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Effects of Peptides and Bioactive Peptides on Acute Kidney Injury: A Review Study

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ABSTRACT

Acute kidney injury is the sudden loss of kidney function that occurs within hours or days, resulting in the accumulation of waste materials in the blood and disruption of fluid balance. AKI is prevalent among hospitalized patients, especially the elderly in the intensive care units. Inflammation, oxidative stress, and apoptosis are typical physiological responses following AKI. Peptides, especially bioactive peptides, exhibit various properties, including immunomodulatory and antihypertensive effects, and functions against diabetes, obesity, and cancer. In recent years, much attention has been drawn to the application of peptides and bioactive peptides in pharmaceuticals, particularly for their potential use, alone or in combination, in the treatment of AKI. Given the critical role of inflammation, oxidative stress, and apoptosis pathways in AKI, along with the anti-inflammatory, anti-apoptotic, and antioxidant effects of peptides, this study was designed to review the effects and underlying mechanisms of peptides in AKI. ***DOI: 10.61882/ibj.5000***

Keywords: Acute kidney injury, Bioactive peptides, Cisplatin, Ischemia, Reperfusion

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INTRODUCTION

Acute kidney injury, formerly termed acute renal failure, is a sudden loss of kidney function[1,2]. This condition is characterized by decreased glomerular filtration rate and elevated serum levels of urea nitrogen and creatinine[3-5]. AKI affects nearly a quarter of hospitalized patients, and its incidence is even higher in intensive care settings, where up to 60% of critically ill patients may be affected[6]. AKI may arise from pre-renal, intrinsic, or post-renal factors, each contributing to impaired renal function. Intrinsic AKI indicates direct damage to the kidney, while pre- and post-renal AKI are typically caused by extrarenal conditions that lead to a reduction in the glomerular filtration rate. If pre- or post-renal conditions persist,

List of Abbreviations:
AKI: acute kidney injury; **AM:** adrenomedullin; **AMBP-1:** adrenomedullin binding protein-1; **ANP:** atrial natriuretic peptide; **BUN:** blood urea nitrogen; **CAT:** catalase; **CCl4:** carbon tetrachloride; **CIS:** cisplatin; DPP-4: dipeptidyl peptidase-4; **eNOS:** endothelial nitric oxide; **EPO:** erythropoietin; **EPOR:** erythropoietin receptor; **FDA:** US Food and Drug Administration; **GLP-1:** glucagon-like peptide-1; **GPCR:** G-protein coupled receptor; **GPx:** glutathione peroxidase; **GSH:** glutathione; **hANP:** human atrial natriuretic peptide; **HBS:** helix B surface peptide; **HIF:** hypoxia-induced factor; **HO-1:** heme oxygenase-1; **I/R:** ischemia/reperfusion; **ICAM-1:** intercellular adhesion molecule 1; **IL:** interleukin; **JAK/STAT:** Janus kinase/signal transducer and activator of transcription; **JNK:** C-Jun-NH2-terminal kinase; **JNKI:** PTD-JNK inhibitor; **MAPK:** mitogen-activated protein kinase; **MCP-1:** monocyte chemoattractant protein-1; **MDA:** malondialdehyde; **MFF:** mitochondrial fission factor; **MPO:** myeloperoxidase; **NF-κB:** nuclear factor-κB; **Nrf2:** nuclear factor erythroid 2-related factor 2; **pHBSP:** pyroglutamate helix B surface peptide; **PKC:** protein kinase C; **PTD:** protein transfer domain; **PTD-JNKI:** protein transduction domain-c-Jun NH2-terminal kinase inhibitor; **rhBNP:** recombinant human brain natriuretic peptide; **ROS:** reactive oxygen species; **SOD:** superoxide dismutase; **TGF-β:** transforming growth factor-beta; **TLR-4:** toll-like receptor-4; **TNF-α:** tumor necrosis factor-alpha; **VCAM-1:** vascular cell adhesion molecule-1; **βcR:** β common receptor

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they can ultimately damage renal cells, resulting in intrinsic renal disease[7]. In the intrinsic renal AKI, four kidney structures are involved: tubules, glomeruli, interstitium, and intrarenal blood vessels[8,9]. The most common cause of intrarenal AKI in hospitalized patients is acute tubular necrosis[10]. Nephrotoxins and renal ischemia are significant contributors to acute tubular necrosis[9-11], accounting for 80-90% of the renal causes[12]. Nephrotoxicity results from various compounds that are toxic to the kidney, including CIS and aminoglycosides, such as gentamicin. Renal ischemia occurs due to a severe or long-term reduction in renal perfusion[12]. The damage induced by renal AKI includes inflammation, oxidative stress, and injury to the endothelial and epithelial cells[4,13].

Peptides are a large group of molecules composed of amino acid residues, with over 13,000 natural peptide molecules identified to date[14]. The activity of a peptide is determined by its structure, which includes the composition of amino acids, types of N- and C-terminal amino acids, length of the peptide chain, charge properties of the amino acids forming the peptide, and the hydrophobic/hydrophilic characteristics of the amino acid chain[15]. Peptides, compared to other compounds, such as small molecules and biological agents, offer high specificity, good efficacy, safety, low immunogenicity, membrane permeability, and low cost[16]. Research has shown that peptides exhibit high solubility, distinct tissue distribution, and a favorable pharmacokinetic profile, leading to enhanced uptake into target tissues and rapid clearance from the blood and non-target tissues[17].

Recent studies have highlighted peptides as promising therapeutic candidates for many diseases[15,16,18]. As of 2023, over 80 peptide drugs have been approved by the FDA, and around 800 more are in various stages of preclinical and clinical development[19]. The pharmaceutical industry recognizes peptide drugs as one of the fastest-growing segments, with significant potential for future growth[20]. The present review focuses on peptides, bioactive peptides, and their mechanism of action in relation to kidney damage. The study also elucidates the molecular events and underlying mechanisms of peptides, as well as effective bioactive peptides against AKI caused by nephrotoxicity. Finally, it discusses the practical application of peptides and bioactive peptides in I/R. The objective of this study was to comprehensively review certain medicinal agents, particularly those implicated in kidney damage via their mechanisms of action.

Peptides are protein fragments that perform various biological functions. The term "peptide" comes from the Greek word "peptós" meaning "digestible", reflecting that peptides are formed by proteolytic cleavage. The first peptides were discovered in the early 19th century[21]. In 1881, the German chemist Theodor Curtius synthesized the first peptide, namely benzoylglycylglycine[22]. However, in 1901, Fischer and the French chemist Ernest Fourneau developed a more efficient synthesis, leading Fischer to be known as the "father" of peptide chemistry[23]. Since the commercialization of insulin as a 51-amino-acid peptide in the early 1920s[23], peptide drugs have significantly influenced the modern pharmaceutical industry. Generally, a peptide comprises a minimum of two amino acids.

An oligopeptide is a short sequence of amino acids, typically comprising a few amino acids. However, a polypeptide is a long sequence of amino acids, often made up of many amino acids. A protein consists of at least one correctly folded polypeptide chain. Apart from the size, there is no sharp boundary between a peptide and a protein or an oligopeptide and a polypeptide. The International Union of Pure and Applied Chemistry (IUPAC) defines oligopeptides as substances that contain fewer than 20 amino acids, while polypeptides comprise more than 50 residues[24]. Research has indicated that peptide hormone receptors are key targets for peptide-based drugs. GPCRs represent the most frequent targets for peptide-based drugs, with more than 40% of peptides entering clinical trials since 2010 acting on GPCRs. In addition to GPCRs, non-GPCR cell surface receptors—such as natriuretic peptide receptors and cytokine receptors that bind natural protein ligands—are also frequently targeted. Other targets include microbial pathogens, ion channels, and various extracellular targets such as structural proteins, adhesion molecules, and secreted enzymes. A few intracellular targets are also explored using cell-penetrating strategies[25]. Bioactive peptides, one of the most abundant types of peptides, are derived from natural sources such as meat, milk, fish, cereals, plants, and vegetables[26]. Bioactive peptides can vary in length from 2 to 20 amino acids and are defined as fragments that remain inactive within the precursor protein sequence. However, when released by proteolytic enzymes, they may interact with specific receptors and regulate the physiological functions of the body[27,28]. These peptides are primarily obtained through enzymatic hydrolysis, microbial fermentation, chemical digestion, recombinant production, and chemical synthesis[29].

Bioactive peptides can be categorized into two primary groups: those produced within the body (endogenous) and those produced from external sources

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(exogenous). Endogenous peptides are synthesized by various types of cells in the body. Neural cells, for instance, produce peptides that have pain-relieving or opioid-like effects. Immune cells generate peptides that play roles in inflammation and combating microbes. Glands, including the pituitary and adrenal glands, also produce various peptides. Exogenous peptides, on the other hand, are introduced into the body from external sources, such as food products, nutritional supplements, and pharmaceutical medications[30]. Recent research has shown that some exogenous bioactive peptides, which are naturally released from precursor proteins and cells, can replicate the functions of endogenous peptides. These peptides are produced through enzymatic hydrolysis of proteins or via biosynthesis or organic synthesis. Some exogenous peptides can also regulate the release of endogenous active peptides, enhancing their synergistic effects[31]. Peptides, compared to other compounds, offer several advantages. They can be synthesized cost-effectively on both small and large scales, exhibit a wide range of chemical diversity, and are also easily modified.

Additionally, peptides demonstrate high bioactivity and are easily absorbed and accessible. Furthermore, they are biodegradable and biocompatible, exhibiting high safety and low toxicity due to their safe metabolites (amino acids). Peptides are generally not highly immunogenic[32]; however, they possess harmful pharmaceutical properties, including instability, short duration of action, and inability to cross cell membranes. Hence, the clinical application of peptides remains restricted due to their short circulation time, limited ability to enter cells, and high structural flexibility, which compromises both stability and efficacy. Nonetheless, through strategic chemical modifications, researchers can manipulate key physicochemical attributes—such as charge, hydrophobicity, conformation, amphiphilicity, and amino acid sequence—that directly influence the behavior and bioactivity of the peptide. These modifications help address the intrinsic limitations of peptides, improving their pharmacokinetics and therapeutic potential while supporting ongoing advancements in peptide-based drug development[33].

Since the beginning of the 21st century, rapid progress in recombinant biotechnology, structural biology, peptide synthesis, and purification methods, along with the emergence of advanced analytical techniques, has significantly accelerated the research and development of peptide-based therapeutics. These advancements have refined the peptide drug development pipeline, paved the way for commercial viability and large-scale manufacturing, and signaled a new era in peptide drug innovation[16]. However, recent research in peptide chemistry has made strides in addressing these challenges. One approach involves capping the peptide ends with N-acetylation or C-amidation, which prevents exopeptidase degradation and enhances plasma stability. Another strategy is to covalently attach fatty acids or polyethylene glycol to the peptide, providing protection from enzymatic degradation and reducing renal excretion. Also, the covalent attachment of different polymers can elevate the molecular weight and hydrodynamic volume of the peptide, thus lowering renal clearance. Encapsulating peptides in liposomes or degradable polymer matrices, such as poly (lactic-co-glycolic acid), can further protect them from degradation and extend their circulation half-life[34]. Research has shown that peptides derived from alpha milk casein protein can inhibit the ACE-1 enzyme activity and lower blood pressure[35]. It has also been shown that ACE-inhibiting peptides stop the activity of the ACE-I enzyme in the renin-angiotensin-aldosterone system, thereby preventing the conversion of angiotensin I, a vasodilator decapeptide, into angiotensin II, a vasoconstrictive octapeptide. This mechanism contributes to maintaining optimal blood pressure levels. Furthermore, these peptides help prevent the breakdown of the vasodilator bradykinin[36,37]. ACE-1 inhibitors also affect the kidneys and can limit kidney damage in animals and humans[38]. Studies have investigated the relationship between the structure and activity of the ACE enzyme and the peptides that block this enzyme. Findings indicate that these peptides contain hydrophobic amino acids, such as tryptophan, tyrosine, phenylalanine, and proline at their C-terminus, enhancing their capacity to inhibit the ACE enzyme[37]. A review by Chakrabarti et al. highlighted the potential anti-inflammatory effects of food-derived peptides, suggesting that their mechanisms of action may involve pathways related to MAPK, NF-κB, cyclooxygenase 1 and 2 enzymes, TGF-β, IL, renin-angiotensin-aldosterone system, and ROS[39]. In the kidney, a protein hydrolysate derived from green peas using bromelain was shown to important kidney function in rats by enhancing antioxidant activity and increasing ANP levels[40]. It has also been indicated that apelin, a bioactive peptide, provides protection against AKI by reducing inflammation, inhibiting apoptosis, preventing lipid oxidation, suppressing MFF expression, and preserving the expression of SIRT3 and OPA1[41]. Therefore, most peptides with anti-inflammatory, anti-apoptotic, and antioxidant properties are effective against kidney damage.

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Peptides and bioactive peptides in nephrotoxicity

The incidence of nephrotoxicity is continually rising due to the widespread availability and uncontrolled use of over-the-counter drugs, inappropriate administration of high-dose drugs, and various drug-drug interactions. The kidneys are vulnerable to drug-induced damage because of their relatively high blood flow and their ability to extract and concentrate toxic water-soluble molecules[42]. Among the different nephron segments, the proximal tubule is particularly susceptible to toxic damage. Owing to its location adjacent to the glomeruli and the presence of specific organic acid-base secretion systems, the proximal tubule is often exposed to higher concentrations of toxins compared to other nephron segments, making it the primary site of nephrotoxic damage[43].

Experimental data suggest that drug-induced nephrotoxicity involves multiple mechanisms, which can be classified as vascular, glomerular, and tubular. Kidney damage typically results from tubular obstruction caused by cell swelling or debris buildup[42]. The administration of certain drugs, such as gentamicin, CIS, and CCl4, significantly reduces renal blood flow and glomerular filtration while promoting vascular resistance[42,44]. Renal studies on gentamicin are characterized by tubulopathy, in which tubular damage and tubular dysfunction are the leading cause of renal failure[45]. Gentamicin-induced tubular toxicity leads to apoptosis and necrosis of tubular epithelial cells, with gentamicin exerting direct and indirect effects, primarily on the proximal tubule[46]. Mitochondria activate the direct apoptosis pathway, alter ATP production, and generate oxidative stress by increasing superoxide anions and hydroxyl radicals, further contributing to cell death[42]. The indirect mitochondrial effect is mediated by decreased expression of Bcl-2 and increased expression of Bax [47]. Additionally, gentamicin has a glomerular effect that impairs filtration, causes mesangial contraction, and reduces the ultrafiltration coefficient and glomerular filtration rate[48,49].

Vascular effects include the enhanced production of several vasoconstrictors from endothelial and mesangial cells, such as endothelin-1, platelet-activating factor, and arachidonic acid metabolites, mainly prostaglandins and thromboxane[45,50]. In addition, leukocyte infiltration, intra-tubular proteinaceous cast, and perivascular edema occur in kidney tissue[51]. This condition also induces an increase in several inflammatory mediators, including the protein levels and mRNA expression of TLR-4, NF-κB, p65, and p38 MAPK, as well as elevated levels of proinflammatory cytokines such as IL-1β, ICAM-1, and TNF-α[51,52]. Furthermore, gentamicin reduces the antioxidant defense of the kidney by increasing MDA levels and decreasing the activities of SOD, CAT, GPx, and GSH. It also reduces the protein levels and mRNA expression of SIRT1, Nrf2, and HO-1 in the kidney[52-54].

CIS is a highly effective and widely used chemotherapy drug for cancer treatment. However, one of its main limiting side effects is nephrotoxicity[55]. The exact mechanism of CIS by which it induces nephrotoxicity is not well understood. It has been known that CIS accumulates in the S3 segment of the proximal tubule and reduces glomerular filtration rate and urine concentrating ability. This accumulation also changes urine output, resulting in increased BUN and creatinine concentrations[56,57]. Furthermore, CIS affects mitochondrial respiratory complexes and function, causing a decline in intracellular ATP levels and subsequent mitochondrial dysfunction. This dysfunction is associated with a reduction in the electrochemical membrane potential, mitochondrial calcium uptake, and deterioration of mitochondrial antioxidant defense systems[58].

In recent years, studies have shown that oxidative stress and nitrosative stress play crucial roles in CIS-induced nephrotoxicity. This condition is characterized by an elevated level of MDA, 4-hydroxy and 8-hydroxydeoxyguanosine, and 3-nitrotyrosine, along with decreased activities of SOD and CAT[59,60]. Oxidative stress can damage cellular proteins, lipids, and DNA by increasing superoxide anions and hydroxyl radicals and generating ROS[61]. The inflammatory response also plays a role in CIS-induced toxicity. Research has shown that TNF-α activates pro-inflammatory cytokines and chemokines, stimulating oxidative stress and ultimately aggravating kidney damage. Hydroxyl free radicals released by CIS are involved in the phosphorylation of p38 MAPK and the regulation of TNF-α synthesis, leading to the activation of NF-κB[58]. Other cytokines, such as TGF-β, MCP-1, ICAM, and HO-1, also contribute to CIS nephrotoxicity[62,63]. Studies on peptides and bioactive peptides in the context of gentamicin and CIS-induced nephrotoxicity have shown that various bioactive peptides, including DEL, with antioxidant properties, offer protective effects against nephrotoxicity induced by gentamicin or CIS[64]. Furthermore, research examining the effects of ANP, a cardiac-secreted substance with multiple biological functions, on CIS-induced toxicity demonstrated that ANP administration markedly reduces BUN and creatinine levels and the urinary albumin-creatinine ratio. Additionally, ANP therapy significantly lowered the mRNA expression levels of IL-1β, IL-6, ICAM-1, and MCP-1 in the kidney[65]. In a recent investigation, formononetin, a

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natural bioactive isoflavone extracted from herbal sources, demonstrated anti-inflammatory properties by reducing the levels of TNF-α, IL-1β, MPO, and oxidative stress markers while simultaneously boosting CAT activity and lowering MDA levels. Furthermore, formononetin, along with eupatilin—a PPARα agonist—enhanced cell viability, upregulated the expression of PPARα, Nrf2, HO-1, and NQO1, and inhibited apoptosis. Importantly, formononetin provided protection against CIS-induced AKI through the activation of the PPARα/Nrf2/HO-1/NQO1 pathway and effectively reduced BUN and creatinine levels[66]. In another research, mangiferin, a naturally occurring polyphenolic compound and one of the most potent bioactive xanthonoid molecules identified to date was found to mitigate CIS-induced toxicity both in vitro and in vivo. It also reduces oxidative stress and enhances Nrf2-mediated pro-survival signaling pathways through PI3K activation. Moreover, mangiferin exhibited synergistic anticancer effects when combined with CIS in cancer cell lines (MCF-7 and SKRC-45) and also in mice with EAC cell-induced solid tumors. The beneficial effects of mangiferin are primarily due to its antioxidant properties, as evidenced by increased levels of GPx, GST, CAT, and SOD, and its anti-inflammatory effects, indicated by decreased levels of NF-κB, TNF-α, IL-1β, IL-6, and IL-10[67]. Another study examined the protective effects of saxagliptin, a DPP-4 inhibitor, against gentamicin-induced nephrotoxicity. The results demonstrated that saxagliptin significantly improved creatinine clearance and reduced serum creatinine, BUN, proteinuria, and albuminuria. It also restored the oxidant/antioxidant balance, as indicated by a significant decline in kidney MDA levels and elevated GSH concentration and CAT activity. Furthermore, saxagliptin notably lowered TNF-α, VCAM-1, and caspase-3 levels. Consequently, saxagliptin administration significantly mitigated necrotic and inflammatory changes caused by gentamicin. These findings suggest that saxagliptin alleviates gentamicin-induced nephrotoxicity by modulating inflammatory cytokines, inhibiting apoptosis, and enhancing antioxidant defenses[68]. Meanwhile, salusin-β, a bioactive peptide consisting of 20 amino acids, has demonstrated significant effects in laboratory settings. The overexpression of salusin-β intensified specific cellular processes in renal tubular cells treated with CIS, including PKC phosphorylation, oxidative stress, activation of p53, and apoptosis. Notably, the apoptotic effects of salusin-β overexpression in these cells were reversed by inhibitors such as Go 6976 (a PKC inhibitor), N-acetylcysteine (a ROS scavenger), apocynin (an NADPH oxidase inhibitor), and pifithrin-α (a p53 inhibitor). In animal models, the suppression of salusin-β attenuated PKC phosphorylation, accumulation of ROS, induction of DNA damage, activation of p53, and mitigation of renal dysfunction in the mice that received CIS. These observations imply that elevated salusin-β exacerbates AKI by activating the PKC/ROS signaling cascade, predisposing renal tubular cells to apoptosis and functional impairment. The findings underscore the involvement of the salusin-β expression in nephrotoxicity induced by CIS or lipopolysaccharide, predominantly through the activation of the PKC/ROS/DNA damage/p53 apoptotic pathway. Functionally, the study proposes that increased PKC phosphorylation, upregulation of NOX4, p47 phox, and p22 phox proteins, translocation of p47 phox to the membrane, activation of Rac1, and reduced antioxidant factors such as SOD, CAT, and GSH, contribute to oxidative stress in AKI caused by salusin-β. Strategies such as blocking or genetically removing salusin-β may offer new approaches for preventing and treating AKI[69]. More explanation is depicted in Table 1 and Figure 1.

Peptides and bioactive peptides in renal I/R

One of the main causes of AKI is renal I/R[5,74]. Although reperfusion is vital for restoring blood flow to ischemic tissue, it also triggers I/R injury, which involves damage from both the ischemic insult and the reperfusion process itself[75]. The pathophysiology of I/R in the kidney is highly complex. Prolonged reduction or interruption of blood supply to the kidneys results in the onset and progression of kidney damage. Renal injuries caused by ischemia are divided into three main categories: damage to the vascular endothelial layer, tubular damage, and inflammation of the interstitial space. Damage to the endothelial layer of blood vessels, exacerbated by vasoconstrictor substances and binding molecules, leads to the adhesion of leukocytes, platelets, and red blood cells to the endothelium, ultimately resulting in congestion within the blood vessel. Tubular injuries can be lethal or sub-lethal. Lethal damage occurs in the form of necrosis or apoptosis in tubular cells. However, sub-lethal damage is characterized by the disruption of tight junctions between tubular epithelial cells, detachment of these cells from the basement membrane, and the shedding of apical membrane fragments into the tubular lumen. Tubular cells and brush-border cells combine with proteins within the tubules and form molds that prevent fluid flow, giving rise to increased pressure within Bowman's capsule[76-78]. Numerous signaling pathways are involved in these processes, including oxygen-sensitive transcription factors such as hypoxia-induced

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Table 1. Protective effects of peptides and bioactive peptides in gentamicin- and CIS-induced nephrotoxicity

Peptides	Characteristics	Experimental models	Mechanisms of action	Ref.
EDL	---	Gentamicin in rat	Enhancement of energy provision to nephrons, inhibition of free radical activity, and maintenance of antioxidant defense enzyme function	[64]
Apelin	---	CIS in mice	Diminishing inflammation, inhibiting apoptosis, preventing lipid oxidation, suppressing MFF expression, and maintaining the expression of Sirt3 and OPA1	[41]
ANP	Atrial natriuretic peptide	CIS in mice	Reduction in serum urea nitrogen and creatinine levels, urinary albumin/creatinine ratio, and renal expression of IL-1β, IL-6, ICAM-1, and MCP-1 mRNAs	[65]
Formononetin	Bioactive isoflavone isolated from *Trifolium pretense*	CIS in rat	Lowering the levels of BUN, creatinine, TNF-α, and IL-1β, decreasing MDA and MPO activity, increasing CAT activity, and elevating levels of PPARα, Nrf2, HO-1, and NQO1 while suppressing apoptosis and MPO activity	[66]
Mangiferin	A non-steroidal polyhydroxy polyphenolic molecule	CIS in mice and in vitro	Antioxidant and anti-inflammatory effects	[67]
Beclin 1		CIS in mice	Through reducing AKI, stimulating of cell growth, and preventing kidney fibrosis	[70]
AEDG	Alanyl-glutamyl-aspartyl-glycine	Gentamicin and CIS in rat	Prevention of oliguria, retention azotemia, hypokalemia, and reduction in the excretion of protein and sodium.	[71]
SS-31	D-Arg-Dmt-Lys-Phe-NH2	CIS in mice and in vitro	antioxidant and anti-apoptotic effects through regulation of the mitochondrial ROS-NLRP3 pathway	[72]
Salusin-β	Bioactive peptide	CIS in mice and in vitro	Activates PKC/ROS pathway, promoting apoptosis and tubular cell death in AKI	[69]
Saxagliptin	Member of the DPP-4 inhibitors	Gentamicin in rat	reduction in the levels of TNF-α, VCAM-1, and caspase-3 in the kidneys	[68]
Megalin ligands and N-WASP180-200	---	Gentamicin in rat renal brush-border membrane	Reducing the renal accumulation of gentamicin by preventing its attachment to the brush-border membrane (BBM) of proximal tubule cells, partly through interaction with megalin	[73]

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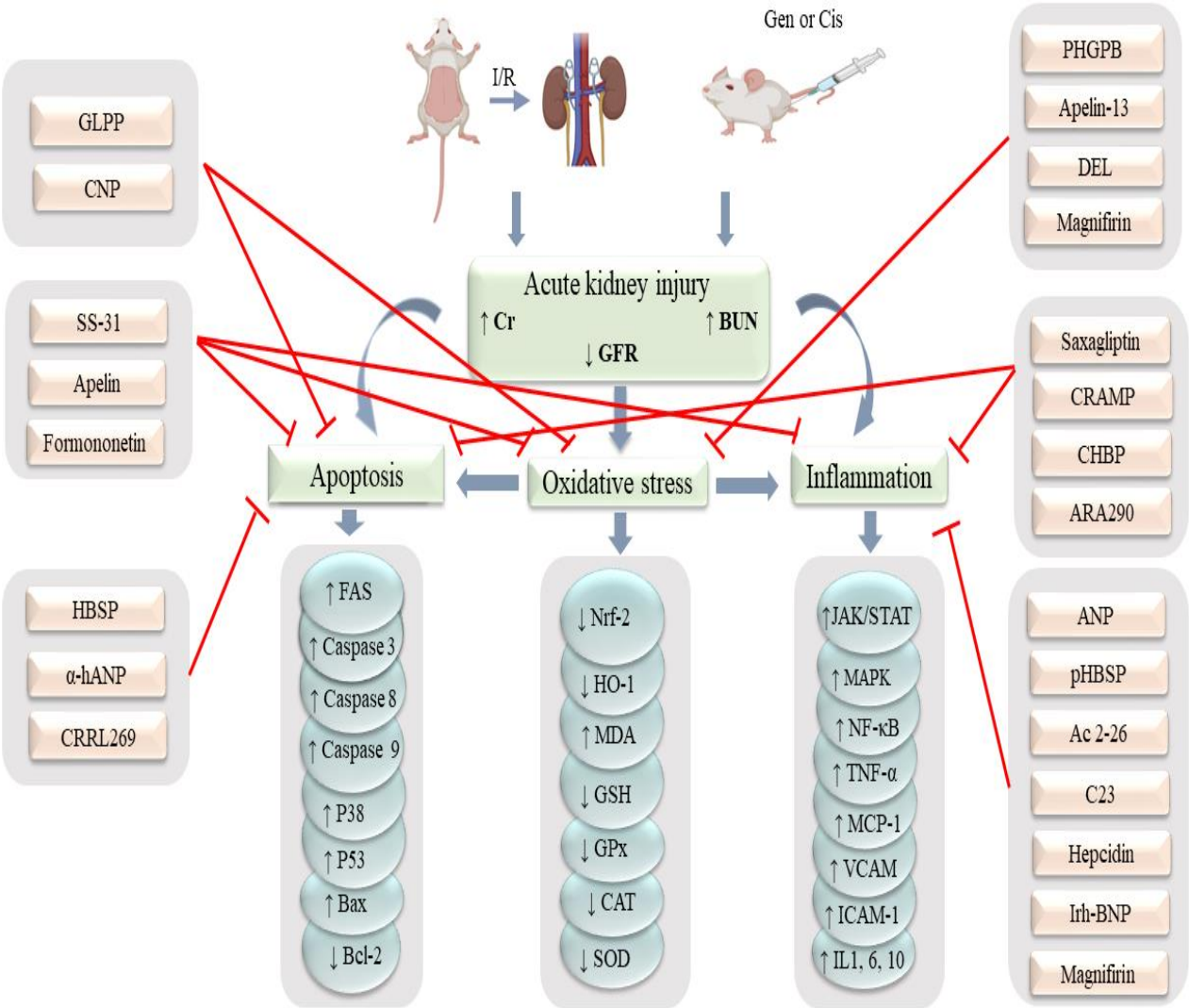

Fig. 1. Schematic overview of the pathophysiological consequences of AKI and the underlying mechanisms by which peptides and bioactive peptides exert their effects.

factor[79], macrophage and leukocyte infiltration[80,81], activation of cell death programs[82], and the JAK/STAT pathway[83]. These pathways lead to the release of various pro-inflammatory and immunomodulatory cytokines such as IL-1, IL-6, IL-10, TGF-β, TNF-α, and MCP-1[80,84]. Additionally, reperfusion ischemia is associated with ATP depletion, elevated intracellular calcium levels[85], increased production of ROS, and reduced activity of antioxidant enzymes such as SOD, CAT, and GP_X[86,87]. Therefore, protecting the kidneys from I/R injuries caused by AKIs is crucial.

A growing number of studies have shown that peptides with anti-inflammatory effects (CRAMP, pHBSP, HBSP, Ac2-26, SS-31, CHBP, C23, Hepcidin, ARA 290, lrh-BNP), antioxidative stress (CNP, RLX, SS-31, EDL, GLPP, Apelin-13), and anti-apoptosis effects (CRAMP, HBSP, SS-31, GLPP, α-hANP, CRRL269) have mitigated the damage caused by I/R in the kidneys. For instance, research on mitochondrial targeting tetrapeptides known as Szeto-Schiller peptides, specifically SS-31 (D-Arg-dimethylTyr-Lys-Phe-NH2), which targets the inner mitochondrial membrane, has shown that SS-31 protects the structure of mitochondria and thus accelerates the recovery of ATP. ATP recovery protects tubular cells from apoptosis and necrosis while maintaining the presence α1-integrin on the basement membrane. Thus, the integrity of the epithelial barrier is preserved, and the return flow of creatinine is minimized. Also, SS-31 significantly reduces oxidative stress and inflammation

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following I/R injury and promotes the proliferation of viable tubular cells. In addition, SS-31 decreases mitochondrial ROS production by lowering GSH levels, reducing lipid peroxidation, and upregulating HO-1. It has also been found that SS-31 protects microvascular endothelial cells, significantly reduces microvascular congestion, enhances reperfusion to the medulla, and improves creatinine clearance after I/R. Moreover, SS-31 inhibits the infiltration of macrophages and neutrophils, decreases the release of MPO, and improves inflammation[88]. Elsewhere, the HBSP, derived from EPO, has been shown to bind to a heteromeric receptor complex composed of the EPOR and βcR. This interaction plays a protective role in I/R induced renal injury. In the present study, HBSP treatment led to a marked reduction in apoptosis and macrophage infiltration, along with a significant upregulation of EPOR/βcR expression. The data indicate that HBSP improves phagocytic function and promotes kidney repair following I/R injury by upregulating EPOR/βcR[89]. In a similar study, administration of pHBSP, a novel non-erythropoietic analog of erythropoietin improved kidney function, either alone or in combination with EPO, in rats subjected to 30 minutes of ischemia followed by 48 hours of reperfusion. Both pHBSP and EPO restored Akt activation and inhibited GSK-3β and NF-κB signaling, which enhanced eNOS activation and increased nitric oxide production. Furthermore, by inhibiting p38 MAPK, these treatments reduced TNF-α, IL-1, and IL-8 levels, thereby mitigating renal injury following IR. These signaling events are believed to contribute to their nephroprotective effects[90]. In a study, apelin-13—the most biologically active form of apelin—exerted protective effects against oxidative stress induced by renal I/R injury. Findings demonstrated that apelin-13 enhanced the activity of antioxidant enzymes such as SOD, CAT, and GSH-Px while lowering the levels of MDA and total oxidant capacity, thus exhibiting significant antioxidant properties. Furthermore, the administration of apelin-13 resulted in decreased levels of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, which reduced urea and creatinine[91]. A study examining the protective effects of salusin-α and salusin-β on renal I/R injury demonstrated that treatment with these peptides significantly reduced the levels of pro-inflammatory cytokines and the infiltration of inflammatory cells into the kidneys following I/R. Moreover, administering the salusin-α and salusin-β enhanced the activation of antioxidant enzymes and mitigated lipid oxidation. Histopathologic findings also showed a notable improvement after the administration of salusin-α and salusin-β[92]. Furthermore, a study investigated the effects of AM, a new vasoactive peptide, combined with AMBP-1, on renal I/R injury. Administration of human AM/AMBP-1 reduced renal water content and plasma levels of creatinine, BUN, as well as aspartate and alanine aminotransferases. Additionally, serum and tissue levels of TNF-α significantly decreased following AM/AMBP-1 treatment. Moreover, treatment with human AM/AMBP-1 in a rat model of renal I/R injury significantly alleviated organ damage and inflammatory response[93]. A study investigating the PTD-JNKI synthetic peptide demonstrated that delivery of the peptide via a protein transduction domain can effectively inhibit the JNK pathway and reduce I/R injury in a porcine model. The JNKI peptide was injected directly into the renal artery, enabling its cellular uptake such as vascular endothelial cells, through PTD-mediated endocytosis. In the PTD-JNKI-treated group, serum creatinine and BUN levels were significantly reduced. Additionally, renal blood flow was maintained, which led to decreased tissue damage and fewer apoptotic cells follpwing peptide administration. These findings suggest that PTD-based delivery of therapeutic peptides may improve outcomes in kidney transplantation[94]. Despite the beneficial effects of peptides, a study investigated the effects of urocortin, a 40-amino acid peptide closely related to corticotropin-releasing factor, on bilateral renal ischemia in rats. The study measured mean arterial pressure, which is indicative of decreased renal perfusion. This observation revealed that urocortin does not reduce renal damage caused by bilateral renal ischemia[95]. More explanation is represented in Table 2 and Figure 1.

Impact of peptides and bioactive peptides on kidney damage: evidence from human studies

To date, no drugs have been approved by the FDA for the prevention or treatment of AKI. Most research on peptide-based therapies for AKI has remained in the preclinical stage, primarily in animal models, with limited studies advancing to clinical trials[114]. For instance, a study evaluating rhBNP in patients with end-stage renal disease and type 4 cardiorenal syndrome demonstrated that rhBNP can improve cardiac and renal function[115]. Similarly, a phase 2b randomized trial of cotadutide, a GLP-1 receptor agonist, showed its beneficial effects in patients with type 2 diabetes and chronic kidney disease without significant adverse effects[116]. In another study, continuous infusion of hANP, a potent endogenous natriuretic and diuretic agent at a dose of 50 ng/kg/min in patients with acute ischemic renal failure following complex cardiac

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surgery, resulted in improved renal function, reduced need for dialysis, and prolonged dialysis-free survival[117]. Moreover, randomized controlled trials have indicated that low doses of ANP may effectively prevent and treat contrast-induced AKI[118,119]. However, a recent randomized, double-blind trial reported that a four-day infusion of ANP at the same dose following heart transplantation did not significantly reduce renal dysfunction or the incidence of AKI[120]. In addition, studies have shown that SS-31, a mitochondria-targeted peptide, has progressed to phase 3 clinical trial for mitochondrial myopathy and a phase 2 trial currently underway for chronic heart failure[121,122]. Given the indicated protective effects in preclinical models of I/R injury and CIS-induced nephrotoxicity[72,88], SS-31 is considered a promising candidate for preventing and treating kidney injury. These peptides offer significant advantages over conventional pharmaceuticals due to their high target specificity and low systemic toxicity. Nevertheless, their clinical application is still constrained by insufficient stability within the biological environment, restricted cellular uptake, and suboptimal pharmacokinetic profiles. These limitations underscore the need for further comprehensive research to fully harness their therapeutic potential in clinical settings.

CONCLUSION

Since oxidative stress, inflammation, and apoptosis are critical mechanisms involved in AKI, many peptides with anti-inflammatory, anti-apoptotic, and antioxidant properties demonstrate promising therapeutic potential. Notably, most studied peptides exhibited beneficial effects against AKI induced by gentamicin, CIS, and I/R. For instance, peptides such as apelin, apelin-13, formononetin, ANP, mangiferin, and pHBSP have shown significant protective effects by modulating oxidative stress, reducing inflammatory responses, and inhibiting apoptotic pathways. These peptides act by elevating the expression levels and activity of the SIRT1, Nrf2, HO-1, GSH, SOD, CAT, TAC, IκB-α, Bcl-2, PI3K, and Akt, while lowering the levels of pro-inflammatory and pro-apoptotic markers such as TLR-4, NF-κB, MAPK, IL-1β, IL-6, VCAM, ICAM-1, MPO, MCP-1, GSK-3β, TNF-α, MDA, cytochrome c, caspase-3, Bax, and the Bax/Bcl-2 ratio. However, it is important to mention that the salusin-β peptide demonstrated harmful effects in the context of AKI. This peptide promotes apoptosis in kidney tubule cells by activating the PKC/ROS signaling pathway, thereby exacerbating kidney injury. These findings contradict the subsequently observed effects of salusin-α and -β on IR injury. Additionally, urocortin could not reduce renal damage caused by bilateral renal ischemia. Despite these exceptions, the overall findings strongly support the potential of peptides as therapeutic agents for AKI. The beneficial effects observed in various studies suggest that bioactive peptides and their combinations, could effectively alleviate the complications associated with AKI. Future research should focus on optimizing peptide therapies, understanding their mechanisms of action in greater details, and evaluating their efficacy in clinical settings. The development of peptide-based treatments can significantly improve outcomes for patients suffering from AKI and reduce the progression to chronic kidney disease.

DECLARATIONS

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Ethical approval

This study was approved by the research deputy of Kermanshah University of Medical Sciences, Kermanshah, Iran (ethical code: IR.KUMS.REC.1401. 424).

Consent to participate

Not applicable

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

HN: project adminstration, conceptualization, supervision, writing–review & editing; ZMY: investigation, writing–original draft preparation, visualization.

Data availability

No datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

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