Chinese Medicine

REVIEW

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Oleanolic acid and its analogues: promising therapeutics for kidney disease

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Abstract

Kidney diseases pose a significant threat to human health due to their high prevalence and mortality rates. Worryingly, the clinical use of drugs for kidney diseases is associated with more side effects, so more effective and safer treatments are urgently needed. Oleanolic acid (OA) is a common pentacyclic triterpenoid that is widely available in nature and has been shown to have protective effects in kidney disease. However, comprehensive studies on its role in kidney diseases are still lacking. Therefore, this article first explores the botanical sources, pharmacokinetics, derivatives, and safety of OA, followed by a summary of the anti-inflammatory, immunomodulatory, anti-oxidative stress, autophagy-enhancing, and antifibrotic effects of OA and its analogues in renal diseases, and an analysis of the molecular mechanisms, aiming to provide further insights for the development of novel drugs for the treatment of kidney diseases.

Keywords Oleanolic acid, Kidney disease, Pharmacokinetics, Anti-inflammatory, Immunomodulatory

Introduction

Kidney diseases are classified as acute or chronic. Acute kidney injury (AKI) is characterised by a sudden decline in renal function, typically occurring within week. It is commonly observed in critically ill patients, and is associated with a high mortality rate [1]. In a large-scale retrospective study (n = 49, 147,878), the incidence of AKI in adults was found to be 21.6%, whereas that in children was 33.7%. The study also revealed that the mortality rate associated with AKI was 23.9% in adults and 13.8% in children [2]. Chronic kidney disease (CKD) is defined as a measured or estimated glomerular filtration rate (GFR) of < 60 mL/(min·1.73 m^2) or a urine protein-to-creatinine ratio of > 30 mg/g, persisting for 90 days or longer [3]. This affects approximately 15–20% of the adult population worldwide, a significantly impacting healthcare and overall wellbeing [4]. CKD can be caused and exacerbated by various factors. Diabetes and hypertension are recognised as the leading causes of CKD [5, 6]. Additionally, research suggests that other factors such as obesity, glaucoma, second-hand smoke exposure, and HIV infection are also associated with its development [7–11]. A comprehensive assessment of CKD prevalence was conducted across 16 Asian countries, revealing an overall prevalence of 7.0–34.3%. Approximately 434 million adults in Asia are estimated to be affected by CKD, of which 65.6 million have advanced-stage CKD. Notably, the number of patients with CKD in China alone is as high as 159.8 million [12]. The global incidence of CKD increased by 88.76% from 1990 to 2016 and the number of related deaths increased by 98.02% [13]. In summary, kidney disease has gradually emerged as a global public health concern owing to its high prevalence and mortality rates, affecting over 750 million people worldwide [14].

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Currently, in clinical practice, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are primarily used for treating kidney disease to control blood pressure and reduce albuminuria [15]. However, ACEI and ARB have serious side effects and are contraindicated in patients with severe renal impairment [16, 17]. Thus, there is an urgent need to identify alternative therapies that are safer and more effective. In recent years, natural medicines have attracted the attention of researchers due to their multiple targets, multiple pathways, and low toxicity. Oleanolic acid (OA) is one such natural compound, numerous preclinical studies have elucidated the therapeutic effects of OA in various animal models for AKI and CKD, including renal ischemia–reperfusion injury, drug-induced renal injury, renal fibrosis, diabetic nephropathy, and lupus nephritis [18–22]. However, to date, no systematic review has evaluated the protective effects and underlying mechanisms of OA on kidney diseases. This study has attempted to address this by providing a systematic review and retrospective analysis of the basic research on the therapeutic effects of OA, its isomer ursolic acid (UA), and derivatives of OA used for treating kidney diseases. The botanical sources, pharmacological actions, pharmacokinetics, and safety aspects of OA are also discussed.

Methodology

Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23], this study employed a comprehensive search strategy to retrieve relevant literature from PubMed, Web of Science, Scopus, Cochrane, and Embase databases. The search keywords used were "oleanolic acid" or "ursolic acid", which is isomer of OA frequently coexisting with it in diverse plant species owing to their structural similarity and shared pharmacological characteristics [24]. The search keywords also encompass "kidney disease", "renal", "nephropathy, "nephrosis", "AKI", "DN", "DKD", "CKD", "LN", or "IgAN".

Inclusion and exclusion criteria

The inclusion criteria were as follows: English research articles published between 2000 and 2023, including studies conducted on animals, cell experiments, clinical trials, and large cohort studies. The exclusion criteria were as follows: non-research articles such as reviews, meta-analyses, and letters.

Literature screening and data extraction

Two researchers independently conducted literature searches, screening, and data extraction based on the inclusion and exclusion criteria. Any disagreements were resolved through consensus by a third researcher.

Results

According to the PRISMA guidelines for study selection and exclusion, a total of 1599 records were identified during the search. Among them, 323 were from PubMed, 593 from Web of Science, 302 from Embase, 365 from Scopus, and 16 from Cochrane. After removing duplicates, there were 831 articles utilised for title and abstract analysis. After an initial screening, 158 reviews, 27 conference abstracts, 3 notes, 12 editorial materials, 9 letters, 3 patents, 1trial registry record, 1 reply and 2 retracted publications were excluded due to the type of study. A further 420 records were excluded after a critical analysis on the title and abstracts, leaving 132 articles for full-text retrieval. Of them, 10 articles were not accessible for retrieval. The full texts of 122 articles were accessed and assessed for eligibility, resulting in the inclusion of 75 articles in this study (Fig. 1).

Oleanolic acid

Physical and chemical properties

OA ($C_{30}H_{48}O_3$) is a commonly occurring pentacyclic triterpenoid compound found in both free acid and glycoside forms. It is often present alongside its structural isomer, UA in various plants. The main difference between OA and UA is the position of the methyl group on the E-ring (Fig. 2). OA, with a molecular weight of 456.7, is a hydrophobic compound, pale yellow, and non-volatile. It is nearly insoluble in water, sparingly soluble in ethanol and acetone, and soluble in 1-butanol, and its solubility increases with temperature [25]. OA exhibits a positive result in the Liebermann–Burchard test, indicating its triterpenoid nature. It does not show any reaction in the Molisch test, confirming the absence of connected glucose. Furthermore, when reacted with acetic anhydride–pyridine, OA forms acetyl esters, providing evidence that there are hydroxyl groups exist in the molecule [26].

Botanical sources

OA is one of the most common pentacyclic triterpenoid compounds found in nature. It is widely distributed in the fruits, peels, leaves, and roots of various plants. Research has revealed that triterpenoid compounds are often concentrated in the wax layer of the plant epidermis, potentially attributed to their hydrophobic nature [27]. Olives are the most important source of OA, and it has been reported that the triterpene content of different varieties of virgin olive oils can be as high as 127–197 mg/kg, with OA being the most abundant, with an average content of 17.75 mg/kg [28]. Fructus

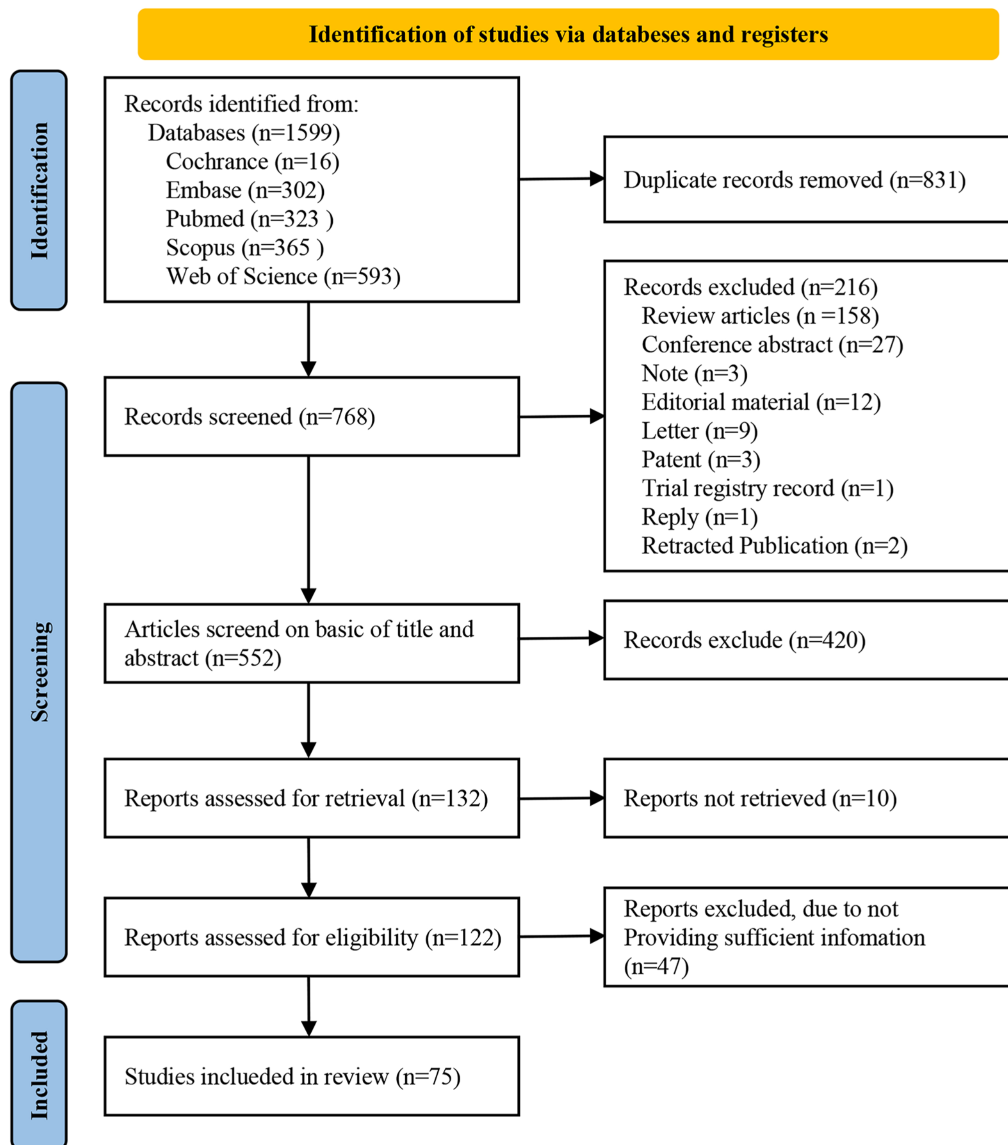

Fig. 1 Flow diagram of the study selection

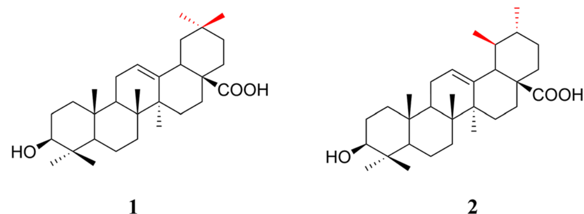

Fig. 2 Chemical structures of oleanolic acid (OA [1]) and ursolic acid (UA [2])

Ligustri Lucidi, a traditional Chinese medicine, is also a rich source of OA that is widely used to treat various diseases [29]. Furthermore, OA has been detected in several common fruits such as apple [30], loquat [31], grape [32], and pomegranate [33]. Other edible medicinal plants, including ginseng [34], mistletoe [32], papaya [35], and hawthorn [36] also contain OA. Furthermore, a significant amount of OA is present in various herbs such as rosemary, thyme, and lavender [32]. OA can also be found in the bark of certain plant species, such as *Eucalyptus globulus* (southern blue gum tree) [37].

Pharmacology

OA exhibits a wide range of pharmacological effects and exerts protective effects in the whole body (Fig. 3). Hepatoprotection is among its most significant pharmacological actions. Multiple studies have demonstrated the hepatoprotective effects of OA against acute liver injury, as well as its potential for alleviating liver fibrosis and cirrhosis. Furthermore, OA has been found to induce apoptosis in liver cancer cells [38–40]. Presently, OA is classified as an over-the-counter drug in China for the treatment of' acute and chronic hepatitis [41]. Various experimental models have also confirmed the cardioprotective effects of OA. For instance, OA can prevent dexamethasone-induced hypertension [42] and regulate the release of prostacyclin (PGI2) from human coronary artery smooth muscle cells to maintain vascular homeostasis [43]. Ischemic stroke is the leading cause of mortality in humans [44]. OA has shown potential in alleviating brain infarction in a transient middle cerebral artery occlusion mouse model following reperfusion, and it can also improve chronic brain damage caused by ischemic stroke [45]. Studies have also reported that OA can improve the inflammatory response and oxidative damage in streptozotocin (STZ)-induced diabetic rats [46]. Recent studies have reported that OA exhibits protective effects on the gastrointestinal tract. Treatment with OA in acetic acid-induced chronic gastric ulcer model rats resulted in a reduction in lesion area and an increase in mucosal thickness, promoting gastric wound healing [47]. Additionally, OA can prevent acute lung injury induced by peroxynitrite and exerts a significant protective effect on pulmonary fibrosis [48, 49]. Another study demonstrated that OA can ameliorate dextran sulphate sodium-induced colitis [50]. In recent years, research has focused on the protective effect against kidney disease. Pre-treatment with OA improves renal injury induced by ischemia/reperfusion (I/R), as well as kidney fibrosis in a unilateral ureteral obstruction (UUO) mouse model [18, 51]. Furthermore, OA has been found to induce apoptosis in various types of tumour cells, including human hepatocellular carcinoma cells [39], breast cancer cells MCF-7 and MDA-MB-231 [52], and non-small cell lung cancer cells [53]. Increasing evidence suggests that OA possesses various biological activities, including anti-inflammatory, antioxidant, immunomodulatory, antibacterial, and antiviral [54–58].

Pharmacokinetics

Pharmacokinetics is the study of the body's role in drug regulation, employing kinetic principles and mathematical models to quantitatively describe drug absorption, distribution, metabolism, and excretion [59].

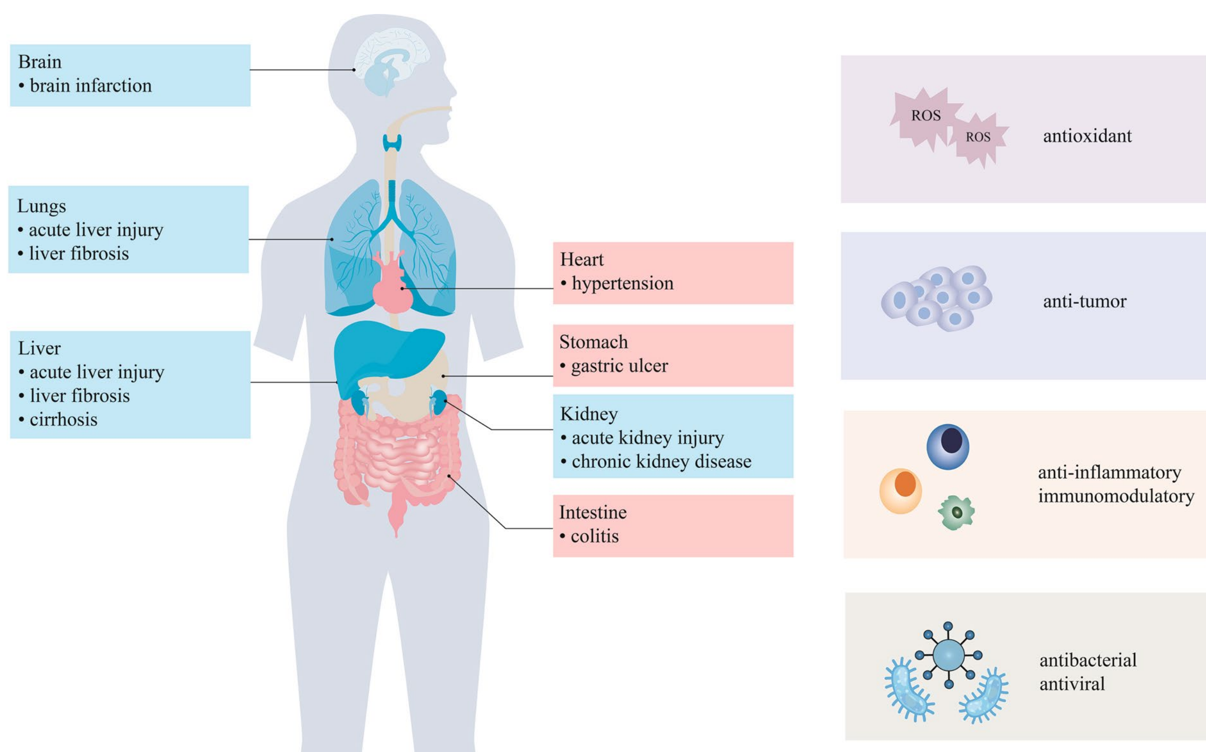

Fig. 3 Potential pharmacological effects of oleanolic acid (OA)

Pharmacokinetic research is crucial in the context of novel drug development. The Caco-2 cell model is commonly used as an in-vitro absorption-prediction model, with experiments conducted using its cell monolayers to evaluate the absorption properties of OA [60]. The obtained apparent permeability coefficient (P_{APP}) values for OA at concentrations of 10 and 20 μM were found to range from 1.1–1.3 $\times 10^{-6}$ cm/s, closely resembling the P_{APP} value of the low-permeability standard drug, atenolol (0.25 $\times 10^{-6}$ cm/s). Consequently, these results indicate a potential limitation in the absorption capacity of OA. Furthermore, Jeong et al. [60] found no significant difference between the apical-to-basolateral P_{APP} and basolateral-to-apical P_{APP}, indicating that the transintestinal barrier transport of OA occurs via passive diffusion. Subsequently, researchers conducted extensive pharmacokinetic studies of OA in both animals and humans (Table 1).The study revealed that OA has a relatively short elimination half-life and very low absolute bioavailability (only 0.7 in rats) [60]. In addition to plasma, OA is widely distributed in tissues, with detectable levels found in the brain, heart, liver, kidneys, colon, and bladder of animals [61]. These data suggest that the very low bioavailability of OA may be attributed to its rapid clearance rate and extensive tissue distribution. Of note, OA is most extensively distributed in the liver, consistent with its established hepatoprotective effects. However, on the other hand, long-term high-dose administration can lead to liver toxicity and bile stasis [62]. This suggests that a balance between the beneficial effects and potential toxicity of OA should be considered when using it clinically. Following coincubation of OA with rat liver microsomes in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), a notable decrease of 60% in peak current was observed, indicating that OA may be metabolised in the rat liver. Subsequent testing of the cultures initially identified the major metabolites of OA as hydroxy- and dihydroxy-OAs [60]. When studying excretion, the minimal levels of OA detected in urine suggest that OA is primarily non-renal in its elimination [60]. However, screening of its phase II metabolites revealed that OA is excreted in urine in the form of sulphate and glucuronide conjugates [63], explaining why intact OA is not detected in urine. In summary, OA, classified as a Class IV compound in the biopharmaceutics classification system due to its low water solubility, poor apparent permeability, and extremely low bioavailability, is somewhat limited in its clinical utility [64].

Oleanolic acid derivatives

OA exhibits a wide range of pharmacological activities, however, it has poor water solubility and low bioavailability. Extensive research has been conducted to enhance its bioavailability, including modifications to OA and the design of a series of derivatives, which have demonstrated potent biological activities such as antitumour, antioxidant and anti-inflammatory effects [66–68]. In 1998, approximately 60 OA derivatives were synthesised to screen for compounds capable of inhibiting the production of nitric oxide (NO) in macrophages. These derivatives were subsequently tested in vitro, and nine were found to exhibit substantial inhibition of INF-γ-induced NO production in macrophages. Among these derivatives, 3,12-dioxoolean-1,9-dien-28-oic acid (Fig. 4(3)) showed the highest inhibitory activity [69]. Based on these findings, a more potent derivative, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) (Fig. 4(4)), was synthesised by introducing an electron-withdrawing cyano group at the C-2 position. This compound exhibited an inhibitory effect on NO that was 400 times stronger than the previously synthesized compounds [70]. CDDO-methyl ester (CDDO-Me) (Fig. 4(5)) is CDDO modified by methyl esterification, and this compound not only possesses potent anti-inflammatory

Table 1 Pharmacokinetic parameters of OA in different formulations

Form	Species	Administration	Dose	AUC	C_{max}	T_{max}	t1/2	CL	References
Capsule	Human	Oral	40 mg/kg	124.29 ng/h/mL	12.12 ng/mL	5.2 h	8.73 h	555.3 L/h	[152]
OA solution	Rats	i.v. injection	0.5 mg/kg 1 mg/kg 2 mg/kg	16 μg min/mL 32.6 μg min/mL 71.6 μg min/mL	NA	NA	41.9 min 52.7 min 48.0 min	31.7 mL/min/kg 33 ml/min/kg 28 mL/min/kg	[60]
OA solution	Rats	Oral	25 mg/kg 50 mg/kg	5.9 μg min/mL 10.7 μg min/mL	NA	25 min 21 min	46.5 min 65.3 min	NA	[60]
OA in olive oil	Human	Oral	30 mg	3181.9 ng h/mL	598.2 ng/mL	3.0 h	4.61 h	35.1L/h	[153]
OA into a metered-dose inhaler	Rats	Inhale	120 μg/mL	428.25 ng/h/mL	22.75 ng/mL	4 h	8.93 h	NA	[65]

Values are expressed as the mean ± standard error of the mean when available

AUC: area under the curve; C_{max}: maximum plasma concentration; T_{max}: time to maximum concentration; t1/2: half-life; CL: clearance; NA: non-available data

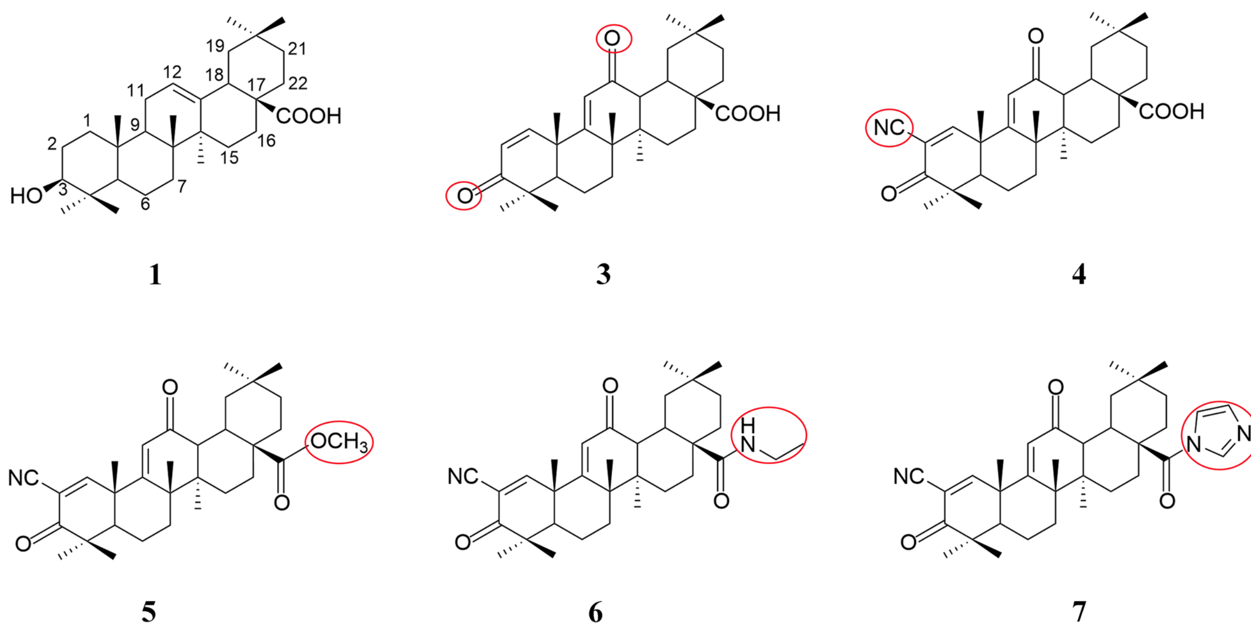

Fig. 4 Oleanolic acid (OA [1]) and its derivatives

activity and antioxidant activity [71]. CDDO-Ethyl Amide (CDDO-EA) (Fig. 4(6)) involves the introduction of an ethyl amide group at the C-17 position of CDDO [72]. Similarly, utilizing CDDO as the precursor material, CDDO-imidazole (CDDO-Im) (Fig. 4(7)) is synthesised by introducing an imidazole ring at the C-28 position [72]. Currently, both of these compounds demonstrate promising anti-cancer effects, exhibiting inhibitory effects on various cancer cells [73–76]. Among them, CDDO series derivatives have shown remarkable therapeutic effects in renal diseases. Pre-treatment with CDDO-Me has been shown to mitigate AKI induced by I/R in rats via its anti-inflammatory, antioxidant, and anti-apoptotic properties [77]. Additionally, CDDO-Im activates the Nrf2 signalling pathway, conferring protective effects against bilateral ischemic AKI in mice [78]. Moreover, CDDO-Me has demonstrated the ability to ameliorate mouse renal fibrosis mediated by aristolochic acid [79].

Safety

OA is a relatively safe natural compound. In an early brine shrimp test, the median lethal concentration (LC50) of OA was determined to be 0.95 mg/mL [80]. A study investigating the acute and chronic toxicity of a mixture of UA and OA reported that single subcutaneous injections of 300 mg/kg in Balb/c mice, which were then observed for 14 days, along with repeated injections of 6.5 mg/kg and 13 mg/kg of UA/OA within 28 days, did not result in any notable alterations or abnormalities in the biochemical indicators or major organ histopathological examinations when compared to the control group. The median lethal dose (LD50) was determined to be greater than 300 mg/kg [81]. Furthermore, the effects of administrating a single dose of 120 μg of UA and 120 μg of OA via a metered dose inhaler in rats were monitored, and the results revealed no signs of clinical toxicity [65]. A clinical trial involving 70 cases of acute hepatitis demonstrated that continuous daily administration of 60–90 mg of OA for 30 days showed no significant adverse effects and exhibited therapeutic efficacy [82].

Role of OA in kidney disease

Currently, research on the therapeutic potentials of OA, UA, and their derivatives in relation to kidney diseases primarily use animal and cellular models, with a specific focus on acute kidney injury and chronic kidney disease.

AKI

Research has indicated that the pathogenesis of AKI is related to several factors, including renal ischemia, nephrotoxins, sepsis, infections, contrast agents, and drug induction [83–85]. In recent years, the application of OA and its analogues as treatment methods for AKI has received considerable attention. OA has been shown to exhibit preventive effects against the occurrence and progression of AKI through various mechanisms, including protection against anti-oxidative stress, inhibition of inflammatory responses, enhancement of autophagy, and exhibiting anti-apoptotic properties [77, 86–88].

Furthermore, compounds related to OA have been found to modulate multiple signalling pathways, thereby improving the renal damage caused by AKI and restoring renal tubular function. For example, UA exerts its protective effects on renal I/R injury in mice by modulating the NF-κB pathway and inhibiting the production of inflammatory factors such as IL-1β, IL-6, TNF-a, and ICAM [89]. Pretreatment with OA can activate the antioxidant factor Nrf2; regulate GCLc; reduce the serum malondialdehyde levels; enhance the activities of SOD, catalase, and glutathione; and alleviate oxidative damage [18]. Additionally, UA can enhance macrophage autophagy and suppress the inflammatory response in LPS-induced AKI mice by modulating the toll-like receptor (TLR)4/MyD88 pathway [88].

CKD

CKD is typically a progressive disease characterised by the gradual deterioration of kidney function, and it is caused by a range of diseases, including diabetes, hypertension, AKI, glomerulonephritis, and obesity [90–92]. Increasing evidence suggests that OA and its analogues exert a protective effect against CKD. Clinical studies have demonstrated that the CDDO-Me can increase the estimated GFR in patients with moderate to severe CKD and type 2 diabetes, while reducing serum creatinine (Scr) and blood urea nitrogen (BUN) levels, indicating that these patients experience a short-term improvement in renal function [93]. Renal interstitial fibrosis is a key characteristic of CKD. Studies have shown that OA regulates the abnormal accumulation of extracellular matrix through the transforming growth factor-β1 (TGF-β1)/Smad pathway, thereby alleviating renal fibrosis in a mouse model for UUO [94]. Furthermore, UA has demonstrated the ability to reduce the expression of inflammatory factors, diminish the excessive accumulation of extracellular matrix, and improve renal injury in db/db mice [95].

The aforementioned evidence suggests that OA-related compounds exert a protective effect against renal diseases. However, the specific mechanisms underlying their effectiveness remain poorly understood. In the following sections, we provide a detailed overview of the mechanisms through which OA and its analogues exert their effects on kidney disease, both in vitro and in vivo. The foundational studies investigating the effects of OA, its isomer UA, and its derivatives on kidney disease, mainly involving disease models, intervention methods, and underlying mechanisms have been summarized in Table 2.

Specific mechanisms of action of OA in relation to kidney disease

Anti-inflammatory

The renal inflammatory response serves as an initial protective reaction against kidney damage. However, unresolved inflammation can recruit additional immune cells and trigger the production of a cascade of proinflammatory factors [96]. Consequently, intrinsic renal cells are activated, leading to the release of profibrotic factors such as α-smooth muscle actin (α-SMA), which promotes renal fibrosis and further exacerbates kidney injury [97]. An increasing body of evidence suggests that OA and its analogues possess significant anti-inflammatory effects by modulating various inflammation-related pathways, including nuclear factor-κB (NF-κB), signal transducer and activator of transcription (STAT), and Toll-like receptor 4 (TLR4) [98, 99].

In a mouse model of carbon tetrachloride (CCl_4)-induced renal injury, UA significantly reduces the production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-17. Subsequent studies have reported that CCl_4 treatment increases the phosphorylation of STAT3 (p-STAT3) and activates the NF-κB pathway, whereas UA treatment inhibits this process. Therefore, the inhibitory effect of UA on inflammatory responses may thus be associated with the modulation of the STAT3 and NF-κB pathways [100]. Additionally, pretreatment with UA has been shown to significantly improve acute kidney injury induced by IR in rats. It reduces the expression of TNF-α, IL-6, IL-1β, STAT3 and NF-κB [101]. Similar effects were observed in a mouse model of cisplatin-induced nephrotoxicity treated with OA [102]. Another study revealed that OA interventions significantly alleviated renal injury in a rat model for diabetic nephropathy (DN). It reduced the expression of macrophage marker CD68 and decreased the relative protein expression levels of TLR4 and nuclear NF-κB [103]. Concurrently, stimulation of HK-2 cells with calcium oxalate monohydrate (COM) crystals significantly increased the expression of TNF-α, IL-1β, and IL-6, and elevated levels of TLR4 and p-NF-κB proteins. However, treatment with UA inhibited this process, suggesting that UA may suppress inflammation through the TLR4/NF-κB pathway [104]. Li et al. found that UA reduced the levels of serum TNF-α, IL-6, IL-1β, and IL-18 in DN rats. It also inhibited the expression of TLR4, myeloid differentiation primary response gene 88 (MyD88), and NF-κB proteins [105]. In conclusion, OA-related compounds may inhibit inflammatory responses and attenuate renal damage via the TLR4/NF-κB signaling pathway.

Table 2 Effects and mechanisms of oleanolic acid (OA) and its analogues for the treatment of kidney disease

Type of study	Cell/animal model	Drug and dose	Targets	References
In vivo	APAP-induced renal damage in Wistar rats	OA (5, 25 mg/kg)	NO↓, GSH↑	[86]
In vivo	STZ-induced DN in SD rats	OA (60 mg/kg)	MAP↓	[147]
In vivo	STZ-induced diabetic C57BL/6 mice with BALB/c islets	OA (0.5 mg/d)	IL-10↑, VEGF↑, IFN-γ↓, IL-4↓, IL-17↓, IL-2↓, CD4+ ↓, CD8+ ↓	[110]
In vivo	STZ-induced DN in Balb/cA mice	OA or UA (0.05%, 0.1%, 0.2% in food)	AR↓, SDH↓, GLI↑	[146]
In vivo	STZ-induced DN in C57BL mice	UA (0.01% in food)	ColIV↓, pSTAT3↓, iNOS↓, p-JNK↓, p-ERK↓	[154]
In vivo	IR in C57BL/6 mice	BARD (20 mg/kg)	Nrf2↑, PPAR-γ↑, HO-1↑	[155]
In vivo	STZ-induced DN in SD rats	OA (30, 60, 120 mg/kg)	Urinary Na^+ output↑	[22]
In vivo	STZ-induced diabetic C57BL/6 mice with BALB/c islets	OA (25 mg/kg)	IL-10↑, VEGF↑, IFN-γ↓, IL-1β↓, IL-4 ↓, IL-17↓, IL-2↓, CD4+ ↓, CD8+ ↓	[156]
In vivo	STZ-induced DN in SD rats	OA (20, 40, 80 mg/kg)	SOD↑, catalase↑	[157]
In vivo	STZ-induced DN in Wistar rats	UA (0.2% in food)	8-OHdG↓, NF-κB↓	[158]
In vivo	UUO in C57BL/6 mice	OA (60 mg/kg)	Bax/Bcl2↓, Nrf2↑, HO1↑, Hsp70↑, NAD(P)H↑	[51]
In vivo	CsA-induced kidney injury in ICR mice	OA (25 mg/kg)	8-OHdG↓, 8-iso-PGF2α↓, nuclear/total Nrf2↑, HO-1↑, Bax/Bcl-2↓	[125]
In vivo In vitro	Bilateral ischemic AKI in wild-type mice glucose/serum starvation-induced in renal epithelial cell	CDDO-Im (30 μmol/kg)	IL-6↓, G-CSF↓, KC↓, Nrf2↑, HO-1↑, Nqo1↑, Gclc↑	[78]
In vivo	CCl_4-induced oxidative damage in ICR mice	UA (25, 50 mg/kg)	ROS↓, 8-OHdG↓, TNF-α↓, IL-6↓, IL-17↓, COX-2↓, p-STAT↓, nuclear/total NF-κB↓	[100]
In vivo	(AA)-induced acute kidney injury in C57BL/6 mice	BARD (10 mg/kg)	Nrf2↑, Keapl↓, HO-1↑, NQO1↑, ROS↓	[159]
In vivo	(AA)-induced acute kidney injury in zebrafish	UA (10 ppm)	TNF-α↓, mpo↓	[160]
In vitro	Rat mesangial cells cultured under HG conditions	UA (2.5 μM)	miRNA21↓, P85PI3K↓, pAkt↓, pmTOR↓, p62/SQSTMI↓, COL-I↓, LC3II↑, PTEN↑	[137]
In vitro	Podocytes cultured under HG conditions	UA (1, 2.5, 5, 7.5 μM)	Synaptopodin↑, podocin↑, nephrin↑, miRNA-21↓, PI3K↓, p-Akt↓, p-mTOR↓, Beclin1↑, p62↓, COL-I↓, LC3II/LCI↑, PTEN↑	[138]
In vivo	IR in Wistar rats	CDDO-Me (20mg/kg)	TAS↑, TOS↓, OSI↓, TT↑, NO↓, ADMA↓, SOD↑, GSH-PX↑, iNOS↓, PPAR-γ↑, Nrf2↑, NF-KB↓	[77]
In vivo	OLETF (type 2 diabetes mellitus model) rats	OA (100 mg/kg/day) OA (5 μM)	Nephrin↑, VEGF↓, ESAM↑, TGF-β↓, p-smad2/3↓, p-ERK↓, p-eIF2α↓, ATF6↓, Bip↓, CHOP↓, Bcl2↑, Bax↓, Caspase 3↓, Nrf2↑, HO-1↑, α-SMA↓	[124]
In vivo	IR in Wistar rats	OA (12.5, 25, 50 mg/kg)	KIM-1↓, MDA↓, SOD↑, CAT↑, GPx↑, GSH↑, IFN-γ↓, IL-6↓, IL-10↑, MPO↓, Caspase 3↓, Nrf2↑, GCLc↑	[18]
In vivo	IR in SD rats	UA (10 mg/kg)	TNF-α↓, IL-1β↓, IL-6↓, IL-10↑, p-STAT3↓, P65↓, Caspase-3↓	[101]
In vivo	STZ-induced DN in SD rats	UA (20 mg/kg)	GR enzyme↓, MDA↓, GSH↑, CAT↑, SOD↑	[161]
In vitro	NRK-52E cell stimulated with TGF-β1	OA (2, 4, 8 μM)	E-cadherin↑, FN↓,α-SMA↓, Nrf2↑, klotho↑, p-Smad2/3↓, ILK↓, Snail↓	[133]
In vivo	STZ-induced DN in Wistar rats	UA (25 mg/kg)	TNF-α↓, IL-1β↓, IL-6↓, IL-18↓, TLR4↓,NF-κB↓, MyD88↓	[105]
In vivo	Adenine-induced CKD in Wistar rats	UA (30 mg/kg)	TGF-β↓, CTGF↓, FN↓, CoL-I↓	[162]
In vivo	STZ-induced DN in SDrats	UA (35 mg/kg)	SOD ↑, MDA↓,TNF-α↓, MCP-1↓, IL-1β↓	[163]
In vivo	CLP in mice	UA (2, 20 mg/kg)	ROS↓, 8-OHdG↓, SOD1↑, SOD2↑, TNF-α↓, IL-1β, IL-6↓, NF-κB↓	[164]
In vitro	NRK-52E cell stimulated with HG	OA (10 μM)	miR-142-5p↓, PTEN↑, p62↓, LC3-II/LC3-I↑, a-SMA↓, CoL-IV↓, PI3K↓, pAKT↓, p-mTOR↓	[21]

Table 2 (continued)

Type of study	Cell/animal model	Drug and dose	Targets	References
In vitro	HEK293T cells stimulated with OTA	UA (1 μM)	ROS↓, Lonp1↑, Aco2↑, Hsp75↑	[165]
In vivo In vitro	db/db Mice Mesangial cells stimulated with HG	UA (0.3% in food) UA (2.5 μM)	ARAP1↓, AT1R↓ 8-OHdG↓, NOX2↓, FN↓, IL1β↓, IL-18↓, TGF-β1↓, CoL-IV↓	[95]
In vivo	Cisplatin-induced nephrotoxicity in mice	OA (10, 40 mg/kg)	HO-1↓, SOD↑, 4-HNE↓, TNF-α↓, p-STAT3↓, NF-κB↓	[102]
In vivo In vitro	UUO in C57BL6 mice HK-2 cells stimulated with TGF-β1	UA (50 and 100 mg/kg) UA (10, 50 μM)	CoL-I↓, FN↓, a-SMA↓, E-cadherin↓, p-Smad3↓	[132]
In vivo In vitro	LPS-induced AKI in BALB/C mice RAW 264.7 stimulated with LPS	UA (100 mg/kg) UA (10 μM)	TNF-α↓, IL-6 ↓, IL-1β↓, F4/80↓, TLR4↓, MyD88↓, LC3B↑, Beclin-1↑	[88]
In vivo	Pristane-induced lupus nephritis in BALB/c mice	AOA (50 mg/kg)	RORγt↓, IL-17A↓, IL-17F↓, IL-22↓, IFN-γ↓, IgG↓,IgM↓, Th17↓	[109]
In vivo	UUO in SD rats	OA (6 mg/kg)	CoL-I↓, CoL-III↓, FN↓, α-SMA↓, TGF-β↓, TβRI↓, TβRII↓,p-Smad2↓	[131]
In vitro	Podocyte stimulated with sC5b-9	OA (10, 20, 40, 80, 160 μM)	nephrin↑, podocin↑, CD2AP↑, Bcl2↑, Bax↓, p-AKT↓, p-mTOR↓	[166]
In vivo	Pristane-induced lupus model in BALB/c mice	OA (50 mg/kg)	Th17↓, IL-17A↓, IFN-γ↓, IgG↓, IgM↓	[20]
In vivo In vitro	COM-induced kidney damage in SD rats HK-2 cells stimulated with COM	UA (20, 40 mg/kg) UA (2.5, 5 μM)	α-SMA↓, CoL-I ↓, Bcl-2↑, Bax↓, Nrf2↑, HO-1↑, TNF-α↓, IL1β↓, IL-6↓, TLR4↓, p-NF-κB↓	[104]
In vivo	CP-induced nephrotoxicity in Wistar rats	UA (5, 10 mg/kg)	GSH↑, SOD↑, CAT↑, MDA↓, IL-1β↓, IL-6↓, TNF-α↓, Caspase-3↓, Caspase-9↓	[141]
In vivo	STZ-induced DN in SD rats	UA (50 mg/kg)	TNF-α↓, IL-1β↓, IL-6↓, SOD↑, MDA↓, GSH↑, CAT↑, NO↓, FN↓, E-cad↑, MMP-9↑,TIMP-1↓, α-SMA↓, TGF-β1↓,SMA3↓, SMA7↓, P38↓	[167]
In vivo	RIRI in SD rats	OA (50 mg/kg)	PI3K↓, p-AKT↓, PDK1↑, p27↑, TRAP1↑, CypD↓	[168]
In vitro	HK-2 cells stimulated with OTA	OA (2 μM)	Bax↓, Bcl-2↑, Cyt-C↓, Caspase-9↓,Caspase-3↓, GRP78↓, CHOP↓	[169]
In vivo	STZ-induced DN in SD rats	OA (50, 100 mg/kg)	nephrin↑, CD68↓, COL-IV↓, p-AMPK/AMPK↑, PGC-1α↑, TLR4↓, NF-κB↓, TGF-β1↓	[103]
In vivo	STZ-induced DN in SD rats	OA (50 mg/kg)	Caspase-3↓, Bax↓, CD31, E-cadherin↑, α-SMA↓, Vimentin↓, TGF-β1↓, p-P38↓, FGFR1↑, SIRT3↑, DPP-4↓	[170]
In vivo	UUO in SD rats	UA (40 mg/kg)	TGF-β1↓, Keap1↓, Nrf2↑, HO-1↑, 8-oxo-dG↓, Caspase-3↓, Caspase-8↓	[171]
In vivo	TAA-induced AKI in BALB/c mice	OA (45, 90 mg/kg)	MDA ↓, NOx ↓, GSH↑, SOD↑, NF-κB↓, TNF-α↓, Bax↓, Bcl2 ↑, Caspase-3↓ Nrf2↑, HO-1↑	[143]
In vitro	HK-2 cells stimulated with OTA	UA (4 μM)	Lonp1↑, Sig-1R↑, GRP78↓, p-ERK↓, p-eIF2α↓, CHOP↓, IRE1α↓, Bcl2↑, Bax↓	[142]

(↑) and (↓) signs show positive and negative effects of oleanolic acid and its analogues on its target molecules, respectively

Immunoregulatory effect

The immune system plays a crucial role in renal diseases. Under steady-state conditions, the kidney harbours immune cells, including macrophages, dendritic cells, and lymphocytes. When the kidneys are damaged, these immune cells release a range of proinflammatory mediators, such as chemokines and cytokines, which further promote the occurrence and progression of inflammation [106]. Furthermore, immune system dysregulation can give rise to the occurrence of autoimmune kidney diseases, including lupus nephritis and IgA nephropathy, which can inflict severe damage upon the kidneys [107].

Lupus nephritis is an immune complex nephritis. T helper cell (Th17) plays an important role in the pathogenesis of lupus nephritis [108]. Research has demonstrated that, in mice with pristane-induced lupus nephritis, treatment with OA reduces dsDNA levels, IL-17A expression and interferon γ (IFN-γ), and alleviate

renal injury by decreasing the deposition of IgG and IgM in the glomeruli [20]. Further studies have revealed that OA inhibits the differentiation of Th17 cells in vitro. Additionally, Zhou et al. found that 3β-acetoxy-oleanolic acid (AOA) exhibits similar beneficial effects in an LN model [109]. Furthermore, OA has been shown to have a preventive effect on immune responses caused by pancreatic islet transplantation. It decreases the expression of IFN-γ, IL-4, IL-2, and IL-17 in T cell populations while markedly increasing the levels of IL-10. OA also reduces the infiltration of CD4+ and CD8+ T cells and extends the survival time [110]. Likewise, in a model where kidneys from BN rats were transplanted into LEW rats, the combined treatment of OA and cyclosporine A decreased the infiltration of CD4+ and CD8+ T cells and ameliorate rejection and inflammatory responses following kidney transplantation in rats [111]. In our investigation, we discovered that human monocytes and mouse macrophages displayed an exaggerated sensitivity to monocyte chemoattractant protein-1 when subjected to modulation by high glucose (HG) and human low-density lipoprotein. Notably, this heightened response was effectively mitigated by UA [112]. Furthermore, the administration of UA in the LPS-induced AKI model reduces the infiltration of F4/80-positive macrophages and a decrease in the expression of proinflammatory cytokines, including TNF-α, IL-6, and IL-β. However, UA demonstrated the ability to decrease the expression levels of TNF-α, IL-6, and IL-1β in RAW264.7 cells stimulated with LPS [88].

Improving oxidative stress

Oxidative stress (OS) refers to the imbalance between oxidation and antioxidant mechanisms in the body, leading to the excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) or insufficient antioxidant defence mechanisms [113, 114]. The kidney is a highly oxygen-consuming organ, second only to the heart, and is thus particularly vulnerable to OS-induced damage [115]. There is growing evidence that OS plays a crucial role as a pathological driving factor in the occurrence and progression of kidney disease. This includes the induction of damage to proximal tubular epithelial cells, resulting in cell death and impairment of proximal tubular reabsorption [116]. Early clinical studies have indicated that patients with sepsis-induced AKI exhibit mitochondrial dysfunction and excessive NO production [117]. Furthermore, OS levels gradually increase with the progression of CKD and are significantly correlated with the level of renal function [118]. OA is an effective antioxidant that directly reacts with ROS, scavenges free radicals, and enhances antioxidant defence. It promotes antioxidant glutathione generation via nuclear factor erythroid 2-related factor 2 (Nrf2) and increases the expression of antioxidant enzymes [119]. Simultaneously, CDDO-Me synthesised from OA as a precursor compound shows stronger antioxidant capacity and is the most effective activator of Nrf2 pathway [120, 121], which can improve the estimated GFR, reduce the urinary albumin-to-creatinine ratio, and restore renal function in patients with moderate to severe CKD [122, 123].

HG-induced OS is believed to be a primary cause of diabetic renal fibrosis. In a 20-week study involving OLETF (type 2 diabetes model) rats, continuous administration of OA resulted in a decrease in the expression of 8-hydroxy-2′-deoxyguanosine (8-OHdG), which is a marker of oxidative DNA damage. Furthermore, the levels of the antioxidant enzyme superoxide dismutase (SOD) were also elevated. Subsequent in-vitro experiments involving stimulation of mouse mesangial cells with high glucose and toxic β-carotene induced endoplasmic reticulum stress, leading to elevated levels of ROS. Results indicate that similar to the action of the endoplasmic reticulum stress inhibitor 4-phenylbutyric acid, OA can reverse this effect. These findings suggest that OA administration can effectively reduce oxidative damage and promote renal repair [124]. Nrf2 is a critical transcription factor that binds to antioxidant response elements and regulates antioxidant responses under OS conditions. In a mouse model of UUO, treatment with OA was observed to decrease renal tubular injury and increase Nrf2, while the expression of Kelch-like ECH-associated protein 1 (Keap1) remained unchanged. These findings indicate that OA facilitates the nuclear translocation of Nrf2, leading to a reduction in renal OS [51]. Similarly, OA intervention markedly increased the nuclear Nrf2/total Nrf2 ratio, as well as the levels of heme oxygenase-1 (HO-1) and SOD in mice with chronic cyclosporine nephropathy. Furthermore, OA treatment reduced the levels of malondialdehyde, a marker of OS [125]. Moreover, pretreatment with OA has been found to decrease NO levels in the kidneys of rats with acetaminophen-induced liver and kidney toxicity. It also elevates the intracellular levels of glutathione in renal cells, leading to the mitigation of liver and kidney injury [86]. Treatment of HK-2 cells exposed to cisplatin with CDDO-Me upregulates mRNA expression of HO-1, NAD(P)H, glutathione peroxidase 1, and catalase, along with other antioxidant enzymes. This upregulation effectively prevents cellular senescence [126].

Anti-fibrosis

Renal fibrosis is a common outcome of many chronic and progressive kidney diseases, characterised by the deposition of extracellular matrix proteins, notably collagen and adhesive glycoproteins such as fibronectin (FN) [127].

Activated myofibroblasts are considered important cells involved in the secretion of these matrix components, including α-SMA which serves as a marker for myofibroblast activation and TGF-β1 which is the key regulatory factor in the modulation of renal fibrosis [128]. Abundant foundational research has demonstrated the potential of OA-related compounds in ameliorating fibrosis in multiple organs, including the heart, lungs, liver, and kidneys [40, 51, 129, 130]. Thus, targeting fibrosis may thus represent a potential therapeutic strategy for OA in the treatment of kidney diseases.

Treatment with OA demonstrates a significant reduction in Scr, BUN, and urinary protein levels in the UUO rat model, thereby mitigating renal collagen deposition. Moreover, OA administration downregulates the mRNA expression of collagen (COL)-I, COL-III, FN, and α-SMA in the kidneys. Additionally, OA decreases the protein levels of TGF-β, TGF-β receptor (TβR) I, TβRII, and phosphorylated Smad2/Smad2 (p-Smad2/Smad2). These results indicate that OA may ameliorate fibrosis in UUO rats by modulating the TGF-β/Smad signalling pathway [131]. Xu et al. also found that UA inhibits epithelial-mesenchymal transition (EMT) by reducing the protein expression of TGF-β1 and p-Smad3, thereby reducing renal fibrosis in the UUO model. Further research has shown that UA can decrease the expression of profibrotic factors in TGF-β1-treated HK-2 cells, lower the protein levels of TGF-β1 and p-Smad3, and inhibit EMT [132]. Similarly, He et al. induced EMT with TGF-β1 and intervened using OA to culture renal tubular epithelial cells NRK-52E. The results demonstrated that TGF-β1 stimulation leads to the downregulation of the epithelial cell marker E-cadherin and the upregulation of α-SMA and FN expression; however, treatment with OA effectively inhibited this process along with the expression of p-Smad2/3, a downstream component of the TGF-β signalling pathway [133]. The aforementioned findings suggest that the inhibitory effects of OA and its analogues on renal fibrosis may be mediated through the TGF-β/Smad signalling pathway.

Enhancing autophagy

Autophagy refers to the cellular process by which damaged organelles, proteins, and other cellular components are degraded through lysosomes, which helps maintain intracellular homeostasis while simultaneously generating energy [134]. Increasing evidence suggests that autophagy plays a protective role in renal diseases. In proximal tubular autophagy-deficient mice, following I/R injury, significant increases in Scr and BUN levels were observed when compared to those in wild-type control mice. Additionally, there was a marked accumulation of p62 and ubiquitin aggregates was observed, indicating prominent proximal tubular injury [135]. Furthermore, in the UUO rat model, continuous intraperitoneal injection of the autophagy inhibitor 3-methyladenine for 7 days exacerbated tubular epithelial cell apoptosis and interstitial fibrosis in the rat kidneys [136]. Chen et al. found that intervention with OA significantly alleviated renal fibrosis in a STZ-induced DN mouse model. OA treatment reduced macrophage infiltration and decreased the expression of α-SMA and CoL-IV. Furthermore, compared with those in the control group, the autophagy markers LC3I and LC3II were downregulated in the DN model, indicating that autophagy levels are suppressed during the progression of diabetic kidney disease. OA may exert a protective effect in diabetic nephropathy by enhancing autophagy [21].

Further studies have revealed revealed that miRNA is associated with autophagy in diabetic nephropathy, and the phosphatase and tensin homolog (PTEN) are the downstream target genes. An in vitro model of autophagy was established by subjecting NRK-52E cells to HG treatment. In the HG group, CoL-IV was upregulated, whereas LC3I and LC3II were downregulated. The expression of miR-142-5p was increased, and PTEN expression was decreased. These results were reversed by OA treatment. Furthermore, OA reduced the expression of PI3K, p-AKT, and p-mTOR proteins [21]. Similarly, in vitro cultures of rat glomerular mesangial cells and podocytes under HG conditions were were treated with UA. The deposition of collagen within the cells decreased, and transmission electron microscopy revealed suppressed autophagosome reduction, and accompanied by the downregulation of the autophagic lysosomal degradation marker p62. Additionally, the expression of LC3I, LC3II, and PTEN was increased, whereas that of miRNA-21 was suppressed, and the PI3K/AKT/mTOR pathway was inhibited [137, 138]. These results indicate that UA may enhance the level of intrinsic cellular autophagy in the kidneys through the PI3K/AKT/mTOR signalling pathway, thereby alleviating renal damage. Furthermore, in an LPS-induced macrophage model, UA was found to regulate the TLR4/MyD88 pathway and inhibit the release of inflammatory factors. This anti-inflammatory action of UA can be blocked by the autophagy inhibitor 3-methyladenine, suggesting that this action is mediated through autophagy [88].

Others

Anti-apoptosis

Cell apoptosis refers to programmed cell death, which typically occurs during development and aging processes to help maintain cellular homeostasis within a population [139]. However, excessive apoptosis can deplete essential functional cells, leading to organ damage and even

triggering inflammation [140]. UA has been reported to down-regulate the expression of IL-1β, IL-6 and TNF-α, reduce the levels of apoptosis markers caspase-3 and -9, and attenuate cisplatin-induced nephrotoxicity [141]. Treatment of HK-2 cells with ochratoxin A (OTA) enhances the expression of the proapoptotic gene Bax and inhibits the expression of the anti-apoptotic gene Bcl-2, leading to cell apoptosis, however, pretreatment with UA can alleviate this situation [142]. Furthermore, in a mouse model of liver and kidney injury induced by thioacetamide (TAA), OA can reduce the expression of Bax and caspase-3, increase the expression of Bcl-2, and alleviate liver and kidney damage [143]. Thus, the OA-related compounds may thus alleviate kidney injury through the anti-apoptotic pathway.

Anti-glycation

Protein glycation is a diverse post-translational modification of proteins that forms advanced glycation end products (AGEs), which can induce protein dysfunction and disrupt homeostasis [144, 145]. OA and UA treatment in diabetic mice has been shown to lower blood glucose levels and improve overall kidney function. To investigate whether their therapeutic effects on the kidneys are related to the anti-glycation properties of these two triterpenoid compounds, the enzymes involved in the polyol pathway of glucose metabolism and the levels of AGEs were examined. The results revealed that OA and UA were able to inhibit the activity of renal aldose reductase, enhance the activity of glyoxalase I, reduce the activity of sorbitol dehydrogenase, and suppress the generation of AGEs, such as plasma glycated haemoglobin, renal *N*-ε-(carboxymethyl)lysine, pentosidine, and urinary glycated albumin. These findings suggest that OA and UA may alleviate kidney damage by exerting anti-glycation effects [146].

Anti-hypertension

Hypertension is widely recognised as a primary catalyst of CKD progression and can significantly exacerbate renal injury [91]. In the STZ-induced diabetic rat model, OA was found to increase the sodium excretion rate without affecting the urine flow, K^+, and Cl^- rates. Additionally, it decreased mean arterial pressure (MAP) in rats and increased creatinine clearance, leading to a reduction in the plasma creatinine concentration. These findings suggest that OA has a protective effect on renal function [147]. Studies have demonstrated that treatment with OA increases urinary Na^+ excretion and decreases MAP in experimental models for hypertension. Furthermore, the reduction in MAP is directly proportional to the increase in urinary Na^+ excretion. Based on these findings, OA is hypothesised to exert its renal protective effects by enhancing Na^+ excretion, thereby lowering MAP [148].

Limitations and optimization of OA for clinical applications

OA exhibits broad biological activity, and numerous studies have confirmed its protective effects on the kidneys. This review has summarized the known mechanisms of action of OA and its analogues in relation to kidney disease (Fig. 5). However, due to its unique chemical structure, poor water solubility, limited permeability, and low bioavailability, the clinical application of OA may be hindered. Therefore, improving the bioavailability of OA is thus a pressing issue that needs to be addressed in future research. A potential approach to address this issue is through the design and synthesis of derivatives using OA as a starting material. In this regard, 3-oxours-oleana-9(11),12-dien-28-oic acid (Oxy-Di-OA) was synthesised and investigated for its protective effects against CCl_4-induced liver injury. The results demonstrated that Oxy-Di-OA could alleviate liver damage. Furthermore, acute toxicity experiments and pharmacokinetic studies revealed that this compound exhibited low toxicity and had a longer half-life when compared with that of OA, indicating its higher bioavailability [40]. Modifications were made to the OA derivative, DKS26, to enable the preparation of lipid nanodiscs (sND/DKS26) and liposomes (sLip/DKS26). Compared to free DKS26, these carrier compounds both exhibited considerably improved oral bioavailability [149]. Luo et al. employed the double emulsion method to prepare multivesicular liposomes encapsulating OA (OA-MVLs). These liposomes were able to increase the solubility of OA and prolong the drug's residence time in the bloodstream [150]. Simultaneous loading of OA and gentiopicrin into the nanostructured lipid carriers (NLCs) resulted in a stronger effect on liver injury when compared to loading OA alone. Furthermore, the NLCs formulation prolonged the maintenance of drug concentration in the plasma [151]. Therefore the design and synthesis of OA derivatives, utilisation of lipid nano-carriers for OA encapsulation, and combination therapy with other drugs were thus identified as effective approaches to enhance the therapeutic efficacy of OA.

Summary and outlook

Currently, the available pharmacological treatments for kidney diseases are limited. Two commonly used treatments are ACEI and ARB, which primarily target blood

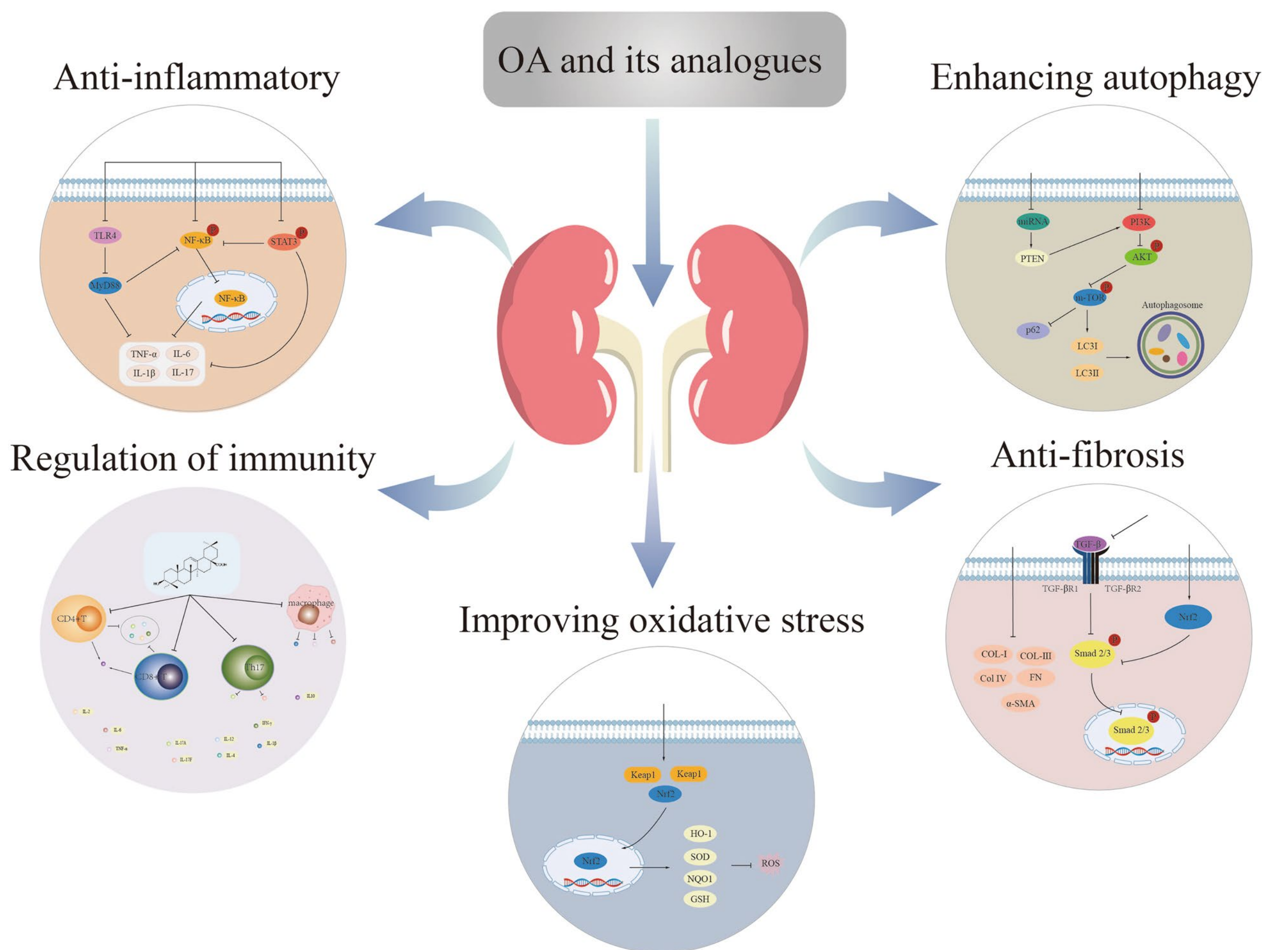

Fig. 5 Main oleanolic acid mechanisms in relation to kidney disease

pressure reduction and diuresis to alleviate renal conditions. However, these medications are associated with significant side effects and may exacerbate renal burden. Therefore, identifying new effective and safe drugs is generally considered the best strategy to prevent and treat kidney diseases.

OA demonstrates preventive and therapeutic effects on kidney diseases by modulating various signalling pathways, including NF- κB, STAT, PI3K/AKT, TLR4, and Nrf2/HO-1. Its actions in relation to kidney diseases primarily involve the inhibition of inflammatory responses, immune modulation, attenuation of OS, enhancement of autophagy function, suppression of renal fibrosis, and the reduction of cellular apoptosis. Thus, OA holds promising potential as a therapeutic agent for treating kidney diseases in the future.

Compared with current clinical therapies for kidney diseases, OA offers advantages such as multi-target effects and a high safety profile. However, its poor water solubility, permeability, and low bioavailability may limit its clinical applications. Therefore, further research to design and synthesise OA derivatives and utilise lipid nano-carriers for OA encapsulation is urgently needed to enhance the bioavailability of OA and maximise its therapeutic potential in treating kidney diseases.

Abbreviations

OA	Oleanolic acid
UA	Ursolic acid
NF-κB	Nuclear factor kappa-B
Nrf2	Nuclear factor erythroid2-related factor 2
HO-1	Heme oxygenase-1
TGF-β	Transforming growth factor β
PI3K	Phosphoinositide 3-kinase
AKT/PKB	Protein kinase B
AKI	Acute kidney injury
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
ACE	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PGI2	Prostacyclin
STZ	Streptozotocin
I/R	Ischemia/reperfusion

UUO	Unilateral ureteral obstruction
CL	Clearance
VSS	Steady-state volume of distribution
AUC	Area under the concentration–time curve
t1/2	Half-life
Cmax	Maximum concentrations
NADPH	Nicotinamide adenine dinucleotide phosphate
Tmax	Time to reach maximum concentration
NO	Nitric oxide
INF-γ	Interferon-γ
CDDO	2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid
LC50	Median lethal concentration
LD50	Median lethal dose
IL-1β	Interleukin-1β
IL-6	Interleukin-6
TNF-a	Tumor necrosis factor-α
ICAM	Intercellular cell adhesion molecule
GCLc	Glutamate-cysteine ligase
MDA	Malondialdehyde
SOD	Superoxide dismutase
CAT	Catalase
GSH	Glutathione
LPS	Lipopolysaccharides
TLR4	Toll-like receptor 4
MyD88	Myeloiddifferentiationfactor88
Scr	Serum creatinine
BUN	Blood urea nitrogen
α-SMA	α-Smooth muscle actin
STAT	Signal transducer and activator of transcription
CCl_4	Carbon tetrachloride
IL-17	Interleukin-17
DN	Diabetic nephropathy
IL-18	Interleukin-18
HG	High glucose
CoL	Collagen
COM	Calcium oxalate monohydrate crystals
LN	Lupus nephritis
IL-2	Interleukin-2
IL-10	Interleukin-10
OS	Oxidative stress
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
8-OHdG	8-Hydroxy-2′-deoxyguanosine
SOD	Superoxide dismutase
Keap1	Kelch-like ECH-associated protein 1
TβR	TGF-β receptor
EMT	Epithelial-to-mesenchymal transition
PTEN	Phosphatase and tensin homolog
mTOR	Mammalian target of rapamycin
Bcl-2	B-cell lymphoma 2
Bax	BCL2-associated X protein
AGEs	Advanced glycation end products
MAP	Mean arterial pressure
NLCs	Nanostructured lipid carriers

Acknowledgements
Not applicable.

Author contributions
XC designed, organized, and supervised the study and helped to coordinate support and funding. DP collected the data and drafted the manuscript. YQ, CS, CX, JZ and HD participated in the revision. All authors read and approved the final manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (No. 32141005), and the State Key Research and Development Program (No. 2019Zx09201-005).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

Received: 13 January 2024 Accepted: 19 April 2024
Published online: 30 May 2024

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