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REVIEW

Folic acid-induced animal model of kidney disease

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Abstract

The kidneys are a vital organ that is vulnerable to both acute kidney injury (AKI) and chronic kidney disease (CKD) which can be caused by numerous risk factors such as 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.[4,5] 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.[12–19]

There are numerous animal models that have been used to elucidate the pathological mechanisms of kidney disease.[19–21] Those induced by ischemia,[14,22,23] lipopolysaccharide, [24–27] cisplatin,[28–30] arsenic,[31–33] adenine,[34–36] cadmium[15,37–40] and diabetes[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.[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.[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.[99] Fourth, depending on the experimental needs, one can investigate AKI or CKD or the AKI–CKD transition using a single injection of FA.[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,[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[101,102] or IgG4-immuned kidney disease.[103–106]

2 | FOLIC ACID AND THE KIDNEYS

FA is also known as vitamin B9.[107,108] It is a cofactor involved in one-carbon metabolism that is essential for cellular proliferation and growth.[109–111] FA can be derived from egg yolk, animal livers, leafy vegetables, and yeast.[112,113] FA is usually absorbed in the small intestine, and converted intracellularly to tetrahydrofolate by dihydrofolate reductase.[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.[113–115]

As a small molecular weight compound, FA or folate is freely filtered by the glomerulus.[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.[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.[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.[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,[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.[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.[117,118] It is stored as folate derivatives that are cell membrane impermeable.[119] Importantly, while folate distributes in all cellular compartments, mitochondria can take up to 40% of the folate pool,[119,120] which can cause mitochondrial oxidative stress and mitochondrial abnormalities.[121–125] Moreover, as folate reduction by dihydrofolate reductase to form tetrahydrofolate uses large amounts of NADPH as a reducing power,[110] high levels of folate in the kidneys can severely compromise cellular antioxidative systems that also require NADPH,[126,127] leading to aggravated redox imbalance and oxidative stress in this organ.[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,[130–133] high doses of FA, e.g., 250 mg/day, as widely used in the induction of animal kidney disease, are highly toxic.[134,135] A search in the PubMed database indicates that the first report of a renal problem caused by FA was published in 1968,[136] and described renal hypertrophy induced by FA. The first report of kidney injury induced by FA was published in Germany in 1969.[137] These studies led to the concepts of “renal folate toxicity” and “folate nephropathy” in 1970s.[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,[145–147] resulting in proteinuria and increased blood urea nitrogen (BUN) and creatinine.[148,149] AKI can be studied within 72 h of FA administration.[55] If left untreated, CKD will develop and can be studied more than 4 weeks or beyond after FA injection (Figure 1).[55] Multiple injections of a lower dose of FA (125–150 mg/kg body weight)[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.[152–154] Moreover, progression of AKI to CKD can also be investigated after a single

TABLE 1 Comparison of animal models of kidney injury induced by a variety of approaches

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.[54] 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.

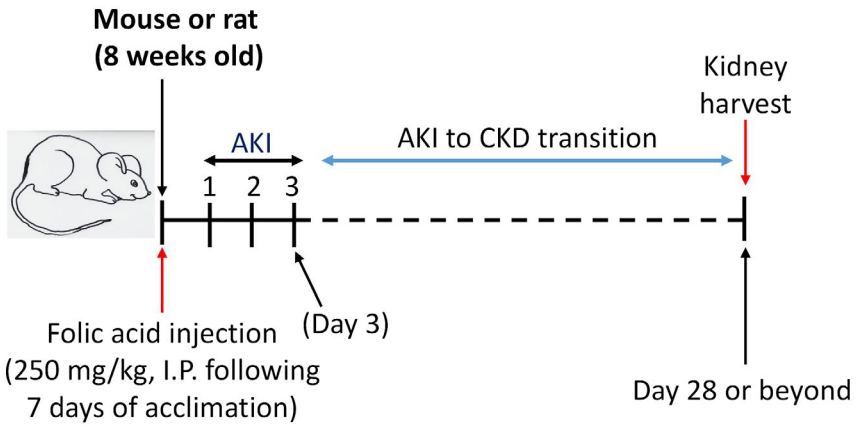

FIGURE 1 General experimental scheme of folic acid (FA)-induced acute kidney injury (AKI) and chronic kidney disease (CKD). FA, usually at a dose of 250 mg/kg body weight, is prepared in 300 mM $NaHCO_3$ and injected intraperitoneally. AKI may be investigated within 3 days of FA injection while CKD may be studied up to or beyond 28 days following FA injection [Colour figure can be viewed at wileyonlinelibrary.com]

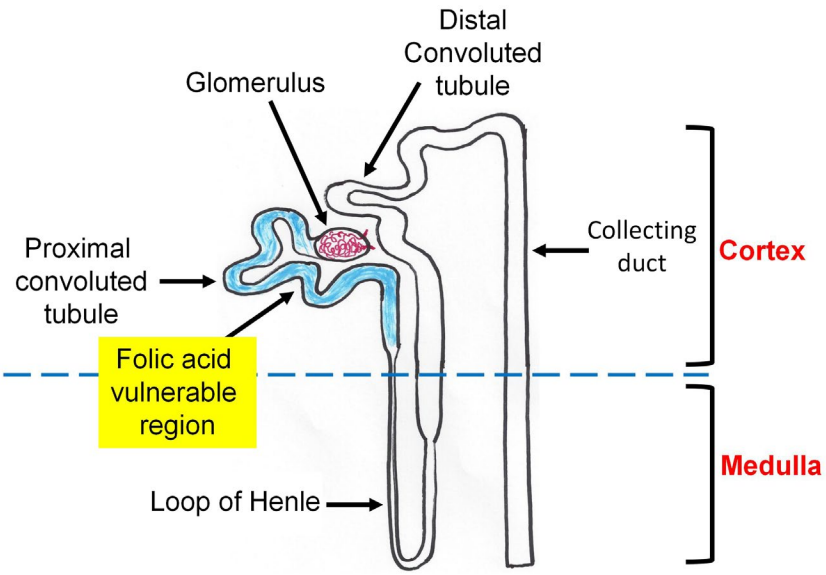

FIGURE 2 Diagram showing the proximal convoluted tubule in the nephron as the most vulnerable region to folic acid (FA)-induced damage. The blue highlighted tubule depicts the proximal convoluted region [Colour figure can be viewed at wileyonlinelibrary.com]

high dose FA injection.[55] Therefore, FA-induced kidney disease can cover AKI, CKD, and the AKI–CKD transition.[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.[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 mode, 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.[18] The low dose cisplatin model, the diphtheria toxin model, and the aristolochi 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.[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.[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).[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.[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.[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.[100] 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,[152,162] In fact, this tubular-glomerular response is a well-known feedback mechanism that also occurs in drug-induced kidney toxicity[163–165] and ureteral obstruction kidney disease.[166,167]

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.[55] Moreover, the FA model is highly reproducible.[55] In these respects, the FA experimental animal model is similar to streptozotocin-induced type 1 diabetes animal models,[74,75] 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 mouse model.[168,169] 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.[170,171]

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,[172–174] and renal fibrosis.[175,176] 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,[128] clinical symptoms of acute renal failure such as attenuated alertness, fatigue or lethargy, and bristling of the coat can also be observed.[128] 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.[55,128,155] For example, in FA-AKI mouse model, Gupta et al.[128] 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.[177] 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 ferropstatin-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.[178,179]

4.3 | Impairment of mitochondrial bioenergetics

In an elegant study exploring the mechanisms of AKI–CKD transition after FA injection, Aparicio-Trejo et al.[55] 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.[180] 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.[181]

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

FGF23 is a protein that regulates phosphate homeostasis and vitamin D metabolism.[182] The content of this protein has been shown to increase rapidly upon FA-induced AKI.[183–185] This upregulation of FGF23 is likely controlled by interleukin-6 (IL-6) as IL-6 inhibition by dexamethasone abolished FGF23 upregulation in FA-induced

AKI.[185] 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 reflected

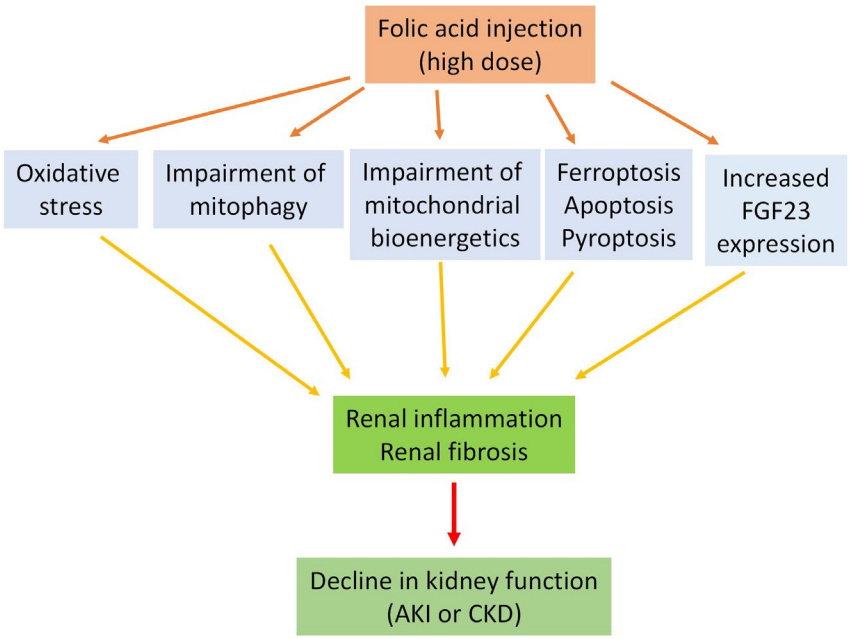

FIGURE 3 Major pathological mechanisms of folic acid (FA)-induced acute kidney injury (AKI) and chronic kidney disease (CKD). These include oxidative stress, impairment of mitophagy and mitochondrial bioenergetics, ferroptosis, apoptosis and pyroptosis as well as increased expression of fibroblast growth factor 23 (FGF23). These mechanisms together result in renal inflammation and renal fibrosis, eventually leading to renal dysfunction or kidney disease. Please note that this figure and this article do not mean to exhaust all the mechanisms implicated in FA-induced kidney disease [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 FA-induced animal model of kidney disease as a platform for testing the therapeutic effects of pharmacological agents, chemicals, and natural products

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
Celastrol	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.

by decreased GFR, and increased BUN and creatinine.[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.

6 | 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.[99] FA-induced CKD can also cause anemia in mouse.[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.[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,[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 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,[217] FA deficiency may serve as a diagnostic indicator and FA administration can slow down the progression of CKD.[217–219] 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.[220,221] High homocysteine is known to pose an independent risk factor for cardiovascular disease.[217,222,223]

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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