Acute kidney injury: microRNAs and new therapeutic opportunities for natural products

Ke Zhong1, 2, Han-Qing Zhang1, 3, Ya-Xuan Fang1, 5, Qiu-Mei Lan1, 5, Zi-Jun Zhou1, 5, Yan-Ru Zhao1, Yan-Heng Qiao1, Jie Li1, Bo Yang1, 3, 4

1Department of Nephropathy, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381, China. 2Department of Medical Imaging, Yubei District Hospital of Traditional Chinese Medicine, Chongqing 401120, China. 3National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300381, China.

*These authors contributed equally to this work and are co-first authors for this paper.

Corresponding to: Bo Yang, Department of Nephropathy, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, No. 88 Changling Road, Xiqing District, Tianjin 300381, China. E-mail: ybb203@126.com.

Abstract

In the past few decades, acute kidney injury (AKI), characterized by an abrupt decrease in kidney filtration rate, has become a public health issue affecting between 1% and 15% of the population, which causes high morbidity and death. There is mounting evidence that miRNAs are noncoding single-stranded RNAs with a short length of about 20 nucleotides and have been highly conserved through evolution. Through targeting miRNAs, miRNA may mediate intercellular communication during AKI's physiological and pathological processes. It is interesting to note that natural products can improve AKI by regulating miRNA expression, which might represent a potentially innovative therapeutic strategy. This review aims at providing an overview of the new data obtained on miRNAs in the treatment and diagnosis of AKI, summarizing studies on natural products improving AKI through regulating miRNAs' expression; in the same time, it will shed new light on AKI risk biomarkers and therapeutic intervention as well. We summarized the roles of miRNAs involved in AKI progression or protection against renal injury in 32 articles; we found five natural products can improve AKI by regulating miRNA expression, which will potentially provide a reference for clinical treatment. Natural products might represent a potentially innovative therapeutic strategy; in the same time, miRNAs will shed new light on AKI risk biomarkers and therapeutic intervention.

Keywords: microRNA; acute kidney injury; natural products; biomarker

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Highlights
1. miRNA, a noncoding single-stranded RNA with a short length, participates in the initiation and development of diseases through a variety of ways, it can also play roles in acute kidney injury. In this article, we summarized the roles of miRNAs involved in acute kidney injury progression or protection against renal injury in 32 articles.
2. Natural products are a rich reservoir for drug discovery and development, which have unique advantages in the treatment of a variety of diseases. We reviewed the mechanism of natural products to protect acute kidney injury by regulating miRNAs, including Curcumin, Dioscin, Honokiol, Paclitaxel and Puerarin, and hope to provide readers with further research ideas.
3. At the same time, as a sensitive biomarker, miRNA also plays an important role in the early diagnosis of acute kidney injury.

Medical history of objective
In traditional Chinese medicine, acute kidney injury is recorded in the ancient book Yellow Emperor’s Cannon of Internal Medicine of the Western Han Dynasty in China [202 B.C.E.–8 C.E.]. Acute kidney injury is a multi-system disease, which is related to the function of lung, spleen, kidney, and bladder etc. Chinese herbs play an important role in protecting kidney injury, and natural products are the effective ingredients in Chinese herbs. For example, Curcumin, the main component of Curcumaria Longa, was first recorded in the Newly Revised Materia Medica of Tang Dynasty [618 CE–907 CE], and was believed to have the effect of activating blood circulation and removing blood stasis (improve blood flow). Magnoliol, extracted from Magnolia Officinalis, was recorded in the Taiping Huimin Heji Jufang of the Song Dynasty [960 CE–1279 CE] as having the effect of drying dampness and removing turbidity (reduce fluid retention).

Background
Multifaceted and heterogeneous disease processes lead to acute kidney injury (AKI), which causes serious complications involving an abrupt and sudden fall in glomerular filtration rate, a rapid spike in serum creatinine concentrations, and, frequently, oliguria or anuria as well [1]. In hospitalized patients, AKI occurs at a rate of 10% to 15%, while the incidence in intensive care patients has been reported to exceed 50% [2]. Until now, molecular mechanisms underlying AKI pathology have not been fully elucidated; renal replacement therapy has been the most effective treatment for AKI [1]. Therefore, it is urgently necessary to investigate, develop, and focus on new therapeutic approaches to preventing and diagnosing this troublesome disease.

Traditionally, the pathogenesis of AKI was distributed into pre-renal, renal, and post-renal causes, which limited the treatment of AKI. Based on studies of cellular and molecular mechanisms, researchers have recently proposed that damage and death of the renal tubular cell are the primary pathological mechanisms of AKI [3]. Through epigenetic mechanisms (shown in Figure 1), miRNAs control gene expression in renal cells and therefore play important roles in regulating AKI pathophysiology, and it may be possible to interfere with miRNAs expression to provide a brand new perspective on improving AKI. Given the single and limited efficacy of current therapeutic approaches for AKI, natural products have been shown by many researchers to be possible new therapeutic approaches for AKI due to their efficacy and safety [4–6]. The new approach based on natural product therapy for AKI can be theoretically justified by the identification of miRNAs as potential targets.

In this article, we summarize how miRNAs affect AKI mechanistically and find that different miRNAs may have opposing effects on the pathophysiology of AKI. Moreover, we further present the experimental results of natural products that ameliorate AKI by targeting miRNAs. Further, we presented a summary of recent studies examining miRNAs as biomarkers of AKI and explored the potential role of miRNAs in the diagnosis of AKI.

Definitions of miRNA
A miRNA is a highly conserved small noncoding RNA molecule about 18–25 nucleotides in length that control gene expression post-transcriptionally [7]. In the beginning, RNA polymerase II transcribes primary miRNA into a large primary transcript, then the primary long hairpin-like miRNA is processed by ribonuclease III endonuclease Drosha to form a precursor miRNA of approximately 60–70 nucleotides. It is further export from the nucleus to the cytoplasm via Ran-GTP and Export-5. The cytoplasmic enzyme Dicer recognizes pre-microRNAs as being unique secondary structures and cuts them into mature miRNAs comprised of 18–25 nucleotides [8]. The determination of target miRNAs is contingent upon the “seed sequence” of miRNAs, wherein each seed sequence possesses a relatively limited length, thereby enabling miRNAs to target as many as 100 distinct miRNAs. The presence of numerous miRNAs and their potential miRNA targets, along with the promiscuous binding of seed sequences, indicates the existence of an intricate regulatory network governing gene expression. This network has the potential to influence the expression of genes that typically participate in interconnected functional pathways [9].

The 3’ untranslated region is generally the region in which miRNAs bind to mRNA, and once they bind, miRNAs may degrade the target miRNAs or more commonly inhibit ribosomal translation [5]. The properties of miRNAs can be modulated by particular inhibitors or analogs, which has been demonstrated in numerous studies of more than 2,000 mature miRNAs in humans [10]. Accordingly, miRNAs may provide a new therapeutic approach in oncology and other disciplines because of their high diversity of expression in diseases, the safety and activity of a selective inhibitor of miR-221 was verified in a phase I clinical trial (NCT04811898) for the treatment of patients with refractory advanced cancer [11–17].

At the same time, miRNAs have been broadly studied in acute organ injury in recent years. Severe acute lung injury is a mortal disease, and a study found that in A549 cells, lung injury may be associated with down-regulation of miR-762 expression or up-regulation of FXI expression [18]. A cytological investigation of acute lymphoblastic leukemia revealed that extracellular vesicle-mediated transport of miRNA-181b-5p into the cytoplasm promotes acute lymphoblastic leukemia cell malignancy [19]. Researchers determined eight potentially atherogenic miRNAs, discovered that there was a significant elevation in plasma miR-21-5p and miR-146a-5p levels in patients with acute coronary syndromes, and a reduction in miR-17-5p level was found in both acute coronary syndromes and stable coronary artery disease patients compared to hypertensive patients without coronary artery disease and healthy controls in both groups [20]. Therefore, as a type of acute organ injury, the relationship between AKI and miRNAs also deserves to be explored.

MiRNA in AKI
MiRNA in ischemia-reperfusion injury (IRI)
IRI is induced by an inflammatory process, it occurs when the blood flow in organs decreases or stops briefly and then restore after the re-establishment of perfusion. When oxygen supply and demand are out of balance, the kidney is especially vulnerable to IRI, which results in cell damage and death, as well as compromised water and electrolyte balance– and this is the reason why IRI is a leading cause of AKI. By generating Dicer knockout mice, Wei et al. [21], demonstrated the pivotal role of miRNAs in ischemic AKI and revealed a specific depletion of over 80% miRNAs from the proximal renal tubules. The remarkable resistance to ischemic AKI observed in these mice strongly suggests that miRNAs may exert a significant influence on the pathogenesis of IRI-induced AKI [22]. There is growing evidence indicating that miRNAs are crucial regulators of IRI [23–25].
Figure 1 Mechanisms of microRNAs

There is cellular damage both after the ischemic insult and after renal reperfusion, especially in the tubular epithelium of the renal tubule [26]. Many researchers have confirmed that specific miRNAs can be induced by animal or cell models of ischemic AKI, which can then regulate cellular damage by preventing the translation of a target-gene miRNA or by inducing degradation: these include miRNA687, miRNA668, miRNA499, miRNA17-5p, miRNA24, miRNA17-92, miRNA204-5p, miRNA205, and miRNA-155[27–35]. Although the induction of miRNA687, miRNA668, and miRNA499 are all mediated by HIF-1 in IRI, their downstream target genes and effects are different. In proximal tubule-specific HIF-1 knockout mouse and cells, decreased induction of miRNA687 were found, which was proved to be achieved by repressing PTEN expression to facilitate cell-cycle progression and apoptosis, thereby aggravating ischemicAKI [27]. In contrast, miRNA687 and miRNA499 played a protective role in ischemic AKI by inhibiting MTP18 and PARP1, respectively. Overexpression of miRNA687 via miRNA668 mimics an in vitro model suppressed MTP18 concerning the mitochondrial dynamics and maintenance of renal tubular cell viability, which in turn ameliorated ischemic AKI [28]. MiRNA489 is differentially expressed in both in vivo and in vitro models, revealing that it can inhibit PARP1, a molecule that causes cell death in ischemic AKI [29]. Unlike HIF-1 induction, P53 upregulate miRNA17-5p, which inhibits DR6 in vitro and provides renal protection in vivo, thereby inhibiting apoptosis in cells [30]. Before these studies, Lorenzen et al. had found that miRNA24 targets S1PR1, H2A.X, and HO-1 (a series of significant antiapoptotic proteins) in vitro, which exacerbated renal ischemia-reperfusion injury [31]. Zhang et al. showed the expression level of miR-155 was upregulated in both the I/R-induced AKI rat model and H/R-treated NRK-52E cells, which promoted cell apoptosis and suppressed cell proliferation, while inhibition of miR-155 expression exerted opposite effects. The findings suggest that miR-155 plays a role in exacerbating acute kidney injury by targeting and regulating the TCF4/Wnt/β-catenin signaling pathway [35].

MiRNAs have also been linked to inflammation and the immune system in ischemic AKI by numerous researchers [36–41]. MiRNA494 has been identified as a key player in promoting AKI through its impact on inflammation, specifically by stimulating ATF3 and NF-κB pathways. In vivo lentivirus-mediated delivery of miR-494 overexpression was found to activate the NF-κB pathway by directly targeting ATF3, resulting in increased secretion of inflammatory factors and adhesion molecules in IRI kidneys [36]. In addition, through urine volume analysis and clinical data, the team found that in patients with AKI, urinary miRNA-494 concentrations were up to 60-fold than in normal controls, therefore miRNA-494 may constitute a novel biomarker [36]. In relation to the NF-κB pathway, miRNA146a also has been shown to modulate the inflammatory response [42, 43]. There was an increase of miR-146a both in allogeneic grafts and in the urine of renal transplant recipients, which might be associated with greater renal IRI severity; it also validated in unilateral IRI induced mice that miR-146a expression was up-regulate and showed more widely tubular damage, inflammation, and fibrosis. In vitro, by overexpressing or downregulating miR-146a, the expression of IL-1 receptor associated kinase1 was reduced or enhanced, respectively, and injured tubular cells expressed CXCL8/CXCL1 in a similar way [38]. MiRNA233 is another miRNA that influences the regulation of inflammation and the immune system in ischemic AKI.

The murine renal tubular epithelial cells line was cocultured respectively with either mesenchymal stem cells (MSCs) or hypoxia-pretreated MSCs (htMSCs) in the H/R model, it is found that adding MSCs or htMSCs to renal tubular epithelial cells increased their viability and decreased their apoptosis rates while inhibiting miR-223 expression in MSCs diminished these benefits in mouse kidneys. In ischemic AKI mice, miR-223 suppressed the expression of the NLRP3, proving its renoprotective role in improving ischemic AKI. In addition, htMSCs demonstrated a protective function associated with the over-expression of miR-223 regulated by Notch1 [39].

There have been extensive studies of miRNA21 for many diseases, including IRI, which is one of the earliest miRNA genes discovered in humans. We noticed that miRNA21 had protective roles in most delayed ischemic preconditioning studies in mice [44–48]. However, other in vitro studies have shown that miRNA21 mimics inhibited the viability of NRK-52E cells and induced cell apoptosis, showed that
overexpression of miRNA21 facilitated apoptosis of rat renal epithelial cells under the condition of hypoxia and reoxygenation, while inhibition of miRNA21 ameliorated autophagy activation by targeting Rab11a—thus protecting the occurrence of renal IRI [49].

**miRNAS in sepsis associated with AKI (SA-AKI)**

As early as 700 B.C., the Greeks recognized that sepsis referred to decomposition or decay, which is a life-threatening disease related to infection. According to current definitions, sepsis is an organ dysfunction caused by a dysregulated immune response to infection that may lead to death [50]. Sepsis shock is a severe type of sepsis that can cause potentially life-threatening circulatory, metabolic, or cellular abnormalities and can significantly increase mortality rates. This is especially true for SA-AKI, which is correlated with high mortality [51]. Of note, unlike AKI caused by IRI, most of the causes of SA-AKI are hyperdynamic, vasodilatory shock, and inflammation [52]. Although it has progressed in exploring the drivers of SA-AKI, it remains a common and highly pathologic complication of critical illnesses.

Recently, researchers have found that miRNAs might affect the pathogenesis of SA-AKI, such as inflammation and renal cell apoptosis [53, 54]. NF-κB is a key transcription factor affecting the expression of inflammation-associated genes, and some miRNAs (such as miRNA21 and miRNA191-5p) have been shown to serve an essential role in altering the NF-κB-induced inflammatory cascade [55, 56]. Pan et al. and Jia et al. found that miRNA21 is renoprotective in remote ischemic preconditioning and xenon preconditioning to sepsis-induced acute kidney injury models. These authors found that the expression of miRNA21 was dramatically upregulated after treatment, targeting the PDPC4/NF-κB and PTEN/AKT-signaling pathways, which can inhibit inflammation and apoptosis—ultimately improving SA-AKI [57]. Similarly, miRNA191-5p also activates the p38 MAPK/NF-κB signal pathway by targeting oxidative stress responsive 1. Researchers performed cecal ligation and puncture (CLP) surgery on rats after injecting miR-191-5p mimics or mimic controls, which found that injecting miR-191-5p mimic could dramatically protect renal function, reduce the inflammatory response and apoptosis in septic rats [56].

There have been numerous studies have revealed that TLR-signaling pathways primarily activated NF-κB, and that miRNA targeted TLR to influence inflammation [58, 59]. In the case of lipopolysaccharide (LPS)-induced septic mice, significant attenuation of LPS-induced AKI was observed after administering adenosine expressing miR-590-3p via mice tail veins. In vitro, the transcription of miR-590-3p mimics restored podocyte growth, mitigated apoptosis as well as excessive production of inflammatory cytokines induced by LPS. It found that miRNA590-3p directly regulated the expression of TRAF6 to improve LPS-induced podocyte apoptosis and ameliorate SA-AKI—which is involved in the TLR4/TRAF6/NF-κB inflammatory-signaling pathway [60].

Many cytokines are overexpressed in the inflammatory state—IL-1β, IL-6, and IL-8—and miRNAs can regulate the production of cytokines to aggravate septic AKI by mediating the inflammatory response. Previous experiments have shown that the expression of miR-23a-3p is reduced in patients with septic AKI, while CLP/LPS studies have shown that miR-23a-3p can improve renal function in septic mice and cells. This process is achieved by targeting FBX5 and inactivating NF-κB signaling to mitigate apoptosis and the release of inflammatory cytokines [61].

Another study found that miRNA106a levels were elevated in serum samples from patients with sepsis, in CLP mouse models, and in LPS-induced tubular epithelial cells, it indicated that miR-106a exacerbated sepsis-induced AKI involved in influencing the level of TNF-α by THBS2 [62]. Additionally, in the rat sepsis-induced AKI model and mouse in vitro cell model, other miRNAs such as miRNA214-5p and miRNA214 have been experimentally validated, suggesting their potential involvement in sepsis-induced AKI through alternative inflammatory signaling pathways [63, 64].

Moreover, in animal and cellular models of sepsis, macrophage and neutrophil infiltration into the kidney was enhanced, and renal and urinary Scr and KIM-1 levels were elevated. Down-regulation of miR-181c increased TLR4 protein in burn sepsis by suppressing KIM-1 mRNA levels, thereby modulating the levels of inflammatory genes (TNF-α, IL-1β) and chemokine genes (MIP-1α, MIP-2, MCP-1), which provided a novel approach to the therapy of SA-AKI [65].

**miRNAS in cisplatin nephrotoxicity**

Although cisplatin (DDP) is an efficient cancer chemotherapy agent for cancer, it shows unfortunate side effects in kidney tissues—the major one being the induction of AKI. There are also mounting proof that inflammation and oxidative stress in proximal tubules play an influential part in the pathophysiological mechanisms of DDP-induced AKI [66]. Therefore, it is necessary to explore new strategies to reduce AKI caused by DDP nephrotoxicity, miRNAs have recently generated much public interest, and studies suggested potential protection in DDP-induced nephrotoxicity [67–69]. It is reported that miR-214-3p is involved in the underlying molecular mechanism of AKI by targeting GPPX4 in DDP-induced ferroptosis of renal tubular epithelial cells, inhibiting miR-214-3p enhanced the expressions of GPPX4 and SLCTA1 while decreasing the ACSL4 expression, protected against tubular epithelial cell death and renal tubule damage both in vitro and in vivo [70]. MiR-132-3p and miR-34a have opposite roles in DDP-induced AKI, but both of which are involved in cisplatin-induced AKI by regulating SIRT1 and NF-κB signaling pathways [71, 72]. Moreover, in vivo and in vitro studies have shown that antagonizing miR-195a-5p with a miR-195a-5p antagonir alleviates DDP-induced kidney injury and mitochondrial dysfunction [73]. As determined by target-scan analysis, miR-194-5p, miR-338-3p, miR-500a-3p, and miR-577 were bound to MLKL and therefore were potential targets of MLKL for regulating tubular epithelial cells during ischemic and toxic conditions [74]. Another study sorted 207 differentially expressed genes analyzed by a DDP-induced AKI rat model and HK-2 cells exposed to cisplatin cocultured with MSCs, the result indicated that miR-107 knockdown promoted RPS19 expression and enhanced cell proliferation, as well reduced DDP-induced cell apoptosis [75].

However, other studies showed some miRNAs might play a positive promote role in DDP-induced nephrotoxicity. DDP-induced AKI was exacerbated by miRNA449 overexpression due to its inhibition of SIRT1 expression, p53 acetylation, and BAX expression. In vitro, miR-449 inhibits DDP-induced apoptosis by preserving SIRT1/p53/BAX signals [76]. Moreover, compared with healthy rats, the expression of miRNA146b in renal tissues from DDP-induced AKI rats was considerably upregulated, which indicated miR-146b may have a contribution to kidney injury. In tubular epithelial cells, inhibition of miR-146b inducing the expression of epidermal growth factor receptor 4, and alleviated the nephrotoxicity of DDP [77]. The expression of miRNA709 was significantly upregulated in mouse and human kidney samples following DDP treatment, leading to mitochondrial dysfunction and cell apoptosis through the negative regulation of TFAM, thereby exacerbating DDP-induced AKI [78]. Moreover, the level of miR-155 was upregulated in mice and HK-2 cells of CAKI models, which indicated that inhibiting miR-155 expression can protect renal function and reduce pathological damage caused by DDP [79].

**miRNAS in contrast-associated AKI**

Contrast-associated acute kidney injury (CA-AKI) is a severe complication of intravascular applied radial contrast media. As intravascular iodinated contrast media is being widely injected in diagnostic and therapeutic procedures, the incidence of CA-AKI is also increased [80]. However, the definite mechanism of CA-AKI remains obscure. A study performed a miRNA expression profile in the kidneys of CA-AKI rats by next-generation sequencing, it demonstrated that 23 miRNAs were down-regulated and 19 were upregulated of the 173 detected, therefore miRNAs might serve as new molecular targets for CA-AKI. CA-AKI cells are sensitive to inflammation, hypoxia, energy depletion, and oxidative stress, therefore, some studies have found
that miR30c and miR429 can regulate AKI by regulating inflammatory response and mitophagy, respectively [81–83].

**MiRNAs in natural products intervention AKI**

Natural products are bioactive, natural functional ingredients derived from abundant natural resources such as plants and are considered to be precious sources of inspiration for drug design. Most of the drugs we use today are extracted from natural products, including polyphenols (e.g., curcumin, resveratrol), cardiac steroids (e.g., digoxin and toadstool), polysaccharides (e.g., shiitake mushroom polysaccharides), and saponins (e.g., licorice and *Ginseng Radix et Rhizoma Rubra*) [84]. Although a large number of bioinformatics analysis techniques have been widely used to reveal the biological activities of numerous natural products, their molecular mechanisms and clinical efficacy remain to be elucidated [85–87]. In recent years, research data suggest that natural products can influence AKI by regulating the expression of one or more miRNAs, and some other research data suggest that natural products can influence AKI so miRNAs may serve as mediators to provide new ideas for natural product therapy for AKI [88–90].

Turmeric contains curcumin, a bioactive polyphenolic compound. Studies have found it to be anti-inflammatory, anti-diabetic, anti-cancer, anti-fibrosis, and antioxidant, which is also identified to prevent septic AKI via targeting the TLR9 signaling pathway [91, 92]. Research established a DDP-induced AKI mouse model, it found that curcumin significantly alleviated renal tubular injury and markedly down-regulated miRNA181a expression compared to the cisplatin injury group without curcumin treatment. It was also validated in cultured human embryonic kidney 293T cells that PTEN was the target of miR-181a, which can reduce renal tubular epithelial cells apoptosis, thereby can protect cisplatin-induced renal damage. It ascertained that curcumin achieves renal protection by inhibiting miR-181a expression level, and restoring inhibition of PTEN in vivo caused by cisplatin [93].

Dioscin (DIO), a naturally steroid saponin occurs in a variety of vegetables and herbs [94]. There were already numerous studies demonstrating its anti-tumor, anti-inflammatory, antiviral, hypolipidemic, and hepatoprotective function, in addition to protective effects against organ damage [95–99]. Several studies have identified miRNAs as possible targets for DIO in the treatment of AKI [100, 101]. A study used a rats model of CDDP-induced nephrotoxity and, in vitro, used NRK-52E and HK-2 cells, found that DIO alleviated CDDP-induced kidney injury in animals and also inhibited cytotoxicity in vitro. Dual luciferase reporter gene assay indicated that Sirt1 would be a target of miR-34a. DIO reversed the effects of DDP-induced upregulation of miR-34a while increasing Sirt1 levels, which exhibit powerful antioxidant effects via stimulating transcription activity of nuclear factor-erythroid 2-related factor 2 in treating AKI. In addition, dioxin altered the levels of HMGB1, COX-2, AP-1, TNF-α, IL-1β, IL-6, noticeably promoting the IκBα expression and decreasing the ratios of acetylated to normal NF-κB, thus suppressing inflammation via the Sirt1/NF-κB signaling pathway. This may be another essential mechanism by which DIO counteracts CDDP-induced kidney damage [100]. Furthermore, DIO-loaded zein nanoparticles (DIO-ZNP) remarkably recovered LPS-induced kidney damage in the cell proliferation and significantly improved the cell viability of NRK-52E in vitro. The RT-PCR analysis showed that DIO-ZNPs restored the down-regulated of miR-let-7i in the LPS-induced epithelial kidney cells, and the expression levels of TLR4 were obviously decreased more than two-fold compared with that of LPS-induced cells, which appeared to provoke significant inflammatory responses and activated a chain of inflammatory responses and endothelial injury. Therefore, it confirms that DIO-ZNP improves LPS-induced AKI by attenuating P38 and Akt inflammatory signaling [101].

Honokiol, a low molecular weight natural product derived from *Magnolia officinalis,* exhibits remarkable cytoprotective effects, including anti-inflammatory and antioxidant properties. Furthermore, it ameliorates cisplatin-induced AKI by preventing mitochondrial dysfunction [102]. Zhang et al. revealed for the first time that honokiol can obviously reverse the CLP-induced over-expression of miR-218-5p and inflammatory factor in mice models and glomerular mesangial cells. MiR-218-5p direct targets HO-1, which can protect cells and organs against injury by anti-inflammation, anti-oxidation, anti-apoptosis, anti-proliferation and immunomodulatory effects. Therefore honokiol may target the miR-218-5p/HO-1 pathway to ameliorate cell apoptosis and inflammation in sepsis AKI [103].

As a broad-spectrum anticancer compound, paclitaxel comes from yew trees, particularly from Taxus brevifolia Nutt, and is obtained from their bark. Furthermore, to investigate the effects of paclitaxel in the sepsis-associated AKI, Xu et al. explored miRNAs and protein expression levels in the serum of sepsis patients and LPS-induced HK-2 cells, and found that Inc-MALAT1 was markedly increased, while the knockdown of miRNA370-3p suppressed the expression of HMG1B1 and cell proliferation but accelerated the cell apoptosis as well as inflammatory factors production in vitro. It reveals that paclitaxel can restrain inflammation and apoptosis via the Inc-MALAT1/miR-370-3p/HMG1B1 axis, which provides a new research direction for sepsis-induced AKI [104].

The Chinese medical herb *Radix Pueraria* contains a natural isoflavonoid known as puerarin, which has been reported to exhibit renal-protective properties, including chronic renal injury and DDP-induced nephrotoxicity in previous research [105, 106]. A study indicated that puerarin may significantly reverse the alterations in renal antioxidant activities, and puerarin suppressed DDP-induced apoptosis associated protein expression by inhibiting miRNA31 expression in DDP-induced rat models and HK-2 cells. It has been confirmed that Numb is a downstream target of miRNA31-5p and negatively regulates the Notch signaling pathway. Researchers detected the expression of Numb and Notch1 in HK-2 cells, which indicated that puerarin might alleviate DDP-induced nephrotoxicity via promoting miR31-mediated Numb activation, thereby blocking the Notch signaling pathway [107].

**MiRNAs as biomarkers in AKI**

Serum creatinine concentration has long been the gold standard for diagnosing AKI; however, in early renal injury, serum creatinine and urine volume may not change easily observable, and the prognosis of AKI is poor if the disease is not diagnosed and treated in an early stage. As relatively stable molecules, miRNAs can be secreted into the extracellular space, making them useful biomarkers, readily detectable in plasma and urine [108]; because of the particular sensitivity to physiologic changes in organisms, miRNAs are superior and earlier predictor of AKI than serum creatinine [109].

Many investigators who used bioinformatics methods have demonstrated that miRNAs can be served as biomarkers of AKI caused by IRI [36, 110, 111]. A study identified that the levels of miR-21 (2842.82-fold) and miR-125b (536.8-fold) were significantly raised in the I/R-induced rats group, which showed that miR-125b may be positioned as a new biomarker of AKI caused by IRI [112]. In addition, a combined set of miRNAs may have the potential to become biomarkers for AKI. For example, a dynamic profiling study of urine miRNAs within 72 hours post-surgery in IRI AKI in both murine models and patients with AKI showed that urinary miRNAs together manifested a better diagnostic value for AKI induced by IRI than either alone. The study explored the miRNA expression profile in I/R-induced AKI rats' urine by the microarray method, the result showed that the levels of miR-192-5p, miR-378a-3p, and miR-30c-5p were enhanced and sooner than the urine NGAL and KIM-1 in rat models. Furthermore, researchers examined the levels of miRNAs in urine samples from patients who underwent cardiac operations. The analysis showed that the miRNA levels at two h post-operation were higher in patients with AKI, and there is an increasing trend that existed in more severe AKI stages. Notably, after the statistical analysis of sensitivity and specificity between miRNA and NGAL in patients’ urine samples, miR-30c-5p showed more sensitivity than NGAL, which demonstrated presentable diagnostic value in

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L/R-induced AKI [113]. Of course, in DDP and sepstop-induced AKI, miRNAs also exhibited excellent potential as biomarkers. A study revealed that in the urine of DDP-treated rats, the expression of kinds of miRNA was obviously up-regulated, thus identifying the potential of using a set of urinary miRNA biomarkers for DDP-induced AKI [114]. In another study, researchers compared the 30 miRNAs expression profile in plasma from sepstop-induced AKI patients with healthy controls, then associated these miRNA levels with prognosis and biochemical indicators of patients, which found that the high expression of mir-210 and mir-494 was positively correlated with blood urea nitrogen, Cr and cystatin C levels of patients, while low expression of mir-205 was negatively correlated [115]. Additionally, in LPS/ CLP-induced AKI mice, the expression of mir-452 was upregulated in renal tubular cells through NF-kB. Urinary miR-452 may be an effective biomarker for the early detection of AKI in sepsis [116]. A recent study about miR-370-3p and miR-495-3p indicated that their expression levels were markedly decreased in the urine of SA-AKI patients, which were negatively correlated with other biochemical indexes of renal injury. Besides, patients with high mir-370-3p and miR-495-3p expression rates had a higher 28 days-survival rate [117]. For CI-AKI, an early diagnosis and taking effective interventions is of key importance in survival and prognosis, miRNAs also have been found to be useful biomarkers in early CI-AKI diagnosis. This was also verified in patients who underwent coronary angiography or PCI and developed CI-AKI. Therefore, CI-AKI patients have significantly higher plasma miRNA levels than those without, suggesting that more sensitive and specific miRNAs of CI-AKI may be used for early detection of the disease [118].

It has been shown in all the aforementioned studies that miRNAs are potential biomarkers of AKI, and they have also been investigated as biomarkers of delayed graft function (DGF)-associated AKI [119, 120]. Khalid et al. found that hypothermic machine perfusion (HMP) was an effective method used in improving the effects of renal transplantation. MiR-21 is a miRNA in HMP that is readily detected by RT-qPCR, these investigators extracted and measured miRNA-21 in HMP fluid samples, and a correlation was found between miR-21 levels at 60 min post-perfusion and epidermal growth factor receptor levels at 6 and 12 months following transplantation, which suggest the predictive role of miR-21 in the early diagnosis of AKI after kidney transplantation [121]. Similarly, a study of vascular bed preservation fluid with kidney transplantation in 2019 indicated a significant association of high miRNAS05-3p levels with DGF, which exhibited high value as a non-invasive biomarker of DGF [122]. Another study showed that the high level of miRNA146a-5p expression has a distinct pattern in the renal tissue, and perhaps in the peripheral blood in the setting of DGF, which provides direction for refinements and strategies studies in the field of non-invasive molecular diagnosis of kidney graft dysfunction [123].

Conclusion

AKI is a disease with high morbidity and mortality rates, which has become a thorny health issue worldwide. Nowadays, the relationship between miRNAs and AKI has been widely studied. MiRNAs, a class of non-coding RNAs, serve a prominent role in AKI by fine-tuning large genetic networks and controlling specific primary targets. Therapeutically, it is noteworthy that some miRNAs appear to be involved in the pathogenesis and progression of AKI, while others may act as protective mediators (Table 1).

There already clinical trials have investigated if miRNA mimics and antagonists can directly intervene in diseases. In a study (NCT03601052) conducted in subjects with a history of keloid disease in which researchers injected remlarase (MRG-201) intradermally and assessed its safety, the results showed no deaths or serious adverse events, although the incidence of adverse events was higher than that of the control group. First-in-human testing (NCT01829971) of miRNA-based cancer therapy produced positive results with MRX34, a liposomal mimic of miRNA-34a, which demonstrated a manageable toxicity profile in most advanced solid tumor patients [124]. MiRNAs can control hundreds of target genes, but it is extremely difficult to identify which miRNAs are controlling cognitive functions, and adverse reactions to some miRNA-mimetic drugs have been documented in clinical trials [125]. Therefore, the research in the field of whether miRNAs that have opposite effects can be combined to treat AKI may become a worthy direction.

Over the past decades, molecular biomarkers are emerging as powerful tools in disease diagnosis. In earlier studies, each model is a particular single method to create, this may not accurately simulate the clinical characteristics of AKI patients, which limits its interpretation and generalizability; secondly, it should be noted that depending on the different methods of preparing blood samples, the type and concentration of miRNAs may vary, and miRNAs may be released into the plasma via exosomes if blood samples are not centrifuged promptly after collection [126]. Therefore, it is crucial to prepare a set of consistent sample collection and assay standards for detecting the expression levels of circulating miRNAs in blood specimens. As far as urinary miRNAs, most urinary miRNAs are derived from renal and urothelial cells, yet other tissues can also actively release miRNAs packaged in extracellular vesicles [127], so most studies on changes in urinary miRNA concentrations after kidney injury are independent exploratory studies. However, exosome-derived miRNAs may not be considered. Furthermore, urine is a metabolite of the kidney and bladder, therefore, it is possible that many miRNAs are released because of impaired renal function, or are destroyed in the urine due to pH and other physiological aspects of urine such as metabolic contaminants. To date, although most experimental studies on biomarkers have yielded results, due to the complex pathophysiological mechanisms of AKI, there are no biomarkers to distinguish specific damage in AKI, and therefore simultaneous measurement of miRNAs in serum and urine in subsequent experimental studies is essential for monitoring AKI. Besides, all these studies were conducted at single centers with finite sample sizes, whose variation across regions and populations limits the further generalization and application of the findings. Therefore, large, high-quality, multicentre clinical trials with long follow-up periods are still needed to validate these findings, and the effectiveness of miRNA as a biomarker for AKI needs to be further explored.

Natural products are a rich reservoir for drug discovery and development. The successful application of artemisinin and the awarding of the 2015 Nobel Prize proved the great value of natural products, but the current lack of clarity on the molecular mechanism has limited further development. We summarized the recent studies of natural products improving AKI via regulating the expression of miRNAs, which provides a novel theoretical and molecular basis for the development of natural products in the therapy of AKI. It is noteworthy that natural products are considered to regulate pathophysiological processes by targeting miRNAs, which first modulate the expression of miRNAs and subsequently mitigate renal damage by reducing inflammation, cell apoptosis, and reactive oxygen species pathways (Table 2, Figure 2), having satisfactory therapeutic effects to the treatment of AKI.

However, the research is still in its early stages, and further confirmation and validation are required before miRNAs may be employed as clinical treatments. Furthermore, there has been growing evidence in recent years that miRNAs are potent biomarkers for early AKI diagnosis, which may aid in the creation of novel AKI diagnostic tools. Nonetheless, differences in experimental design, sample collection methods, and analytical platform application are bottlenecks in the evaluation of miRNAs as biomarkers; however, these areas are likely to see additional work in the coming years, and overcoming these issues will propel the field forward. Although miRNAs appear to have limitations as therapeutic targets and
<table>
<thead>
<tr>
<th>Model type</th>
<th>miRNA</th>
<th>Target</th>
<th>Signaling pathway</th>
<th>Function</th>
<th>Sample</th>
<th>Reference</th>
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<td>miR-687</td>
<td>PTEN</td>
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<td>Bhatt et al. [27]</td>
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<td>p53/miR-17-5p/DR6</td>
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<td>HO-1, H2AX, S1PR1</td>
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<td>Cisplatin</td>
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<td>PDCD4</td>
<td>PDCD4/NF-κB and PTEN/AKT</td>
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<td>miR-590-3p</td>
<td>TLR4/TRAf6</td>
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<td>MicroRNA-23a-3p</td>
<td>FKBP5</td>
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<td>THBS2</td>
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<td>miR-214</td>
<td>PTEN</td>
<td>PTEN/AKT/mTOR</td>
<td>Anti-apoptosis, antioxidative stress</td>
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<td>miR-214-5p</td>
<td>GLP-1R</td>
<td>GLP-1R/AMPK</td>
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<td>GPX4</td>
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<td>miR-132-3p</td>
<td>Sirt1</td>
<td>NF-κB</td>
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<td>miR-34a</td>
<td>Sirt1</td>
<td>NF-κB</td>
<td>Anti-inflammatory, anti-apoptosis, antioxidative stress</td>
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<td>miR-195a-5p</td>
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<td>miR-107</td>
<td>RPS19</td>
<td>KEGG</td>
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<td>miR-449</td>
<td>SIRT1</td>
<td>SIRT1/p53/BAX</td>
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<td>miR-146b</td>
<td>ErbB4</td>
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<td>miR-709</td>
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<td>miR-429</td>
<td>PDCD4</td>
<td>NF-κB</td>
<td>Anti-inflammatory, anti-apoptosis</td>
<td>kidney tissue</td>
<td>Niu et al. [83]</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; IRI, ischemia-reperfusion injury.
### Table 2 The roles of natural products in different AKI models

<table>
<thead>
<tr>
<th>Natural Product</th>
<th>Structure</th>
<th>Model</th>
<th>Target miRNA</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td><img src="curcumin_structure.png" alt="Curcumin Structure" /></td>
<td>DDP-induced mouse</td>
<td>miR-181a</td>
<td>Down-regulate miR-181a expression, reduce renal tubular cell apoptosis.</td>
<td>[93]</td>
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<td>Dioscin</td>
<td><img src="dioscin_structure.png" alt="Dioscin Structure" /></td>
<td>CDDP-induced mouse, NRRK-52E and HK-2 cells</td>
<td>miR-34a</td>
<td>Reverse the up-regulation of miR-34a induced by cisplatin, increase the antioxidation activities.</td>
<td>[100]</td>
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<tr>
<td></td>
<td></td>
<td>LPS-induced epithelial kidney cells</td>
<td>miR-let-7i</td>
<td>Restore the LPS-induced downregulation of miR-let-7i, alleviate inflammatory responses and endothelial injury.</td>
<td>[101]</td>
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<tr>
<td>Huperzine</td>
<td><img src="huperzine_structure.png" alt="Huperzine Structure" /></td>
<td>CLP-induced mice models and glomerular mesangial cells</td>
<td>miR-218-5p</td>
<td>Reverse the CLP-induced overexpression of miR-218-5p, ameliorate cell apoptosis and inflammation.</td>
<td>[103]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td><img src="paclitaxel_structure.png" alt="Paclitaxel Structure" /></td>
<td>LPS-induced HK-2 cells</td>
<td>miR-370-3p</td>
<td>Restrain inflammation and apoptosis via Inc-MALAT1/miR-370-3p/HMG1 axis.</td>
<td>[104]</td>
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<tr>
<td>Puerarin</td>
<td><img src="puerarin_structure.png" alt="Puerarin Structure" /></td>
<td>DDP-induced rat models and HK-2 cells</td>
<td>miR-31</td>
<td>Suppress DDP-induced apoptosis-associated protein expression by inhibiting miRNA31 expression, reverse the alterations in renal antioxidant activities.</td>
<td>[108]</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury.

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**Figure 2** Curcumin, dioscin, honokiol, paclitaxel, and puerarin modulate the expression of their target miRNAs and mitigate renal damage by reducing inflammation, cell apoptosis, and reactive oxygen species pathways.
diagnostic tools for AKI, it is undeniable that the above studies open a new chapter in the treatment of acute kidney injury.

References


32. Song T, Chen M, Rao Z, et al. miR-17-92 ameliorates renal


