From these studies, a number of compounds demonstrating actual inhibitory effects have been identified and classified according to their degree of specificity toward individual NOX isoforms, ranging from low to highly selective [63]. Examples include APX-115 (3-phenyl-1-(pyridin-2-yl)-4-propyl-1-5-hydroxypyrazole HCl), an orally administered compound that has shown nephroprotective activity in experimental models of diabetic kidney injury in mice [64]; NOS31, produced by Streptomyces sp., which selectively inhibits NOX-1 activity [65]; and GLX7013114, a selective NOX-4 inhibitor [66], among others. Among the compounds currently investigated for potential clinical use as NOX inhibitors, only one – GKT137831, a direct inhibitor of NOX-1 and NOX-4 – has advanced to clinical trials [67], but the results have not yet been published.

3.1.3. Inhibition of xanthine oxidase

During ischemia and reperfusion, ROS are generated through the xanthine oxidase reaction involved in purine nucleotide catabolism. Under hypoxic conditions, suppression of ATP biosynthesis occurs alongside an increase in intracellular calcium levels. This rise in Ca^{2+} activates Ca^{2+}-dependent proteases, which induce partial proteolysis of xanthine dehydrogenase – an enzyme that normally catalyzes the formation of uric acid from xanthine under physiological conditions. As a result of this proteolytic modification, xanthine dehydrogenase is irreversibly converted into xanthine oxidase (XO). The XO enzyme subsequently catalyzes the conversion of xanthine to uric acid with simultaneous formation of the superoxide anion radical ($O_2^{\cdot-}$).

At present, the xanthine oxidase reaction is considered one of the principal sources of superoxide generation during oxygen deprivation and subsequent reoxygenation [68]. Consequently, the XO enzyme is a promising pharmacological target for the prevention and mitigation of IRI through the use of XO inhibitors.

Currently available inhibitors of xanthine oxidase include Allopurinol, Oxypurinol (alloxanthine), Febuxostat, and Topiroxostat [69]. These drugs are widely used in clinical practice for the treatment and prevention of hyperuricemia of various origins and gout. However, the feasibility, efficacy, and safety of their use for the prevention and treatment of IRI remain under study.

Allopurinol (a structural isomer of hypoxanthine, a natural endogenous purine) and oxypurinol (a primary metabolite of allopurinol), as pharmacological agents capable of limiting ROS formation through inhibition of xanthine oxidase during renal ischemia–reperfusion, have been investigated in experimental studies by Eremina et al. (2024), Choi et al. (2015), Prieto-Moure et al. (2017), Kang et al. (2023), and Soliman et al. (2023), among others. In these preclinical randomized controlled studies, renal IRI in small laboratory animals (rats or mice) was modeled by subjecting one kidney to approximately 30 minutes of total ischemia while performing nephrectomy of the contralateral kidney. The efficacy of the investigated drugs was evaluated using histological analyses aimed at identifying structural changes in renal tubules and apoptotic cells, together with assessments of renal function, severity of oxidative stress and inflammatory responses, and immunological parameters. The findings of these studies demonstrated the clear therapeutic potential of allopurinol and oxypurinol in reducing renal IRI [70–74].

The nephroprotective properties of febuxostat under conditions of renal ischemia and subsequent reperfusion were investigated by Tsuda et al., with the results published in 2012. The study was conducted on Sprague–Dawley rats and included a control group, a placebo group, and a group treated with febuxostat. According to the findings, animals receiving febuxostat showed significantly lower levels of xanthine oxidase activity and oxidative stress compared with those in the control and placebo groups. Oxidative stress was assessed by

measuring urinary levels of nitrotyrosine, thiobarbituric acid, and 8-isoprostane. In addition, febuxostat-treated animals exhibited improved renal function – evidenced by lower serum creatinine and urea levels – together with reduced tubular damage, a weaker monocyte–macrophage inflammatory response, and fewer apoptotic tubular epithelial cells based on histological examination. As noted by Tsuda et al., these findings collectively indicate the protective potential of febuxostat and support further investigation of this agent as a potential drug for renal protection during IRI [75].

3.2. Neutralization of reactive oxygen species and enhancement of antioxidant protection

Among pharmacological agents capable of neutralizing or removing ROS from the body's internal environment, two major groups are distinguished: enzymatic and non-enzymatic antioxidant drugs [76].

3.2.1. Use of enzymatic antioxidants (SOD, catalase) and their mimetics

Enzymatic antioxidant agents include exogenously administered synthetic analogues of endogenous enzymes that constitute the cellular antioxidant defense system. These enzymes – such as superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferases, thioredoxins, and peroxiredoxins – play a key role in regulating free radical oxidation processes under physiological conditions [77].

Superoxide dismutase (SOD) catalyzes the conversion of the superoxide anion radical into molecular oxygen and hydrogen peroxide according to the reaction: $2H^+ + 2O_2^{\cdot -} \rightarrow O_2 + H_2O_2$. Subsequently, catalase (CAT) decomposes hydrogen peroxide into water and molecular oxygen: $2H_2O_2 \rightarrow 2H_2O + O_2$. Both enzymes are highly specific.

Based on the metal cofactors present in their active sites, SOD isoforms in the human body are classified into copper/zinc-containing SOD (Cu/Zn-SOD) and manganese-containing SOD (Mn-SOD). The enzymatic antioxidant activity of SOD was first described in 1968 by Irwin Fridovich and Joe McCord. Shortly thereafter, research into SOD-based therapeutics began, with their clinical potential being actively explored from the late 1980s.

Initial sources of SOD-based preparations were animal tissues and organs. Subsequently, alternative production methods were developed, including microbiological synthesis [78] using specific strains of yeast, yeast-like fungi, and bacteria, as well as genetic engineering techniques [79, 80]. These methods enabled the isolation of SOD from microbial cells followed by purification using chromatographic techniques [81].

Certain plants also serve as SOD sources, including some melon varieties [82], Rauvolfia serpentina [83], and Scots pine seedlings [84], among others. However, native SOD preparations exhibit limited stability and low resistance to proteolysis, with a circulating half-life of no more than 6 minutes. This limitation was recognized soon after methods for isolating SOD from animal and plant tissues were developed. It was precisely this circumstance at that time (the late 1980s and 1990s) that was linked to the highly inconsistent results observed in experimental studies evaluating the therapeutic potential of native (natural) SOD in animal models of IRI affecting various tissues and organs, including the kidneys. Subsequently, more stable and long-acting formulations were developed, including modified forms created by conjugating native SOD with polyethylene glycol (PEG). In addition, low-molecular-weight compounds that mimic the antioxidant activity of SOD – so-called SOD mimetics, which are synthetic metal complexes capable of selectively catalyzing the *in vivo* neutralization of superoxide anion ($O_2^{\cdot -}$) to form hydrogen peroxide and molecular oxygen – were introduced [85].

As noted by R.G. Goncharov et al. (2023), evidence from specialized medical journals supports the efficacy of exogenous PEG-modified Cu/Zn-SOD in experimental models of IRI affecting skeletal muscle, heart, brain, and liver [86]. Investigations into the effects of native and conjugated SOD preparations in renal IRI began in the late 1980s, with findings reported in studies published between 1985 and 1996 (identified through PubMed database searches). All of these studies were experimental, and most concluded that SOD preparations exert a protective effect, significantly reducing the risk and severity of acute kidney injury associated with renal ischemia–reperfusion.

Despite these encouraging findings from the final decades of the 20th century, this line of research has seen limited advancement since the early 2000s. In this regard, Veronese et al. (2002) observed that both native and PEG-conjugated SOD reduce reperfusion injury in renal and hepatic ischemia. Notably, they highlighted the paradox that, despite a substantial body of positive experimental evidence supporting PEG-SOD, no clinically approved therapeutic applications for humans had been developed at the time [87]. Meanwhile, SOD represents the principal enzymatic defense against the damaging effects of the superoxide anion ($O_2^{\cdot -}$) in living organisms [88]. As noted in the literature, "…*despite limitations, the SOD enzyme has proved as a powerful tool against diseases, and various forms of conjugates and mimetics have been developed and reported to make it more efficient. Extensive studies are needed in this direction for use of natural SOD-based therapeutics for the prevention and cure of diseases*…" (P. Saxena et al., 2022) [89].

During the 1980s and 1990s, and into the early 2000s, several classes of catalytic ROS scavengers were develo-

ped. These compounds, designed as functional mimetics of SOD and CAT, include manganese-based complexes with selenium, porphyrins, corrole derivatives, and non-aromatic macrocycles. Many of these agents are capable of simultaneously neutralizing both superoxide anion radicals and hydrogen peroxide. While they exhibit broadly comparable SOD-like activity, their catalase-like activity varies depending on structural modifications; for example, the EUK-8 derivative (manganese N,N-bis(salicylidene)ethylenediamine chloride) demonstrates notably enhanced catalase activity [90–96].

The therapeutic potential of several of these compounds in renal IRI has been demonstrated in experimental studies by Gianello et al. (1996), Chatterjee et al. (2004), and others [97, 98]. More recent research has focused on improving existing compounds and developing new manganese-based complexes with novel ligands that function as highly efficient catalytic ROS scavengers and dual SOD/CAT mimetics. Numerous studies have described their biosynthesis, molecular structure, physicochemical properties, and antioxidant activity, supporting their potential for preclinical evaluation as pharmacological agents for the prevention and treatment of IRI in various organs, including the kidneys [99–109].

3.2.2. Use of non-enzymatic antioxidants (ascorbic acid, α-tocopherol, N-acetylcysteine)

As part of ongoing efforts to prevent and treat the consequences of IRI, including in the kidneys, increasing attention is being given to the therapeutic potential of non-enzymatic antioxidant agents. These include ascorbic acid, α-tocopherol, and N-acetylcysteine, as well as mitochondria-targeted compounds such as mitoquinone and elamipretide.

According to Spoelstra-de Man et al. (2018), recent years have seen growing interest in the potential use of ascorbic acid for the pharmacological management of IRI. Its antioxidant efficacy is attributed to its ability to scavenge peroxynitrites (ONOO), hypochlorous acid (HOCl), and superoxide anion radicals. In addition, ascorbic acid inhibits the activity of xanthine oxidase and NADPH oxidases, and facilitates the regeneration of key molecules such as α-tocopherol and tetrahydrobiopterin from dihydrobiopterin. It also supports endothelial nitric oxide synthase function, thereby enhancing nitric oxide bioavailability in the vascular endothelium, among other protective effects [110].

According to studies by Fowler et al. (2014), Zabet et al. (2016), Marik et al. (2016), and others, parenteral administration of high (supraphysiological) doses of vitamin C has been associated with accelerated recovery in both experimental animals and patients in randomized preclinical and clinical studies. Beneficial effects have been reported in conditions such as severe sepsis and septic shock [111–113], post–cardiac arrest states [114], myocardial infarction [115], reperfusion arrhythmias [116, 117], and ischemia–reperfusion brain injury [118]. Several studies have also reported a significant therapeutic effect of high-dose parenteral ascorbic acid in experimental models of IRI [119–121]. However, despite accumulating evidence supporting its potential efficacy, a number of important issues remain unresolved. These include optimal dosing strategies, timing and duration of administration, and the role of combination therapy with other agents, all of which continue to be subjects of ongoing debate [122].

The antioxidant activity of α-tocopherol has been demonstrated in numerous studies. *In vivo*, it regulates the intensity of lipid peroxidation by scavenging lipid and lipid peroxyl radicals, effectively acting as a "chain-breaking" antioxidant. In addition, α-tocopherol contributes to the regeneration of coenzyme Q and modulates the activity of phospholipase A_2, thereby indirectly influencing arachidonic acid metabolism and the synthesis of prostaglandins and leukotrienes. Under conditions of increased oxidative stress, it helps preserve the biological activity of vitamin A by interrupting peroxidation chains involving polyunsaturated fatty acids. Furthermore, as a synergist of selenium – a cofactor of glutathione peroxidase – it plays an indirect role in the detoxification of lipid hydroperoxides.

Due to its pronounced lipophilicity and hydrophobicity, endogenous α-tocopherol is predominantly localized within the lipid bilayer of biological membranes, contributing to their structural stability. However, these same physicochemical properties limit its clinical use: α-tocopherol cannot be readily incorporated into intravenous perfusion solutions, and when administered parenterally by other routes, its antioxidant effects typically become evident only after 17–24 hours [123].

N-acetylcysteine (NAC) is a cysteine derivative containing a sulfhydryl group and has been used in clinical practice for over 60 years, initially as a mucolytic agent. Subsequently, its antioxidant properties were identified and extensively studied. NAC exerts its antioxidant effects through multiple mechanisms. First, it directly neutralizes ROS via its free sulfhydryl group. Second, it serves as a precursor for glutathione synthesis, contributing cysteine following its deacetylation. Glutathione, synthesized from glutamate, cysteine, and glycine, is a central component of the cellular defense system against oxidative stress [124].

To date, the efficacy of NAC in renal IRI has been primarily investigated in experimental models involving 30–45 minutes of ischemia followed by 1–24 hours of reperfusion. These studies have evaluated parameters such as renal function, mitochondrial activity, mitochondrial homeostasis, and histological changes. Overall, the findings support the protective role of NAC in this context and underscore the need for further investigation in clinical settings [125–128].

3.2.3. Mitochondria-targeted therapy (mitoquinone, elamipretide)

In experimental models of renal IRI in small laboratory animals, Liu et al. (2021), Mao et al. (2022), and others observed pronounced nephroprotective effects following intravenous administration of the mitochondria-targeted antioxidant mitoquinone (MitoQ). This compound consists of ubiquinone (coenzyme Q10) conjugated to a triphenylphosphonium cation, which facilitates its targeted delivery to mitochondria.

Under IRI conditions, MitoQ effectively protected the kidneys from the negative effects of free radicals, maintained adequate renal function, reduced mitochondrial damage and the formation of ROS. In addition, it reduced apoptosis in proximal tubular epithelial cells, and contributed to the restoration of mitochondrial membrane potential and ATP synthesis [129–132].

Elamipretide, also known as peptide SS-31, is a mitochondria-targeted tetrapeptide synthesized in 2000 by Hazel Szeto and Peter Schiller (reflected in the abbreviation "SS"). Structurally, it is D-Arg-dimethylTyr-Lys-Phe-NH_2 and is capable of selectively accumulating within mitochondria, where it exerts antioxidant effects by neutralizing mitochondrial ROS [133].

According to studies by Szeto et al. (2017) and Huang (2024), administration of SS-31 for six weeks following experimentally induced renal ischemia in rats primarily preserves mitochondrial integrity, demonstrating a pronounced mitoprotective effect. This is accompanied by reduced expression of inflammatory markers, preservation or restoration of the structure of tubular epithelial cells, glomerular endothelial cells, and podocytes, decreased rates of apoptosis and necrosis in tubular epithelium, and inhibition of glomerulosclerosis and interstitial fibrosis.

These findings support the concept that mitochondrial protection with SS-31 represents a promising therapeutic strategy. As highlighted by Szeto et al. (2017), targeting mitochondrial dysfunction in IRI may offer a novel approach to preventing the progression to chronic kidney disease following renal IRI [134–136].

4. CURRENT CLINICAL AND EXPERIMENTAL APPROACHES TO MINIMIZING RENAL IRI

In addition to pharmacological strategies aimed at correcting oxidative stress, hypothermia plays a fundamental role in the prevention of renal IRI, particularly in the context of transplantation. Topical cooling of the isolated kidney using saline or preservation solutions supplemented with pharmacological cryoprotectants remains the gold standard for extending the organ's tolerance to ischemia and reducing the severity of reperfusion injury [137, 138]. This approach is designed to decrease tissue metabolic activity, thereby limiting the production of ROS and the development of lactic acidosis during the ischemic phase. Russian research in cryobiology and organ preservation have also contributed significantly to the development of effective perfusion and storage solutions for transplant organs [139, 140].

Among pharmacological interventions used in clinical practice, N-acetylcysteine (NAC) has attracted considerable attention. Owing to its antioxidant properties and its ability to enhance intracellular glutathione levels, NAC has been evaluated in multiple studies as a potential agent for prevention of contrast-induced nephropathy and for mitigating renal IRI [141, 142]. However, its routine clinical application for prevention of renal IRI in kidney transplantation still requires validation through large-scale, well-designed clinical trials.

Thus, the most promising strategy appears to be a combined approach that integrates mechanical methods of organ protection (such as hypothermia) with adjunct pharmacotherapy targeting key links in oxidative stress pathogenesis.

5. CONCLUSION

During organ-preserving renal surgeries and, in particular, kidney transplantation under conditions of warm ischemia, the risk of renal IRI is present in all patients. Therefore, such procedures should ideally incorporate preventive and corrective strategies aimed at minimizing IRI-induced structural and functional impairments to the kidney.

The first kidney resection in the history of organ-preserving surgery was performed in 1887 by the surgeon Vincenz Czerny (German Bohemia). Since that time, and up to the present day (the end of the first quarter of the 21st century), clinically validated and effective methods for protecting organs and tissues – including the kidney – from IRI have not yet been fully developed. However, the active search for such technologies has never ceased and continues today.

Given the central role of ROS in the free-radical mechanisms underlying IRI, numerous studies have focused on developing pharmacological strategies for organ protection that target ROS generation, neutralization, and clearance. At the current stage of medical science, particular attention is given to agents capable of inhibiting the molecular mechanisms of mitochondrial membrane permeability transition pore opening, as well as suppressing ROS production through inhibition of NADPH oxidase and xanthine oxidase.

The therapeutic potential of exogenous enzymatic preparations (e.g., superoxide dismutase, catalase), low-molecular-weight catalytic ROS scavengers, and non-enzymatic antioxidants such as supraphysiological doses of ascorbic acid, as well as mitochondria-targeted agents like mitoquinone and elamipretide, are being investigated. It is anticipated that the outcomes of these studies will contribute to the development of effective antioxidant-based strategies for the prevention and treat-

ment of renal IRI during organ-preserving kidney surgery and transplantation.

The authors declare no conflict of interest.

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The article was submitted to the journal on 8.07.2025