INTRODUCTION

Kidney disease may be generally classified clinically into two categories: acute kidney injury (AKI) and chronic kidney disease (CKD), both of which are tightly interconnected.1–3 AKI can often develop in clinical settings in critically ill patients, leading to increased morbidity and mortality.1,4 AKI is manifested by a rapid decline in the glomerular filtration rates (GFRs)6 and its pathogenesis is complex, involving ischemia, sepsis, drug toxicity and drug overdose, exposure to heavy metals, and diabetes. In spite of the advances in our understanding of the pathogenesis of AKI and CKD as well AKI transition to CKD, there is still no available therapeutics that can be used to combat kidney disease effectively, highlighting an urgent need to further study the pathological mechanisms underlying AKI, CKD, and AKI progression to CKD. In this regard, animal models of kidney disease are indispensable. This article reviews a widely used animal model of kidney disease, which is induced by folic acid (FA). While a low dose of FA is nutritionally beneficial, a high dose of FA is very toxic to the kidneys. Following a brief description of the procedure for disease induction by FA, major mechanisms of FA-induced kidney injury are then reviewed, including oxidative stress, mitochondrial abnormalities such as impaired bioenergetics and mitophagy, ferroptosis, pyroptosis, and increased expression of fibroblast growth factor 23 (FGF23). Finally, application of this FA-induced kidney disease model as a platform for testing the efficacy of a variety of therapeutic approaches is also discussed. Given that this animal model is simple to create and is reproducible, it should remain useful for both studying the pathological mechanisms of kidney disease and identifying therapeutic targets to fight kidney disease.

KEYWORDS
acute kidney injury, chronic kidney disease, ferroptosis, fibroblast growth factor 23, folic acid, mitochondria, mitophagy, oxidative stress, pyroptosis

1 | INTRODUCTION

Kidney disease may be generally classified clinically into two categories: acute kidney injury (AKI) and chronic kidney disease (CKD), both of which are tightly interconnected.1–3 AKI can often develop in clinical settings in critically ill patients, leading to increased morbidity and mortality.1,5 AKI is manifested by a rapid decline in the glomerular filtration rates (GFRs)6 and its pathogenesis is complex, involving ischemia, sepsis, drug toxicity, and trauma.7 If left unmanaged, AKI can develop into CKD, which is characterized by a progressive decrease in GFR, culminating in a gradual loss of renal function.8 The transition from AKI to CKD can also be hastened by numerous risk factors such as obesity, hypertension, diabetes, and chronic inflammation.9–11 Currently, there are no effective treatments for either AKI or CKD, stressing a continual need to elucidate the underlying pathological mechanisms of AKI and CKD. In this regard, animal models of kidney disease have been invaluable in that utilization of these animal models not only facilitates our understanding of the
pathogenesis of kidney disease, but also provides excellent platforms for disease intervention whereby efficacy of testing compounds or pharmacological agents can be quantitatively assessed.\textsuperscript{12–19}

There are numerous animal models that have been used to elucidate the pathological mechanisms of kidney disease.\textsuperscript{19–21} Those induced by ischemia,\textsuperscript{14,22,23} lipopolysaccharide,\textsuperscript{24–27} cisplatin,\textsuperscript{28–30} arsenic,\textsuperscript{31–33} adenine,\textsuperscript{34–36} cadmium\textsuperscript{15,37–40} and diabetes\textsuperscript{41–46} are widely used as animal models of kidney disease. These models have also been used to test the therapeutic effect of a given drug or compound.\textsuperscript{19,21,47,48} However, this article will focus on a very popular kidney disease animal model, the folic acid (FA)-induced rodent model involving the use of both mouse and rat.\textsuperscript{49–53} A comparison of the FA model with other chemically induced kidney injury animal models is given in Table 1.

It is worth noting that among all the animal models of kidney disease induced by the variety of approaches highlighted in Table 1, the FA-induced model provides certain advantages that are lacking in other models. First, FA is a vitamin and is not environmentally toxic, therefore routine handling in laboratories does not pose any hazards. Second, unlike ischemic surgery of kidney injury, of FA is administered as a simple injection, which does not require surgery and is noninvasive and animal friendly. Third, unlike the cadmium and cisplatin toxicity models, which induce multiple organ injury, the FA model mainly injures the kidney and has no deleterious effects on other organs.\textsuperscript{59} Fourth, depending on the experimental needs, one can investigate AKI or CKD or the AKI–CKD transition using a single injection of FA.\textsuperscript{55} Undeniably, the FA-induced kidney injury model has its own disadvantages. These include the high dose of FA that needs to be injected and the failure as yet to identify a specific biomarker of FA-induced kidney injury. Moreover, although FA-induced kidney injury occurs mainly to proximal tubules,\textsuperscript{54,100} a detailed molecular and biochemical mechanism underlying FA-induced nephron injury remains to be unraveled. It should be noted that the FA kidney injury model does not mimic patients with membranous nephropathy or glomerulonephritis\textsuperscript{101,102} or IgG4-immuned kidney disease.\textsuperscript{103–106}

2 | FOLIC ACID AND THE KIDNEYS

FA is also known as vitamin B\textsubscript{9}.\textsuperscript{107,108} It is a cofactor involved in one-carbon metabolism that is essential for cellular proliferation and growth.\textsuperscript{109–111} FA can be derived from egg yolk, animal livers, leafy vegetables, and yeast.\textsuperscript{112,113} FA is usually absorbed in the small intestine, and converted intracellularly to tetrahydrofolate by dihydrofolate reductase.\textsuperscript{112,113} FA deficiency can cause megaloblastic anemia and neural tube defect in the fetus due to its indispensable role in the synthesis of RNA and DNA molecules.\textsuperscript{113–115}

As a small molecular weight compound, FA or folate is freely filtered by the glomerulus.\textsuperscript{109} In fact, little folate renal excretion can be observed under normal folate concentrations and renal reabsorption of folate is nearly 100%. Renal reabsorption of folate is achieved by a high affinity folate receptor (folate receptor 1) that is abundant on the luminal side of proximal tubular epithelial cells.\textsuperscript{109} Once folate is bound to the receptor, an endocytosis process occurs which is followed by release of folate via vesicle budding and recycling of the receptor onto the epithelial cell membranes. The released folate is believed to be trapped in endosomal vesicles, as no freely floating folate has been observed in the cytosol.\textsuperscript{109} Subsequently, these endosomal vesicles could fuse with the membranes of other organelles and release folate, thereby leading to functional impairment of these organelles. Such is the case for mitochondria which can accumulate folate.\textsuperscript{55} It should be noted that non-endocytosis-dependent folate transport systems also exist on tubular epithelial membranes but folate receptor-mediated folate endocytosis is the most well elucidated mechanism. In mice lacking folate receptor due to folate receptor gene knockout,\textsuperscript{116} folate clearance is nearly 100% and no reabsorption of folate could be observed, indicating that folate renal toxicity, as well as downstream signaling, is mediated by the folate receptor.\textsuperscript{109}

As mentioned above, FA can accumulate in larger amounts in the kidney than in other tissues because of the high content of folate receptors in the kidneys.\textsuperscript{117,118} It is stored as folate derivatives that are cell membrane impermeable.\textsuperscript{119} Importantly, while folate distributes in all cellular compartments, mitochondria can take up to 40% of the folate pool,\textsuperscript{119,120} which can cause mitochondrial oxidative stress and mitochondrial abnormalities.\textsuperscript{121–125} Moreover, as folate reduction by dihydrofolate reductase to form tetrahydrofolate uses large amounts of NADPH as a reducing power,\textsuperscript{110} high levels of folate in the kidneys can severely compromise cellular antioxidative systems that also require NADPH,\textsuperscript{126,127} leading to aggravated redox imbalance and oxidative stress in this organ.\textsuperscript{128,129}

3 | HIGH DOSES OF FA AND RENAL INJURY

While low doses of FA (usually less than 10 mg/day) are beneficial and against oxidative stress,\textsuperscript{130–135} high doses of FA, e.g., 250 mg/day, as widely used in the induction of animal kidney disease, are highly toxic.\textsuperscript{134,135} A search in the PubMed database indicates that the first report of a renal problem caused by FA was published in 1968,\textsuperscript{136} and described renal hypertrophy induced by FA. The first report of kidney injury induced by FA was published in Germany in 1969.\textsuperscript{137} These studies led to the concepts of “renal folate toxicity” and “folate nephropathy” in 1970s.\textsuperscript{138–144} Now, the procedures of FA-induced kidney injury in mice and rats are well established and widely used. As outlined in Figure 1, in both mouse and rat models of acute kidney injury, a single injection of FA at a dosage of 250 mg/kg body weight intraperitoneally can cause AKI,\textsuperscript{145–147} resulting in proteinuria and increased blood urea nitrogen (BUN) and creatinine.\textsuperscript{148,149} AKI can be studied within 72 h of FA administration.\textsuperscript{55} If left untreated, CKD will develop and can be studied more than 4 weeks or beyond after FA injection (Figure 1).\textsuperscript{55} Multiple injections of a lower dose of FA (125–150 mg/kg body weight)\textsuperscript{150,151} or a single injection of lower dose of FA (less than 200 mg/kg body weight) can also produce symptoms of kidney disease that can be used to investigate the pathological mechanisms of AKI or CKD.\textsuperscript{152–154} Moreover, progression of AKI to CKD can also be investigated after a single
| Models     | Species       | Does range/duration GFR/BUN/Cre | Comments/advantages/disadvantages | Refs. |
|------------|---------------|---------------------------------|-----------------------------------|-------|
| Folic acid | Mouse/rat     | 250 mg/kg, 1 time I.P. Injection, 24–48 h AKI BUN: 65–80 AKI BUN: 300–350 (CKD) Cre: 1.2–1.4 (AKI) Cre: 6–7 (CKD) GFR: N.D. | Reproducible and simple, useful for studying AKI–CKD transition but no clinical correlation | 54, 55 |
| LPS        | Mouse/rat     | 10–15 mg/kg, single I.P. usually for AKI BUN: 38–45 Cre: 0.5–0.7 GFR: N.D. | Inexpensive, simple Response may vary between models | 19    |
| Cisplatin  | Mouse/rat     | Single I.P. injection with widely ranging dose, 6–20 mg/kg, up to 3 days for AKI BUN: 70–80 Cre: 2.4–2.8; GFR: N.D. | Reproducible and simple toxic to other organs, high dose needed for AKI induction | 56–58 |
| Cadmium    | Mouse/rat     | 1.2–6 mg/kg/day, oral administration or injection up to weeks for CKD induction BUN: 13–15 Cre: 1.4–1.8; GFR: N.D. | Varying dosage and duration toxic to other organs, epidemiological relevant, single I.P. injection for AKI | 15, 59–62 |
| Arsenic    | Mouse/rat     | Varying dosage I.P injection for AKI induction, chronic drinking for CKD induction BUN: 28–38 Cre: 1.7–1.9; GFR: N.D. | Varying dosage and duration, toxic to other organs, epidemiological relevant | 63–65 |
| Adenine    | Mouse/rat     | 0.15%–0.75% (w/w) in diet, Up to 16 weeks for CKD BUN: 90–120 Cre: 2.8–3.1; GFR: N.D. | Not for AKI induction, time-consuming for CKD | 66–68 |
| Ischemia   | Mouse/rat     | 30–40 min ischemia, 6–48 h reperfusion, AKI BUN: 160–280 Cre: 0.9–1.5; GFR: N.D. | Requires surgery, reproducibility maybe an issue, clinical relevant | 69–73 |
| DKD        | Mouse/rat     | Streptozotocin, 60–65 mg/kg single I.P. injection for rats, 30–40 mg/kg 5 injections for mice, type 2 diabetes can be induced by high fat diet-streptozotocin administration BUN: 25–30 mM Cre: 58–65 μM, GFR: N.D. | Not for AKI, time-consuming, duration varies from lab to lab, streptozotocin handled with care, genetic models also available | 42, 74–80 |
| 5/6 Nx     | Mouse/rat     | Invasive surgery required, for CKD induction, at least 1 week duration BUN: 17–19 mM Cre: 45–60 μM; GFR: N.D. | Infection and kidney bleeding may occur | 81–84 |
| Nicotine   | Mouse/rat     | 0.6–2.5 mg/kg I.P. injection up to 4 weeks for CKD induction BUN: 36–45 Cre: 0.75–0.82; GFR: N.D. | Noninvasive and simple, good model for podocyte injury, requires long term treatment | 85–88 |
| c-BSA      | Mouse/rat     | 50 mg/kg c-BSA via tail vein injection for up to 5 weeks for CKD induction, c-BSA dosage and duration could vary BUN: 18–25 Cre: 2.3–2.6; GFR: N.D. | Good model for membrane glomerulonephritis, chronic treatment required, c-BSA Needs to be self-prepared | 89–93 |
| UUO        | Mouse/rat     | 7–14 days, longer time for induction of kidney fibrosis BUN: 3.5–4.5 mM Cre: 42–58 μM, GFR: N.D. | Facile, reproducible, requires surgery, not popular for creating an AKI model | 19, 94–98 |

Note: This table is not meant to cover all the animal models of kidney injury in the literature. Rather, only popular and widely used animal models are listed. It should also be noted that when rats or mice are used, most investigators choose to use young adult animals aged from 4 to 8 weeks. Therefore, the reported kidney dysfunctional parameters may be different from those derived from old animals. Nonetheless, for a given age group of the same gender in a particular animal species, data may be comparable. For example, in the same lab setting, if every experimental condition is strictly followed, the severity of kidney disease induced by a single injection of FA may be classified based on BUN content as: mild, 40–80 mg/dl; moderate, 100–200 mg/dl; severe, greater than 200 mg/dl. The values shown in the Table for blood BUN and creatinine as well as GFR, if any, are for reference only as these numbers may vary from investigator to investigator.

The unit for BUN and Cre is mg/dl unless otherwise indicated.

Abbreviations: 5/6 Nx, 5/6 nephrectomy; BUN, blood urea nitrogen (mg/dl); c-BSA, cationic bovine serum albumin; Cre, creatinine (mg/dl); DKD, diabetic kidney disease; GFR, glomerular filtration rate; LPS, lipopolysaccharide; N.D., not determined; UUO, unilateral ureteral obstruction.
high dose FA injection.\textsuperscript{55} Therefore, FA-induced kidney disease can cover AKI, CKD, and the AKI–CKD transition.\textsuperscript{54} Additionally, as FA is water-soluble and the injection is intraperitoneal, the procedure of kidney disease induction is simple and straightforward, without the need for surgery. Importantly, FA-induced kidney disease can recapitulate the clinical symptoms of human kidney disease and the model is highly reproducible.\textsuperscript{128,155}

With respect to the FA-induced AKI–CKD transition, the FA model may provide certain advantages over other models of AKI–CKD transition including the ischemic reperfusion injury model, the cisplatin toxicity model, the diphtheria toxin model and the aristolochic acid model. As described above, the major advantage of the FA model is the one-time administration of a high FA concentration, which leads to reproducibility. In contrast, in ischemic reperfusion injury studies of AKI–CKD transition, more ischemic surgeries may be required following the initial surgery, which can cause preconditioning effects and may also result in loss of animals during the study, thereby causing reproducibility issues.\textsuperscript{18} The low dose cisplatin model, the diphtheria toxin model, and the aristolochic acid model all require repeated dosing of the animals in order for AKI to progress to CKD. An excellent review of animal models of AKI–CKD transition is provided by Fu et al.\textsuperscript{18} Given that the mechanisms underlying AKI–CKD transition still remain elusive, cross-examination and comparison of different AKI–CKD models may provide comprehensive insights into the mechanisms of AKI–CKD transition. Nonetheless, in the FA-induced AKI–CKD transition model, it is clear that mitochondrial abnormalities, redox imbalance, oxidative stress, and deranged fatty acid oxidation are involved in AKI–CKD transition.\textsuperscript{3,55,156,157}

With respect to which site or region in the nephron is vulnerable to FA-induced damage, it has been well established that FA damage occurs mainly to the proximal tubular epithelial cells (Figure 2).\textsuperscript{151,158–161} After FA injection, urinary volume shows a decrease, as does GFR and the filtration fraction. This is followed by an elevation in the concentration of blood urea nitrogen and creatinine.\textsuperscript{99,100} It should be noted that the concentration of folic acid used for intraperitoneal injection at a dose of 250 mg/kg body weight should not be higher than 12.5 mg/ml, as death of the animals has been observed when 25 mg/ml or 50 mg/ml of folic acid solution was used for AKI induction.\textsuperscript{100} For administration doses of folic acid solution at 12.5 mg/ml, the death rate of animals beyond 28 days has not been well documented because the duration of studies after FA injection varies from laboratory to laboratory.
One question arising herein is that, if FA mainly damages the proximal tubules, then how does this damage lead to the lowered GFRs that have been observed in the FA rodent model. This is likely caused by a tubular-glomerular interplay response to intratubular pressure created collectively by FA crystallization in the renal tubules, blockage of the proximal tubules, and induction of tubular injury and cell death. In fact, this tubular-glomerular response is a well-known feedback mechanism that also occurs in drug-induced kidney toxicity and ureteral obstruction kidney disease.

It should also be noted that the FA-induced kidney injury model is only an experimental animal model because high levels of FA have not been observed in patients with CKD or associated with kidney disease progression. Nonetheless, the FA model recapitulates all the human AKI pathologies observed in the clinic. Moreover, the FA model is highly reproducible. In these respects, the FA experimental animal model is similar to streptozotocin-induced type 1 diabetes animal models, in that STZ does not exist at high levels in type 1 diabetic patients yet STZ diabetes induction recapitulates many of the clinical manifestations of these patients. As is inherent in all animal models of human diseases, any animal model of kidney disease will serve only as a proxy and will never be identical to human kidney disease.

Despite the inherent drawbacks, the FA model is also clinically relevant because accidental folic acid overdose can occur and cause AKI in humans that shares the major pathological processes of inflammation, fibrosis, cell death and proliferation seen in the FA rodent model. Another clinical factor that supports the experimental utilization of the FA kidney disease model is use of the broadly employed anti-cancer drug methotrexate, which is a derivative of folic acid and is highly toxic to the kidneys.

4 | MAJOR MECHANISMS OF FA-INDUCED KIDNEY INJURY

After a high dose of FA administration via IP injection, FA can quickly form crystals in the kidney within renal tubules, followed by acute tubular necrosis, epithelial regeneration, and renal cortical scarring, culminating in renal injury reflected by decreased glomerular filtration rates (GFRs), renal inflammation, and renal fibrosis. While this sequence of events sounds simple, the underlying biochemical and molecular mechanisms are complex and multifaceted. In general, after FA injection, renal hypertrophy occurs, serum BUN and creatinine are elevated, clinical symptoms of acute renal failure such as attenuated alertness, fatigue or lethargy, and bristling of the coat can also be observed. Here, the major mechanisms involved in FA-induced kidney disease are summarized.

4.1 | Oxidative stress

Numerous studies demonstrate renal oxidative stress in the FA-induced kidney disease model. For example, in FA-AKI mouse model, Gupta et al. found that lipid peroxidation was increased with a decreased level of the reduced form of glutathione. In the meantime, levels of hydrogen peroxide were increased, SOD activity was decreased, and glutathione peroxidase activity was also decreased, so was glutathione-s-transferase. These results indicate a redox imbalance status induced by FA injection.

4.2 | Ferroptosis

Martin-Sanchez et al. demonstrated the involvement of ferroptosis in FA-induced AKI. When ferroptosis was inhibited by ferrostatin-1, a ferroptosis inhibitor, renal injury induced by FA could be prevented, together with a decreased occurrence of lipid peroxidation. The authors also found that ferroptosis triggered inflammation in the kidney upon FA injection was also attenuated by ferrostatin-1 treatment, further demonstrating the role of ferroptosis in FA-induced AKI. Moreover, when apoptosis or necrosis was targeted, no protection against AKI was observed, indicating that ferroptosis plays a more important role in AKI induced by FA, at least in the authors’ experimental settings. It should be noted that other types of cell death such as pyroptosis and apoptosis have also been reported in FA-induced kidney disease.

4.3 | Impairment of mitochondrial bioenergetics

In an elegant study exploring the mechanisms of AKI–CKD transition after FA injection, Aparicio-Trejo et al. demonstrated that impaired mitochondrial bioenergetics was involved in FA-induced renal injury. The authors analyzed mitochondrial complex I-linked respiration using isolated mitochondria and found that state 3 respiration (in the presence of ADP) was decreased at the acute stage of renal injury, but returned to normal after 7 and 14 days, respectively, indicating that decreased complex I-linked respiration could last up to 7 days. There was also a progressive electron leakage from AKI to CKD, further demonstrating the involvement of mitochondrial uncoupling in kidney disease transition from AKI to CKD. During this process, fatty acid β-oxidation was also impaired, which may also contribute to the AKI–CKD transition process as well as renal fibrosis. This study demonstrates that impairment of mitochondrial bioenergetics is involved in AKI, CKD, and AKI–CKD transition, further highlighting a key role of mitochondrial dysfunction in FA-induced kidney disease.

4.4 | Increased levels of fibroblast growth factor 23 (FGF23)

FGF23 is a protein that regulates phosphate homeostasis and vitamin D metabolism. The content of this protein has been shown to increase rapidly upon FA-induced AKI. This upregulation of FGF23 is likely controlled by interleukin-6 (IL-6) as IL-6 inhibition by dexamethasone abolished FGF23 upregulation in FA-induced
In contrast, overexpression of IL-6 could further increase FGF23 levels both in vivo and in vitro. These results demonstrate the involvement of increased FGF23 content in FA-induced AKI, likely due to dysregulation of phosphate homeostasis and vitamin D metabolism. However, whether there is a link between increased FGF23 and elevated oxidative stress in the FA-induced AKI model remains elusive at the present time.

4.5 | Impaired mitophagy

Mitophagy is a mechanism by which damaged mitochondria are eliminated within a cell after stress challenges.\(^{186,187}\) It is regulated by, among others, PINK1 (PTEN-induced putative kinase 1)\(^{28,188}\) and autophagy proteins microtubule-associated protein 1A/1B-light chain 3I (LC-3I) and p62 in proximal tubules.\(^{188,189}\) Using rat as an FA-AKI model, Aparicio-Trejo et al.\(^{155}\) demonstrated that PINK1 and p62 were increased 24 h after FA injection with concurrent decreases in LC-3I and LC-3II contents, indicating an impaired process of mitophagy. Moreover, the authors also demonstrated a compromised process of mitochondrial fission and fusion process that is regulated by Opa1 and mitofusion-1, as increased levels of mitochondrial fragments could be clearly detected in the FA-AKI model. This study suggests that impaired mitophagy and mitochondrial dynamics are involved in FA-induced AKI. Interestingly, N-acetylcysteine pretreatment could prevent all these impairments,\(^{155}\) implying the involvement of oxidative stress in the pathogenesis of AKI-induced by FA. All the above-described potential mechanisms of FA-induced AKI or CKD are schematically represented in Figure 3.

Overall and mechanistically, it should be pointed out that FA injection mainly damages the kidney and does not affect other organs,\(^{99}\) and the damage mainly occurs to the proximal tubules. While it is well established that oxidative damage reflected by enhanced lipid peroxidation and deceased levels of glutathione and antioxidant capacity is the culminating event leading to cell death of tubular epithelial cells including apoptosis, necrosis, and ferroptosis, the upstream signaling processes are multifactorial. These include downregulation of klotho,\(^{177,190}\) and increased expression of FGF21 and FGF23,\(^{183,184,191}\) the latter of which is likely regulated by interleukin-6.\(^{185}\) FGF21 also relies on beta-klotho protein to bind fibroblast growth factor receptor to exert its biological function in the kidney.\(^{191}\) In addition, among the genes affected by FA-induced kidney injury, c-myc and c-fos, involved in initiating cell cycle events, are believed to be the primary response genes.\(^{192}\) Nonetheless, the exact roles of these response genes in FA-induced kidney injury remains to be comprehensively evaluated.

5 | APPLICATION OF THE FA-INDUCED KIDNEY DISEASE MODEL IN TESTING THE THERAPEUTIC EFFECTS OF A VARIETY OF PHARMACOLOGICAL COMPounds

In addition to being used to elucidate the pathological mechanisms underlying kidney disease, the FA-induced animal model of kidney disease, like many other animal models, has also been used to test the therapeutic effects of pharmacological agents, chemicals, and natural compounds. Table 2 lists selectively some of the tests using the FA-induced animal model of kidney disease as a platform. It should be noted that all the listed compounds are at a pre-clinical stage as the tests of their beneficial effects on kidney disease all involve laboratory animals.

Relevant to Table 2, all animal models of kidney disease, regardless of the inducers or triggers applied, may end up with increased oxidative damage as a common mechanism that leads to renal inflammation and fibrosis, followed by kidney functional decline.
by decreased GFR, and increased BUN and creatinine.\textsuperscript{213,214} Therefore, natural products possessing antioxidant powers, such as those listed in Table 2, could offer potential benefits in treating FA-induced kidney injury. One caveat is that while the FA-induced kidney injury model can be used to test numerous natural products, identification of the most potent one would be challenging because testing conditions and experimental designs vary from laboratory to laboratory and no single laboratory can test all the available natural products. It is likely that administration of multiple products that are tolerable will offer synergistic benefits to CKD patients.

### MISCELLANEOUS

As well as being an experimental tool for elucidating the mechanisms underlying kidney injury, the FA-induced animal model has also been used for identification of biomarkers of kidney injury. For example, using a proteomic approach Rattanasinganchan et al. reported biomarkers of tubulointerstitial fibrosis from urinary exosomes derived from FA-treated rats, demonstrating the feasibility of using this model for renal fibrosis biomarker identification.\textsuperscript{99} FA-induced CKD can also cause anemia in mice.\textsuperscript{215} Additionally, in terms of CKD model creation, the FA-induced model will certainly take less time than does the adenine-induced CKD model, which requires at least 16 weeks of adenine (0.25%) administration.\textsuperscript{68} It should also be noted that while most studies using this FA animal model involve young adult mice or rats, FA-induced kidney injury in aged animals has also been investigated. Marquez-Exposito et al. have found that aging can aggravate AKI induced by FA,\textsuperscript{216} indicating that age should be factored into an experimental design when the FA-induced kidney injury model is to be utilized. Future studies using the FA-induced animal model may also shed light on the role of age in kidney injury progression.

### TABLE 2

| Compound/or chemical | Model                          | Mechanism                                      | References |
|----------------------|--------------------------------|------------------------------------------------|------------|
| Ancrod               | CKD/mouse                      | Decreased renal fibrosis                       | 193        |
| Cyclosporine A       | AKI/mouse                      | Decreased apoptosis                            | 194        |
| Fraxinellone         | CKD/mouse                      | Decreased renal fibrosis                       | 195        |
| Ibudilast            | AKI/mouse                      | Blocking pyroptosis                            | 179        |
| Nicorandil           | AKI/mouse                      | Decreased oxidative stress                     | 196        |
| Curcumin             | AKI/rat                        | Improved kidney structure                      | 197        |
| Nuciferine           | AKI/mouse                      | Inhibition of ferroptosis                      | 198        |
| Fluorofenidone       | AKI/mouse                      | Decreased ROS/NLRP3                            | 199        |
| Lactoferrin          | AKI-CKD/patients               | Autophagy activation                           | 178        |
| Curcuminoid          | AKI/mouse                      | Inhibition of apoptosis                         | 190        |
| Nilotinib            | AKI/mouse                      | Hsp70 activation                               | 200        |
| Salidroside          | AKI/mouse                      | MAPK signaling                                 | 201        |
| Celestrol            | AKI/mouse                      | Increased cannabinoid receptor 2               | 202        |
| Metformin            | CKD/mouse                      | Attenuation of renal fibrosis                  | 203        |
| Nintedanib           | AKI-CKD/mouse                  | Decreased renal fibrosis                       | 153        |
| Melatonin            | AKI/mouse                      | HMGB1 translocation                            | 151        |
| Tanshinone IIA       | AKI/mouse                      | Attenuation of renal fibrosis                  | 204        |
| Tanshinone IIA       | AKI-CKD/mouse                  | Targeting GSK3β                                 | 205, 206   |
| N-acetylcysteine     | AKI/mouse                      | Increased glutathione                           | 207        |
| N-acetylcysteine     | AKI/rat                        | Mitophagy activation                           | 155        |
| Angiopoietin-1       | AKI/mouse                      | Enhancing fibrosis                             | 208        |
| Anti-TNF antibody    | AKI/mouse                      | Inhibition of cell death                        | 209        |
| PFI-2                | CKD/mouse                      | Decreased renal fibrosis                       | 166        |
| Citrus pectin        | AKI/mouse                      | Decreased renal fibrosis                       | 210        |
| Quercetin            | AKI/mouse                      | Inhibition of ferroptosis                      | 211        |
| Roxadustat           | AKI/mouse                      | Anti-ferroptosis                               | 212        |

Abbreviations: GSK3β, glycogen synthase kinase 3β; HMGB1, high mobility group box 1; PFI-2, 8-Fluoro-N-(1-oxo-1-(pyrrolidin-1-yl)-3-(3-(trifluoromethyl)phenyl)propan-2-yl)-1,2,3,4-tetrahydroisoquinoline-6-sulfonamide hydrochloride.
light on effects of other risk factors such as hypertension, obesity and diabetes on FA-induced kidney disease. It is conceivable that such risk factors would also exacerbate FA-induced kidney injury. Sex-linked susceptibility of the kidneys to FA-induced injury, if any, should also be investigated.

It should be emphasized once again that while high doses of FA administered intentionally can cause renal diseases including AKI and CKD, the nutritional and therapeutic value of low levels of FA or purposefully fortified FA supplements cannot be discounted. In fact, given that high levels of blood homocysteine occur in approximately 85% of CKD patients, FA deficiency may serve as a diagnostic indicator and FA administration can slow down the progression of CKD. This is due to the mechanism whereby FA is involved in lowering the blood levels of homocysteine by converting it to methionine in a methionine cycle pathway. High homocysteine is known to pose an independent risk factor for cardiovascular disease.

7 | SUMMARY

High doses of FA can induce both AKI and CKD in mice and rats. This FA-induced animal model can also be used to study the AKI–CKD transition or progression. The procedure for establishing the model is easy as FA is water soluble and its administration is achieved by intraperitoneal injection. More importantly, the model is reproducible and can recapitulate most, if not all, of the human kidney disease phenotypes. Therefore, this model should continue to play a key role in the field of kidney disease research. In addition, future studies are needed to evaluate any potential cardiovascular disease caused by FA-induced CKD, and will require analysis of changes in the profiles of blood mineral including phosphate, calcium, and magnesium. Any detrimental effects of FA-induced kidney disease on other organs such as the liver and the brain will also need to be comprehensively evaluated.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

LJY conceived the idea and wrote the paper.

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REFERENCES

1. Fiorentino M, Grandaliano G, Gesualdo L, Castellano G. Acute kidney injury to chronic kidney disease transition. Contrib Nephrol. 2018;193:45-54. doi:10.1159/000484962
2. He L, Wei Q, Liu J, et al. AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. Kidney Int. 2017;92(5):1071-1083. doi:10.1016/j.kint.2016.06.030
3. Jiang M, Bai M, Lei J, et al. Mitochondrial dysfunction and the AKI-to-CKD transition. Am J Physiol Renal Physiol. 2020;319(6):F1105-F1116. doi:10.1152/ajpregnal.00285.2020
4. Al-Jaghbeer M, Dealmeida D, Biderback A, Ambrosino R, Kellum JA. Clinical decision support for in-hospital AKI. J Am Soc Nephrol. 2018;29(2):654-660. doi:10.1681/ASN.2017070765
5. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-c184. doi:10.1159/000339789
6. Horne KL, Packington R, Monaghan J, Reilly T, Selby NM. Three-year outcomes after acute kidney injury: results of a prospective parallel group cohort study. BMJ Open. 2017;7(3):e015316. doi:10.1136/bmjopen-2016-015316
7. Huang J, Bayliss G, Zhuang S. Porcine models of acute kidney injury. Am J Physiol Renal Physiol. 2021;320(6):F1030-F1044. doi:10.1152/ajpregnal.00022.2021
8. Levey AS, Becker C, Inker L. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837-846. doi:10.1001/jama.2015.0602
9. Chintam K, Chang AR. Strategies to treat obesity in patients with CKD. Am J Kidney Dis. 2021;77(3):427-439. doi:10.1016/j.ajkd.2020.08.016
10. Lamprea-Montalegre JA, Shlipak MG, Estrella MM. Chronic kidney disease transition, staging and treatment in cardiovascular disease prevention. Heart. 2021;107(16):1282-1288. doi:10.1136/heartjnl-2020-318004
11. Stenvinkel P, Chertow GM, Devarajan P, et al. Chronic inflammation in chronic kidney disease progression: role of Nrf2. Kidney Int. 2021;97(6):1775-1787. doi:10.1016/j.kint.2021.04.023
12. Nogueira A, Pires MJ, Oliveira PA. Pathophysiological mechanisms of renal fibrosis: a review of animal models and therapeutic strategies. In Vivo. 2017;31(1):1-22. doi:10.21873/invivo.11019
13. Thornton MA, Winn R, Alpers CE, Zager RA. An evaluation of the neutrophil as a mediator of in vivo renal ischemic-reperfusion injury. Am J Pathol. 1989;135(3):509-515
14. Dare AJ, Bolton EA, Pettigrew GJ, Bradley JA, Saeb-Parsy K, Murphy MP. Protection against renal ischemia-reperfusion injury in vivo by the mitochondria targeted antioxidant MitoQ. Redox Biol. 2015;3:163-168. doi:10.1016/j.redox.2015.04.008
15. Almeer RS, AlBasher GI, Alarifi S, Alkahtani S, Ali D, Abdel Moneim AE. Royal jelly attenuates cadmium-induced nephrotoxicity in male mice. Sci Rep. 2019;9(1):5825. doi:10.1038/s41598-019-42368-7
16. Ning YC, Cai GY, Zhuo LJ, et al. Beneficial effects of short-term calorie restriction against cisplatin-induced acute renal injury in aged rats. Nephron Exp Nephrol. 2013;123(4-5):19-27. doi:10.1159/000357380
17. Shi Q, Lang W, Wang S, et al. Echinacea polysaccharide attenuates lipopolysaccharide-induced acute kidney injury via inhibiting inflammation, oxidative stress and the MAPK signaling pathway. Int J Mol Med. 2021;47(1):243-255. doi:10.3892/ijmm.2020.4769
18. Fu Y, Tang C, Cai J, Chen G, Zhang D, Dong Z. Rodent models of AKI–CKD transition. Am J Physiol Renal Physiol. 2018;315(4):F1098-F1106. doi:10.1152/ajpregnal.00199.2018
19. Bao YY, Yuan Y, Chen JH, Lin WQ. Kidney disease models: tools to identify mechanisms and potential therapeutic targets. Zool Res. 2018;39(2):72-86. doi:10.24272/j.issn.2095-8137.2017.055
20. Singh AP, Muthuraman A, Jaggi AS, et al. Animal models of acute renal failure. Pharmacol Rep. 2012;64(1):31-44. doi:10.1016/s1734-1140(12)70728-4
21. Rabe M, Schaefer F. Non-transgenic mouse models of kidney disease. Nephron. 2016;123(1):53-61. doi:10.1159/000445171
22. Zhu YB, Zhang YP, Zhang J, Zhang YB. Evaluation of vitamin C supplementation on kidney function and vascular reactivity following renal ischemic injury in mice. Kidney Blood Press Res. 2016;41(4):460-470. doi:10.1159/000443447
23. Zhuang S, Lu B, Daubert RA, Chavin KD, Wang L, Schnellmann RG. Suramin promotes recovery from renal ischemia/reperfusion.
in mice. Kidney Int. 2009;75(3):304-311. doi:10.1038/ki.2008.506

24. Zhang W, Guan Y, Bayliss G, Zhuang S. Class IIa HDAC inhibitor TMP195 alleviates lipopolysaccharide-induced acute kidney injury. Am J Physiol Renal Physiol. 2020;319(6):F1015-F1026. doi:10.1152/ajprenal.00405.2020

25. Sun M, Li J, Mao L, et al. p53 deacetylation alleviates sepsis-induced acute kidney injury by promoting autophagy. Front Immunol. 2021;12:685523. doi:10.3389/fimmu.2021.685523

26. Liu X, Lu J, Liao Y, et al. Dihydroartemisinin attenuates lipopolysaccharide-induced acute kidney injury by inhibiting inflammation and oxidative stress. Biomed Pharmacother. 2019;117:109070. doi:10.1016/j.biopha.2019.109070

27. Tran M, Tam D, Bardia A, et al. PGC-1alpha promotes recovery after acute kidney injury during systemic inflammation in mice. J Clin Invest. 2011;121(10):4033-4044. doi:10.1172/JCI58662

28. Wang Y, Tang C, Cai J, et al. PINK1/Parkin-mediated mitophagy is activated in cisplatin nephrotoxicity to protect against kidney injury. Cell Death Dis. 2018;9(11):1113. doi:10.1038/s41419-018-1152-2

29. Mapuskar KA, Wen H, Holanda DG, et al. Persistent increase in mitochondrial superoxide mediates cisplatin-induced chronic kidney disease. Redox Biol. 2019;20:98-106. doi:10.1016/j.redox.2018.09.020

30. Wen J, Zeng M, Shu Y, et al. Aging increases the susceptibility of cisplatin-induced nephrotoxicity. Age (Dordr). 2015;37(6):112. doi:10.1007/s11357-015-9844-3

31. Riaz MA, Nisa ZU, Mehmood A, Anjum MS, Shahzad K. Metal-induced nephrotoxicity to diabetic and non-diabetic Wistar rats. Environ Sci Pollut Res Int. 2019;26(30):31111-31118. doi:10.1007/s11356-019-06022-x

32. Kimura A, Ishida Y, Hayashi T, et al. Interferon-gamma plays protective roles in sodium arsenite-induced renal injury by up-regulating intrarenal multidrug resistance-associated protein 1 expression. Am J Pathol. 2006;169(4):1118-1128. doi:10.2353/ajpath.2006.060024

33. Lee JY, Eom M, Yang JW, Han BG, Choi SO, Kim JS. Acute kidney injury by arsenic poisoning: the ultrastructural pathology of the kidney. Ren Fail. 2013;35(2):299-301. doi:10.3109/088622X.2012.745117

34. Hussein AM, Eldosoky M, Abdel Malek H, Elshafey M, El Nachar E, Dahab G. Effects of nicorandil on vascular and renal dysfunctions in adenine-induced nephropathy: possible underlying mechanisms. Gen Physiol Biophys. 2019;38(6):545-556. doi:10.4149/gpb_2019034

35. Liu X, Huang S, Wang F, et al. Ginger alleviates hyperglycemia-induced oxidative stress, inflammation and apoptosis and protects rats against diabetic nephropathy. Biomed Pharmacother. 2018;106:381-389. doi:10.1016/j.biopha.2018.06.148

36. Alhaidar AA, Korashy HM, Sayed-Ahmed MM, Mobark M, Kfoury H, Mansour MA. Metformin attenuates streptozotocin-induced diabetic nephropathy in rats through modulation of oxidative stress genes expression. Chem Biol Interact. 2011;192(3):233-242. doi:10.1016/j.cbi.2011.03.014

37. Ogura Y, Kitada M, Monno I, Kanasaki K, Watanabe A, Koya D. Renal mitochondrial oxidative stress is enhanced by the reduction of Sirt3 activity, in Zucker diabetic fatty rats. Redox Rep. 2018;23(1):153-159. doi:10.1080/13510002.2018.1487174

38. Ogura Y, Kitada M, Xu J, Monno I, Koya D. CD38 inhibition by apigenin ameliorates mitochondrial oxidative stress through restoration of the intracellular NAD(+)/NADH ratio and Sirt3 activity in renal tubular cells in diabetic rats. Aging. 2020;12(12):11325-11336. doi:10.18632/aging.103410

39. Gao P, Yang M, Chen X, Xiong S, Liu J, Sun L. DsbA-l deficiency exacerbates mitochondrial dysfunction of tubular cells in diabetic kidney disease. Clin Sci. 2020;134(7):677-694. doi:10.1042/CSS200005

40. Sharma K, McCue P, Dunn SR. Diabetic kidney disease in the db/db mouse. Am J Physiol Renal Physiol. 2003;284(6):F1138-F1144. doi:10.1152/ajprenal.00315.2002

41. Becker GJ, Hewitson TD. Animal models of chronic kidney disease: useful but not perfect. Nephrol Dial Transplant. 2013;28(10):2432-2438. doi:10.1093/ndt/gft071

42. Yang HC, Zuo Y, Fogo AB. Models of chronic kidney disease. Drug Discov Today Dis Models. 2010;7(1-2):13-19. doi:10.1016/j.ddmod.2010.08.002

43. Martin-Sanchez D, Fontecha-Barriuso M, Carrasco S, et al. TWEAK and RIPK1 mediate a second wave of cell death during AKI. Proc Natl Acad Sci U S A. 2018;115(6):4182-4187. doi:10.1073/pnas.1716578115

44. Zheng S, Liu J, Zhao Z, Song R. Role of STAT3/mTOR pathway in diabetic kidney injury. Am J Transl Res. 2020;12(7):3302-3310.

45. Guo L, Zhang T, Wang F, et al. Targeted inhibition of Rev-erb-alpha/beta limits ferroptosis to ameliorate folic acid-induced acute kidney injury. Br J Pharmacol. 2021;178(2):328-345. doi:10.1111/bph.15283

46. Chen B, Wang P, Liang X, et al. Permissive effect of GSK3beta on profibrogenic plasticity of renal tubular cells in progressive chronic kidney disease. Cell Death Dis. 2021;12(5):432. doi:10.1038/s41419-021-03709-5

47. Santos S, Bosch RJ, Ortega A, et al. Up-regulation of parathyroid hormone-related protein in folic acid-induced acute renal failure. Kidney Int. 2001;60(3):982-995. doi:10.1046/j.1523-1755.2001.06003982.x

48. Perales-Quintana MM, Saucedo AL, Lucio-Gutiérrez JR, et al. Metabolomic and biochemical characterization of a new model of the transition of acute kidney injury to chronic kidney disease induced by folic acid. Proc Natl Acad Sci U S A. 2018;115(6):4182-4187. doi:10.1073/pnas.1716578115

49. Perse M. Cisplatin mouse models: treatment, toxicity and translatability. Biomedicines. 2021;9(10):1406. doi:10.3390/biomedicines9101406
58. Morsy MA, Heeba GH. Nebivolol ameliorates cisplatin-induced nephrotoxicity in rats. Basic Clin Pharmacol Toxicol. 2016;118(6):449-455. doi:10.1111/bcpt.12538
59. Chen Q, Zhang R, Li WM, et al. The protective effect of grape seed procyanidin extract against cadmium-induced renal oxidative damage in mice. Environ Toxicol Pharmacol. 2013;36(3):759-768. doi:10.1016/j.etap.2013.07.006
60. Claudio SR, Pidone Ribeiro FA, De Lima EC, et al. The protective effect of grape skin or purple carrot extracts against cadmium intoxication in the kidney of rats. Drug Res. 2020;70(11):503-511. doi:10.1055/a-1221-4733
61. Handan BA, De Moura CFG, Cardoso CM, Santamarina AB, Pisani LP, Ribeiro DA. Protective effect of grape and apple juices against cadmium intoxication in the kidney of rats. Drug Res. 2018;70(11):503-511. doi:10.1055/a-1221-4733
62. Yan L-J, Allen DC. Cadmium-induced kidney injury: oxidative damage as a unifying mechanism. Biomolecules. 2021;11(11):1575.
63. Dutta S, Saha S, Mahalanobish S, Sadhukhan P, Sil PC. Melatonin attenuates arsenic induced nephropathy via the regulation of oxidative stress and inflammatory signaling cascades in mice. Food Chem Toxicol. 2018;118:303-316. doi:10.1016/j.fct.2018.05.032
64. Liu P, Yue Y, Zheng B, et al. Crocetin attenuates the oxidative stress, inflammation and apoptosis arsenic trioxide-induced nephrotoxic rats: implication of PI3K/AKT pathway. Int Immunopharmacol. 2020;88:106959. doi:10.1016/j.intimp.2020.106959
65. Robles-Osorio ML, Sahab-Silva E, Sahab E. Arsenic-mediated nephrotoxicity. Ren Fail. 2015;37(4):542-547. doi:10.3109/01915320.2015.103149
66. Liu X, Deng R, Wei X, et al. Jian- Pi- Yi- Shen formula enhances oxidative stress, inflammation and apoptosis in arsenic trioxide-induced nephrotoxicity. Int Immunopharmacol. 2016;40:305-312. doi:10.1016/j.intimp.2016.09.006
67. Kim K, Anderson EM, Thome T, et al. Skeletal myopathy in CKD: a comparison of adenine-induced nephropathy and 5/6 nephrectomy models in mice. Am J Physiol Renal Physiol. 2021;321(1):F106-F119. doi:10.1152/ajprenal.00117.2021
68. Diwan V, Brown L, Gobe GC. Adenine-induced chronic kidney disease in rats. Nephrology. 2018;23(5):5-11. doi:10.1111/nep.13180
69. Yan Y, Bai J, Zhou X, et al. P2X7 receptor inhibition protects against cadmium intoxication in the kidney of rats. Drug Res. 2018;70(11):503-511. doi:10.1055/a-1221-4733
70. Ohkita M, Hayashi H, Ito K, et al. Preventive effects of grape skin or purple carrot extracts against cadmium intoxication in the kidney of rats. Drug Res. 2021;8:719950. doi:10.3389/fmed.2021.719950
71. Akan E, Cetinkaya B, Kipmen-Korgun D, et al. Effects of amnion derived mesenchymal stem cells on fibrosis in a 5/6 nephrectomy model in rats. Biotech Histochem. 2021;1-14. doi:10.1080/105295.2021.1875502
72. Liu X, Luo D, Huang S, et al. Impaired nicotinamide adenine dinucleotide biosynthesis in the kidney of chronic kidney disease. Front Physiol. 2021;12:723690. doi:10.3389/fphys.2021.723690
73. Wang JS, Tsai PH, Tseng KF, Chen FY, Yang WC, Shen MY. Sesamol ameliorates renal injury-mediated atherosclerosis via inhibition of oxidative stress/KKalpha/p53. Antioxidants. 2021;10(10):1519. doi:10.3390/antiox10101519
74. Tan RZ, Zhong X, Li JC, et al. An optimized 5/6 nephrectomy model based on unilateral kidney ligation and its application in renal fibrosis research. Ren Fail. 2019;41(1):555-566. doi:10.1080/0886022X.2019.1627220
75. Kim HJ, Park KK, Chung WY, Lee SK, Kim KR. Protective effect of white-fleshed peach (Prunus persica (L.) Batsch) on chronic nicotine-induced toxicity. J Cancer Prev. 2017;22(1):22-32. doi:10.15430/JCP.2017.22.1.22
76. Lan X, Lederman R, Eng JM, et al. Nicotine induces podocyte apoptosis through increasing oxidative stress. PLoS One. 2016;11(12):e0167071. doi:10.1371/journal.pone.0167071
77. Ramalingam A, Santhanathas T, Shaukat Ali S, Zainalabidin S. Resveratrol supplementation protects against nicotine-induced kidney injury. Int J Environ Res Public Health. 2019;16(22):4445. doi:10.3390/ijerph16224445
78. Salahshoor MR, Roshankhah S, Motavalian V, Jalihi C. Effect of harmine on nicotine-induced kidney dysfunction in male mice. Int J Prev Med. 2019;10:97. doi:10.4103/ijpvm.IJPVM_85_18
79. Pan P, Wang YJ, Han L, Liu X, Zhao M, Yuan YF. Effects of soybean houttuynifone on expression of NF-kappaB and MCP-1 in membranous glomerulonephritis. J Ethnopharmacol. 2010;131(1):203-209. doi:10.1016/j.jep.2010.06.020
80. Liu L, Xu Q, Zhang L, et al. Fe3O4 magnetic nanoparticles ameliorates tubulointerstitial fibrosis by autophagy related to Rab7. Colloids Surf B Biointerfaces. 2021;198:111470. doi:10.1016/j.colsurfb.2021.111470
81. Song J, Wang Y, Liu C, et al. Cordyceps militaris fruit body extract ameliorates membranous glomerulonephritis by attenuating oxidative stress and renal inflammation via the NF-kappaB pathway. Food Funct. 2016;7(4):2006-2015. doi:10.1039/c6fo01017a
82. Liu Y, Xu X, Xu R, Zhang S. Renoprotective effects of isoliquiritin against cationic bovine serum albumin-induced membranous glomerulonephritis in experimental rat model through its anti-oxidative and anti-inflammatory properties. Drug Des Devel Ther. 2019;13:3735-3751. doi:10.2147/DDDT.S123088
83. Zhang S, Xin H, Li Y, et al. Skimmia, a coumarin from Hydrangea paniculata, slows down the progression of membranous glomerulonephritis by anti-inflammatory effects and inhibiting
immune complex deposition. Evid Based Complement Alternat Med. 2013;2013:819296. doi:10.1155/2013/819296
94. Zhang Y, Hao J, Ma X, et al. Huoxue Jiedu Huayu Recipe ameliorates mesangial cell pyroptosis in contralateral kidney of UUO rats. Evid Based Complement Alternat Med. 2020;2020:2530431. doi:10.1155/2020/2530431.
95. Hanifah N, Achmad YF, Humaira A, Salasia SIO. Red ginger-extract nanomulsion modulates high blood pressure in rats by regulating angiotensin-converting enzyme production. Vet World. 2021;14(1):176-181. doi:10.14202/vetworld.2021.176-181
96. Yu RX, Lin W, Yang K, et al. Transcriptome-based network analysis reveals hirudin potentiates anti-renal fibrosis efficacy in UUO rats. Front Pharmacol. 2021;12:741801. doi:10.3389/fphar.2021.741801
97. Huang J, Zhang Z, Liu B, et al. Identification of circular RNA expression profiles in renal fibrosis induced by obstructive injury. Ren Fail. 2021;43(1):1368-1377. doi:10.1080/0886022X.2021.1979040
98. Su CT, Jao TM, Urban Z, et al. LTBP4 affects renal fibrosis by influencing angiogenesis and altering mitochondrial structure. Cell Death Dis. 2021;12(10):943. doi:10.1038/s41419-021-02414-5
99. Rattanasinganchan P, Sopitthummakhun K, Doi K, et al. A folic acid-induced rat model of renal injury to identify biomarkers of tubulointerstitial fibrosis from urinary exosomes. Asian Biomed. 2016;10(5):491-502.
100. Li X, Zou YU, Fu YY, et al. A- lipoic acid alleviates folic acid-induced renal damage through inhibition of ferroptosis. Front Physiol. 2021;12:680544. doi:10.3389/fphys.2021.680544
101. Murtas C, Ghiggeri GM. Membranous glomerulonephritis: histological and serological features to differentiate cancer-related and non-related forms. J Nephrol. 2016;29(4):469-478. doi:10.1007/s40602-016-0268-7
102. Huart J, Grosch S, Bovy C, Moutschen M, Krzesinski JM. IgG4-related membranous glomerulonephritis and generalized lymphadenopathy without pancreatitis: a case report. BMC Nephrol. 2017;18(1):139. doi:10.1186/s12882-017-0561-2
103. Mann S, Seidman MA, Barbour SJ, Levin A, Carruthers M, Chen LY. Recognizing IgG4-related tubulointerstitial nephritis. Can J Kidney Health Dis. 2016;3:34. doi:10.1186/s40697-016-0126-5
104. Zhang P, Cornell LD. IgG4-related tubulointerstitial nephritis. Adv Chronic Kidney Dis. 2017;24(2):94-100. doi:10.1053/j.ackd.2016.12.001
105. Jain K, Sengupta M, Basu K, Rau B, Roychowdhury A, Bandopadhyay S. The program of renal fibrogenesis is controlled by microRNAs regulating oxidative metabolism. Redox Biol. 2021;40:101851. doi:10.1016/j.redox.2020.101851
106. Justo P, Sanz A, Lorz C, et al. Expression of Smac/Diablo in tubular epithelial cells and during acute renal failure. Kidney Int Suppl. 2003;86:S52-S56. doi:10.1046/j.1523-1755.64.s86.10.x
107. Ruiz-Andres O, Suarez-Alvarez B, Sanchez-Ramos C, et al. The inflammatory cytokine TWEAK decreases PGC-1alpha expression and mitochondrial function in acute kidney injury. J Pharmacol Exp Ther. 2013;347(3):626-634. doi:10.1124/jpet.113.208017
108. Jen YJ, Rajasekaran NS, Sathyarayarayan S, Benjamin J. Mouse HSFl disruption perturbs redox state and increases mitochondrial oxidative stress in kidney. Antioxid Redox Signal. 2005;7(3-4):465-471.
109. Jen YJ, Christians ES, Liu L, Xiao X, Sohal RS, Benjamin J. Mouse heat shock transcription factor 1 deficiency alters cardiac redox homeostasis and increases mitochondrial oxidative damage. EMBO J. 2002;21(19):5164-5172.
110. Gupta A, Puri V, Sharma R, Puri S. Folic acid induces acute renal failure (ARF) by enhancing renal prooxidant state. Exp Toxicol Pathol. 2012;64(3):225-232. doi:10.1016/j.etp.2010.08.010
111. Yan LJ, Rajasekaran NS. Folic acid supplementation inhibits NADPH oxidase-mediated superoxide anion production and increases mitochondrial oxidative stress in kidney. Antioxid Redox Signal. 2005;7(3-4):465-471.
production in the kidney. Am J Physiol Renal Physiol. 2011;300(1):F189-F198. doi:10.1152/ajpregu.00272.2010

132. Akgun E, Boyacioglu M, Kum S. The potential protective role of folic acid against acetaminophen-induced hepatotoxicity and nephrotoxicity in rats. Exp Anim. 2021;70(1):54-62. doi:10.1538/expandim.20-0075

133. Shulpekovita Y, Nechaev V, Kardashev S, et al. The concept of folic acid in health and disease. Molecules. 2021;26(12):3731. doi:10.3390/molecules26123731

134. Schubert GE. Folic acid-induced acute renal failure in the rat: morphological studies. Kidney Int Suppl. 1976;546-550.

135. Doi K, Okamoto K, Negishi K, et al. Attenuation of folic acid-induced renal inflammatory injury in platelet-activating factor receptor-deficient mice. Am J Pathol. 2006;165(5):1413-1424. doi:10.2353/ajpath.2006.050634

136. Taylor DM, Threlfall G, Buck AT. Chemically-induced renal hypertrophy in the rat. Biochem Pharmacol. 1968;17(8):1567-1574. doi:10.1016/0006-2952(68)90216-5

137. Brade W, Herken H, Merker HJ. [Lesion and regeneration of renal tubule cells following administration of folic acid]. Naunyn Schmiedebers Arch Exp Pathol Pharmacol. 1969;262(2):228-250. Schadigung und Regeneration renaler Tubuluszellen nach Folsauregabe.

138. Hseuh W, Rostorfer HH. Chemically induced renal hypertrophy in the rat. Lab Invest. 1973;29(5):547-555.

139. Schmidt U, Schlumpf V, Josch W, Dubach UC. Acute renal failure in the rat after folate intoxication: diagnostic value of lactate dehydrogenase and alkaline phosphatase measurements in serum and urine. Clin Nephrol. 1974;2(2):104-112.

140. Schmidt U, Dubach U. Acute renal failure in the folate-treated rat: early metabolic changes in various structures of the nephron. Kidney Int Suppl. 1976;6:539-545.

141. Searle CE, Blair JA. The renal toxicity of folic acid in mice. Food Cosmet Toxicol. 1973;11(2):277-281. doi:10.1016/s0015-6264(73)80494-8

142. Schubert GE, Welte K, Otten G. Chronic folic acid nephropathy. Schmiedebers Arch Exp Pathol Pharmacol. 1969;262(2):228-250. Schadigung und Regeneration renaler Tubuluszellen nach Folsauregabe.

143. Kirschbaum BB. Alterations of mitochondrial properties in folate nephrotoxicity in rats. Exp Anim. 2021;70(1):54-62. doi:10.1538/expandim.20-0075

144. Kirschbaum BB. Alterations of mitochondrial properties in folate nephrotoxicity in rats. Exp Anim. 2021;70(1):54-62. doi:10.1538/expandim.20-0075

145. Zhu F, Chong Lee Shin OL, Xu H, et al. Melatonin promoted renal regeneration in folic acid-induced acute kidney injury via inhibiting nucleocytoplasmic translocation of HMGB1 in tubular epithelial cells. Am J Transl Res. 2017;9(4):1694-1707.

146. Jiang K, Ponzo TA, Tang H, Mishra PK, Macura SI, Lerman LO. Multimetric MRI detects longitudinal evolution of folic acid-induced nephropathy in mice. Am J Physiol Renal Physiol. 2018;315(5):F1252-F1260. doi:10.1152/ajpregu.00128.2018

147. Liu F, Wang LJ, Qi H, et al. Nintedanib, a triple tyrosine kinase inhibitor, attenuates renal fibrosis in chronic kidney disease. Clin Sci. 2017;131(16):2125-2143. doi:10.1042/CS20170134

148. Burgos-Silva M, Semedo-Kuriki P, Donizetteli-Oliveira C, et al. Adipose tissue-derived stem cells reduce acute and chronic kidney damage in mice. PLoS One. 2015;10(11):e0142183. doi:10.1371/journal.pone.0142183

149. Aparicio-Trejo OE, Reyes-Fermin LM, Briones-Herrera A, et al. Protective effects of N-acetyl-cysteine in mitochondria bioenergetics, oxidative stress, dynamics and S-glutathionylation alterations in acute kidney damage induced by folic acid. Free Radic Biol Med. 2019;130:379-396. doi:10.1016/j.freeradbiomed.2018.11.005

150. Zhang X, Agborbesong E, Li X. The role of mitochondria in acute kidney injury and chronic kidney disease and its therapeutic potential. Int J Mol Sci. 2021;22(20):11253. doi:10.3390/ijms222011253

151. Lu M, Wang P, Qiao Y, et al. GSK3beta-mediated Keap1-independent regulation of Nrf2 antioxidant response: a molecular rheostat of acute kidney injury to chronic kidney disease transition. Redox Biol. 2019;26:101275. doi:10.1016/j.redox.2019.101275

152. Bengatta S, Arnould C, Letavernier E, et al. MMP9 and SCF protect from apoptosis in acute kidney injury. J Am Soc Nephrol. 2009;20(4):787-797. doi:10.1681/ASN.2008050515

153. Jung JH, Choi JE, Song JH, Ahn SH. Human CD36 overexpression in renal tubules accelerates the progression of renal diseases in a mouse model of folic acid-induced acute kidney injury. Kidney Res Clin Pract. 2018;37(1):30-40. doi:10.23876/j.krcp.2018.37.1.30

154. Henry MA, Harris PJ, Naughton RJ, Walker LL, Skinner SL, Tange JD. Filtration failure induced by p-aminophenol in rats is due to raised intratubular pressure and not changes in glomerular function. Clin Exp Pharmacol Physiol. 1990;17(9):613-626. doi:10.1111/j.1440-1681.1990.tb01362.x

155. Hasegawa K. Novel tubular-glomerular interplay in diabetic kidney disease mediated by sirtuin 1, nicotinamide mononucleotide, and nicotinamide adenine dinucleotide Oshima Award Address 2017.

156. Tanner GA. Tubuloglomerular feedback after nephron or ureteral obstruction. Am J Physiol. 1985;248(5 Pt 2):F688-F697. doi:10.1152/ajprenal.1985.248.5.F688

157. Vaneková A, Berzl S, Ocaña-Salceda C, et al. A polymeric nanomedicine diminishes inflammatory events in renal tubular cells. PLoS One. 2013;8(1):e51992. doi:10.1371/journal.pone.0051992
169. Martín-Sanchez D, Poveda J, Fontecha-Barriuso M, et al. Targeting of regulated necrosis in kidney disease. Nefrologia. 2018;38(2):125-135. doi:10.1016/j.nefro.2017.04.004

170. Severin MJ, Campagna RV, Brandoni A, Torres AM. Time evolution of mitophagosome-induced kidney injury: a comparative study between different biomarkers of renal damage in rats. Clin Exp Pharmacol Physiol. 2019;46(9):828-836. doi:10.1111/1440-1681.13122

171. Severin MJ, Torres AM. Time course effects of mitophagosome on renal handling of water and electrolytes in rats. Role of aquaporin-2 and Na-K-2Cl cotransporter. Toxicol Lett. 2019;311:27-36. doi:10.1016/j.toxlet.2019.04.018

172. Kozioljek MJ, Muller G-A, Zapf A, et al. Role of CX3C-mechokine CX3C-L/fractalkine expression in a model of slowly progressive renal failure. Nephrol Dial Transplant. 2010;25(3):684-698. doi:10.1093/ndt/gfp602

173. Rayego-Mateos S, Morgado-Pascual JL, Rodrigues-Diez RR, et al. Connective tissue growth factor induces renal fibrosis via epidermal growth factor receptor activation. J Pathol. 2018;244(2):227-241. doi:10.1002/path.5007

174. Luan J, Fu J, Wang D, et al. miR-150-Based RNA interference attenuates tubulointerstitial fibrosis through the SOCS1/JAK/STAT pathway in vivo and in vitro. Mol Ther Nucleic Acids. 2020;22:871-884. doi:10.1016/j.mtna.2020.10.008

175. Mullin EM, Bonar RA, Paulson DF. Acute tubular necrosis. An experimental model detailing the biochemical events accompanying renal injury and recovery. Invest Urol. 1976;13(4):289-294.

176. Bosch RJ, Woolf AS, Fine LG. Gene transfer into the mammalian kidney: direct retrovirus-transduction of regenerating tubular epithelial cells. Exp Nephrol. 1993;1(1):49-54.

177. Martín-Sánchez D, Ruiz-Andres O, Poveda J, et al. Ferroptosis, but not necroptosis, is important in nephrotoxic folic acid-induced AKI. J Am Soc Nephrol. 1994;5(6):1324-1332. doi:10.1618/asn.V561324

178. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

179. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

180. Scrolls LJ, Whitaker RM, Schnellmann RG. Suppressed mitochondrial biogenesis in folic acid-induced acute kidney injury and early fibrosis. Toxicol Lett. 2014;224(3):326-332. doi:10.1016/j.toxlet.2013.11.014

181. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res. 2004;19(3):429-435. doi:10.1359/JBMR.0301264

182. Christov M, Waiker SS, Pereira RC, et al. Plasma FGF23 levels increase rapidly after acute kidney injury. Kidney Int. 2013;84(4):776-785. doi:10.1038/ki.2013.150

183. Egli-Spichtig D, Zhang MYH, Perfad W. Fibroblast growth factor 23 expression is increased in multiple organs in mice with folic acid-induced acute kidney injury. Front Physiol. 2018;9:1494. doi:10.3389/fphys.2018.01494

184. Durlacher-Betzer K, Hassan A, Levi R, Axelrod J, Silver J, Naveh-Many T. Interleukin-6 contributes to the increase in fibroblast growth factor 23 expression in acute and chronic kidney disease. Kidney Int. 2018;94(2):315-325. doi:10.1016/j.kint.2018.02.026

185. Zuo Z, Jing K, Wu H, et al. Mechanisms and functions of mitophagy and potential roles in renal disease. Front Physiol. 2020;11:935. doi:10.3389/fphys.2020.00935

186. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

187. Nguyen TN, Padman BS, Lazarou M. Deciphering the molecular signals of PINK1/Parkin mitophagy. Trends Cell Biol. 2016;26(10):733-744. doi:10.1016/j.tcb.2016.05.008

188. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

189. Wang Y, Zhu J, Liu Z, et al. The PINK1/PARK2/autopineurin pathway of mitophagy is activated for protection in septic acute kidney injury. Redox Biol. 2021;38:101767. doi:10.1016/j.redox.2020.101767

190. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

191. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

192. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

193. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

194. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

195. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

196. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

197. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503

198. Higgins GC, Coughlan MT. Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol. 2014;171(8):1917-1942. doi:10.1111/bph.12503
206. Jiang C, Zhu W, Yan X, et al. Rescue therapy with Tanshinone IIA hinders transition of acute kidney injury to chronic kidney disease via targeting GSK3beta. *Sci Rep*. 2016;6:36698. doi:10.1038/srep36698

207. Wang HZ, Peng ZY, Wen XY, Rimmelte T, Bishop JV, Kellum JA. N-acetylcysteine is effective for prevention but not for treatment of folic acid-induced acute kidney injury in mice. *Crit Care Med*. 2011;39(11):2487-2494. doi:10.1097/CCM.0b013e31822575fc

208. Long DA, Price KL, Ioffe E, et al. Angiopoietin-1 therapy enhances fibrosis and inflammation following folic acid-induced acute renal injury. *Kidney Int*. 2008;74(3):300-309. doi:10.1038/ki.2008.179

209. Wan B, Hao L, Qiu Y, et al. Blocking tumor necrosis factor-alpha inhibits folic acid-induced acute renal failure. *Exp Mol Pathol*. 2006;81(3):211-216. doi:10.1016/j.yexmp.2006.02.005

210. Kolatsi-Joannou M, Price KL, Winyard PJ, Long DA. Modified citrus pectin reduces galectin-3 expression and disease severity in experimental acute kidney injury. *PLoS One*. 2011;6(4):e18683. doi:10.1371/journal.pone.0018683

211. Wang Y, Quan F, Cao Q, et al. Quercetin alleviates acute kidney injury by inhibiting ferroptosis. *J Adv Res*. 2021;28:231-243. doi:10.1016/j.jare.2020.07.007

212. Li X, Zou Y, Xing J, et al. Pretreatment with roxadustat (FG-4592) attenuates folic acid-induced kidney injury through antiferroptosis via Akt/GSK-3beta/Nrf2 pathway. *Oxid Med Cell Longev*. 2020;2020:6286984. doi:10.1155/2020/6286984

213. Gyuraszova M, Gurecka R, Babickova J, Tothova L. Oxidative stress in the pathophysiology of kidney disease: implications for noninvasive monitoring and identification of biomarkers. *Oxid Med Cell Longev*. 2020;2020:5478708. doi:10.1155/2020/5478708

214. Palipoch S. A review of oxidative stress in acute kidney injury: protective role of medicinal plants-derived antioxidants. *Afr J Tradit Complement Altern Med*. 2013;10(4):88-93. doi:10.4314/ajtcam.v10i4.15

215. Estrela GR, Freitas-Lima LC, Budu A, et al. Chronic kidney disease induced by cisplatin, folic acid and renal ischemia reperfusion induces anemia and promotes GATA-2 activation in mice. *Biomedicines*. 2021;9(7):769. doi:10.3390/biomedicines9070769