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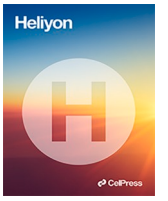

Review article

Lipidomics-based natural products for chronic kidney disease treatment

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ABSTRACT

Chronic kidney disease (CKD) is by far the most prevalent disease in the world and is now a major global public health problem because of the increase in diabetes, hypertension and obesity. Traditional biomarkers of kidney function lack sensitivity and specificity for early detection and monitoring of CKD progression, necessitating more sensitive biomarkers for early diagnostic intervention. Dyslipidemia is a hallmark of CKD. Advancements in mass spectrometry (MS)-based lipidomics platforms have facilitated comprehensive analysis of lipids in biological samples and have revealed changes in the lipidome that are associated with metabolic disorders, which can be used as new biomarkers for kidney diseases. It is also critical for the discovery of new therapeutic targets and drugs. In this article, we focus on lipids in CKD, lipidomics methodologies and their applications in CKD. Additionally, we introduce novel biomarkers identified through lipidomics approaches and natural products derived from lipidomics for the treatment of CKD. We believe that our study makes a significant contribution to literature by demonstrating that natural products can improve CKD from a lipidomic perspective.

Abbreviations: AKI, acute kidney injury; Ali-B 23, Alisol B 23-acetate; Apo AI, apolipoprotein A-1; AM, Astragalus Membranaceus; AR, Alismatis Rhizoma; AS-IV, Astragaloside IV; AMPK, AMP-activated protein kinase; BBR, berberine; BU, butanol extract; CC, Coptis Chinensis; Cer, ceramides; CKD, chronic kidney disease; Cpt-1, Carnitine palmitoyltransferase-1; CVD, cardiovascular disease; CRF, chronic renal failure; DCA, Deoxycholic acid; DN, diabetic nephropathy; EA, ethyl acetate extract; ESKD, end-stage kidney disease; ESRD, End stage renal disease; FAs, fatty acids; FABPs, fatty acid binding proteins; FATPs, fatty acid transport proteins; FAO, fatty acid oxidation; HD, hemodialysis; HDL, high-density lipoprotein; HFD, high-fat diet; HRMS, high-resolution mass spectrometry; IDL, intermediate-density lipoproteins; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LDL, low-density lipoprotein; LFD, low-fat diet; LPL, lipoprotein lipase; LPC, lysophosphatidylcholine; MS, mass spectrometry; MUFA, monounsaturated fatty acids; NEFAs, non-esterified fatty acids; OMM, outer membrane; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PUFA, polyunsaturated fatty acids; PGC-1α, PPARγ coactivator-1α; ROS, reactive oxygen species; Sph, sphingosine; SM, sphingomyelin; SREBP-1, sterol regulatory element-binding protein-1; STZ, streptozotocin; TAG, triacylglycerols; TG, triglycerides; TRLs, triglyceride-rich lipoproteins; UHPLC, ultra-high performance liquid chromatography; UPLC-Q-TOF/MS, ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry; VLDL, very-low-density lipoproteins.

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1. Introduction

The burden of chronic kidney disease (CKD) worldwide is on the rise due to rising prevalence and rates of mortality [1].Early screening, diagnosis, and management are crucial in preventing adverse outcomes of CKD, such as cardiovascular diseases, end-stage renal disease, and death [2]. Common clinical biomarkers for renal function impairment and staging in CKD patients include urinary protein excretion and serum creatinine [3]. However, due to their lack of specificity and sensitivity in diagnosing the disease, there is an urgent need for more sensitive biomarkers for renal diseases [4].

CKD is a global health concern with a prevalence ranging from 8 % to 16 % and a high risk of progressing to end-stage renal disease [5,6]. The pathogenesis of CKD involves multiple processes including inflammation [7,8], oxidative stress [9,10], renal fibrosis [11], and lipid abnormalities [12]. The accumulation of lipids can also induce mitochondrial and renal cell damage by activating the immune system and promoting inflammation through fibrosis, further demonstrating the role of lipids in the progression of CKD [13]. Dyslipidemia is a common problem in patients with CKD [14]. The disturbed lipid metabolism that is associated with CKD further accelerates the progression of the disease and the onset of cardiovascular diseases [15]. In the past, clinical research on lipids was restricted to measuring lipoproteins and triglycerides (TG). However, advances in lipidomics technology, based on modern mass spectrometry (MS) platforms, have enabled the quantification and identification of a broader spectrum of lipids [16,17]. Lipidomics is a branch of metabolomics [18]. Metabolomics and lipidomics have evolved into analytical sciences that employ holistic approaches for metabolite analysis and provide comprehensive insights into metabolic processes [19,20]. Therefore, advancements in lipid analysis offer powerful tools for research in nephrology, facilitating the discovery of biomarkers and a deeper understanding of the molecular mechanisms underlying diseases [21]. Natural products are increasingly utilized in clinical settings, and lipidomics-based natural products therapy offers new insights for studying the treatment of CKD.

2. Lipids and lipidomics

Lipids are essential constituents of biological membranes and are structurally and functionally diverse molecules [22]. They primarily serve roles in cell structure, signal transduction, energy storage and metabolism, and other varied functions [23]. These structures consist of tens of thousands, if not more, lipid molecular species [24]. Lipid classification includes fatty acyls, glycerophospholipids, glycerolipids, sphingolipids, prenol lipids, sterol lipids, and glycolipids [25]. Within each category, individual lipid molecules can be further classified based on their polar head groups, and species within a class can be further divided into subclasses due to specific structural similarities [26]. The diversity of lipid molecular species and their homeostasis are related to various pathological conditions [27]. Abnormalities in lipid metabolism have been associated with numerous diseases, including neurodegenerative disorders [28], cardiovascular diseases [29], cancer [30], and obesity [31].

Lipidomics is a branch of metabolomics. Similar to metabolomics, it enables a comprehensive and detailed analysis of the lipidome in a biological system and the detection of changes in specific lipids in response to internal and/or external stimuli (such as drug intervention, disease, environmental stress and genetic mutations) [32]. As an emerging field, lipidomics has made significant strides

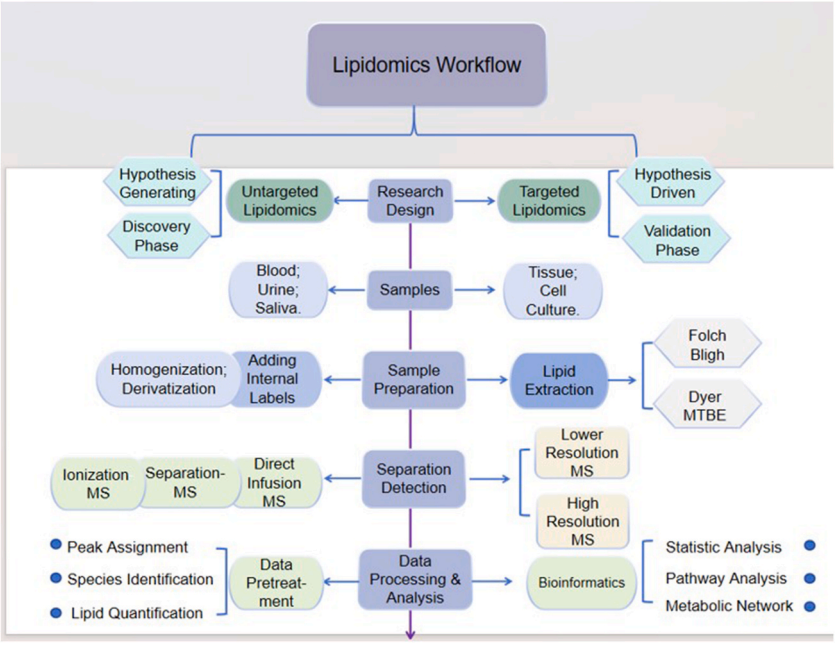

Fig. 1. Lipidomics workflow schematic.

in recent years, primarily due to advancements in MS [33,34]. Without cutting-edge mass spectrometric analytical techniques, lipidomics would not be feasible. Current lipidomic analysis methods include non-targeted high-resolution mass spectrometry (HRMS), targeted lipidomics using liquid chromatography-tandem mass spectrometry (LC-MS/MS), and shotgun lipidomics based on direct infusion [35]. It is roughly estimated that there are about 180,000–200,000 different lipid species in nature [36]. However, to date, only a small fraction of lipids can be identified, demonstrating the lack of understanding of lipid identification and analysis as well as the implications of using high-throughput screening methods. The workflow of lipidomic studies varies according to research but generally includes study design, sample preparation, separation and detection, and data processing (Fig. 1) [37,38]. Targeted and non-targeted lipidomics are two methodologies with distinct characteristics, advantages, and disadvantages [39]. Therefore, researchers should determine whether to conduct targeted or non-targeted lipidomic research prior to commencing their studies. The two basic steps in sample preparation are adding internal standards and extracting lipids. Given the diversity of lipid molecules, successful lipidomic analysis depends on the efficient extraction of lipid molecules. Typically, a two-phase system such as the Bligh and Dyer (B&D) chloroform-based system is employed [40]. Nowadays, lipidomic studies adopt single-step extractions for ease of use. In the technological platforms used to address chemical diversity, nuclear magnetic resonance spectroscopy and MS are two majors widely used techniques for extensive metabolite and lipid analysis [41]. Liquid chromatography coupled with MS is the most common and versatile separation technique in MS-based metabolomics and lipidomics, suitable for both targeted and non-targeted determinations [42,43]. In the past decade, the introduction of ultra-high performance liquid chromatography (UHPLC), which employs sub-2 μm particle columns and core-shell particles, has improved the resolution and sensitivity of LC-MS analyses, significantly increasing the number of metabolites detected in complex biological matrices [44]. In summary, the progress in MS-based lipidomic technologies allow for a more comprehensive analysis of lipids and have wider applicability in early disease diagnosis, predicting treatment responses, and prognosis.

3. Applications of lipidomics in CKD

Dyslipidemia is common in the early stages of CKD and becomes more severe as kidney function deteriorates [45]. During the course of CKD, several lipid disorders are commonly observed: increased levels of very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL), increased triglycerides (TG), normal to elevated levels of along with an increase in ox-LDL, deficiency and dysfunction of high-density lipoprotein (HDL), decreased levels of apolipoprotein A-1 (Apo AI), accumulation of lipoproteins containing Apo B, and an increased ratio of Apo C-III/C-II [46]. The most prominent lipid abnormalities are hypertriglyceridemia (elevated TG) and low levels of HDL; Both of these are serious risk factors for cardiovascular diseases [47,48]. Studies suggest that these lipid abnormalities linked to CKD are predominantly associated with disturbed metabolism of triglyceride-rich lipoproteins (TRLs), including VLDL, IDL, and, to a lower extent, chylomicrons [49–51].

The occurrence of hypertriglyceridemia is mainly due to a delay in catabolism and an increase in hepatic production of TG-rich TRLs [52,53]. The delay in catabolism is related to a reduction in the levels of lipoprotein lipase (LPL) activity [54]. Apo C-III, acting as an inhibitor of LPL, impedes the activity of LPL and the hepatic uptake of TRL remnants, thereby leading to hypertriglyceridemia [55]. Patients with CKD have lower levels of HDL compared to patients with normal renal function [56]. First, the amounts of Apo AI and Apo AII (major components of HDL) are reduced in patients with impaired renal function [57]. Additionally, the function of lecithin-cholesterol acyltransferase, which is responsible for the incorporation of free cholesterol into HDL, is impaired [58]. Furthermore, the activity of cholesteryl ester transfer protein increases, leading to enhanced transfer of cholesteryl esters from HDL to TG-rich TRLs. This is a primary reason why patients with CKD are prone to hypertriglyceridemia and low levels of HDL.

Advances in lipidomics platform technology have more profound implications for the discovery of lipid disorders in CKD. The applications of lipidomics in CKD cover several research goals, including the identification of new diagnostic biomarkers, indicators of

Table 1
Lipidomics of lipids in CKD.

Analyte	Lipid analysis showed an increase	Lipid analysis showed a decrease	References
Fatty acids	Free fatty acids	/	[74]
	Monopolyunsaturated fatty acid	n-3 and n-6 polyunsaturated fatty acids	[75]
	Free fatty acid (FFA)16: 1/FFA 16:0 and FFA 18:1/FFA 18:0	/	[78]
Glycerides	Medium-chain length (52–56) TAG	Shorter TAG (42–48)	[89]
	TAG (12:0/16:1/18:2, 18:0/18:1/18:1, 12:0/16:0/18:2, 14:0/16:0/18:1)	/	[90]
Phospholipids	Lysophosphatidylcholine (LPC)	Phosphatidylcholine (PC)	[93]
	PC, LPC	/	[94]
	PC aa C38:0	/	[95]
	PC (36:5e), phosphatidylethanolamine (PE (36:4e)), and PE (38:7e)	/	[97]
	/	Phospholipids (C-30:0)	[99]
Sphingolipids	Ceramides (Cer(d18:1/16:0, d18:1/18:0, d18:1/20:0, d18:1/22:0, d18:1/24:0, d18:1/24:1))	/	[109]
	/	Cer, sphingomyelin (SM)	[110]
	Cer 22:0 and 24:1, capryloyl Cer 16:0, and SM 16:0	/	[111]
Sterols	Cholesterol	/	[115]
	Bile acids	/	[119]
	Deoxycholic acid	/	[120]

disease severity, therapeutic targets, predictors of disease course and patient prognosis, as well as providing insights into lipid abnormalities and associated comorbidities [59,60]. Lipidomic analysis methods can assist us in better identifying changes in lipid metabolism in patients with renal diseases. Here, we highlight some representative lipid categories and their lipidomics findings to explore their impact on CKD (Table 1).

3.1. FFAs in Lipidomic studies of CKD

In proximal renal tubular cells, fatty acids (FAs) can be absorbed through fatty acid transport proteins (FATPs) such as CD36 and fatty acid binding proteins (FABPs) [61]. Moreover, FAs can be reabsorbed from the glomerular filtrate via endocytosis mediated by various receptors (megalin, cubilin, and CD36) and FABPs [62,63]. FAs can be activated to acyl-CoA by acyl-CoA synthetase in the cytoplasm, allowing them to cross the mitochondrial outer membrane (OMM) [64,65]. Carnitine palmitoyltransferase-1 (Cpt-1), which is located on the OMM, catalyses the conversion of acyl-CoA to acylcarnitine [66,67]. Acylcarnitine is then transported into the mitochondrial matrix via carnitine-acylcarnitine translocase (CACT) and Cpt-2 to form acetyl-CoA [68,69]. Finally, acetyl-CoA is converted into NADH and FADH2 through the tricarboxylic acid cycle (TCA), thereby generating energy for the cell (Fig. 2). So FFAs and non-esterified fatty acids (NEFAs) are important in the lipid metabolism and renal cell profile of patients with CKD.

Many studies have shown that CKD patients generally display a specific fatty acid profile: increased serum monounsaturated fatty acids (MUFA) and decreased polyunsaturated fatty acids (PUFA) levels [70,71]. A total of 214 patients in various stages of chronic renal failure were selected and measured their plasma lipids and acylcarnitines using LC-MS/MS. It was found that patients with stage

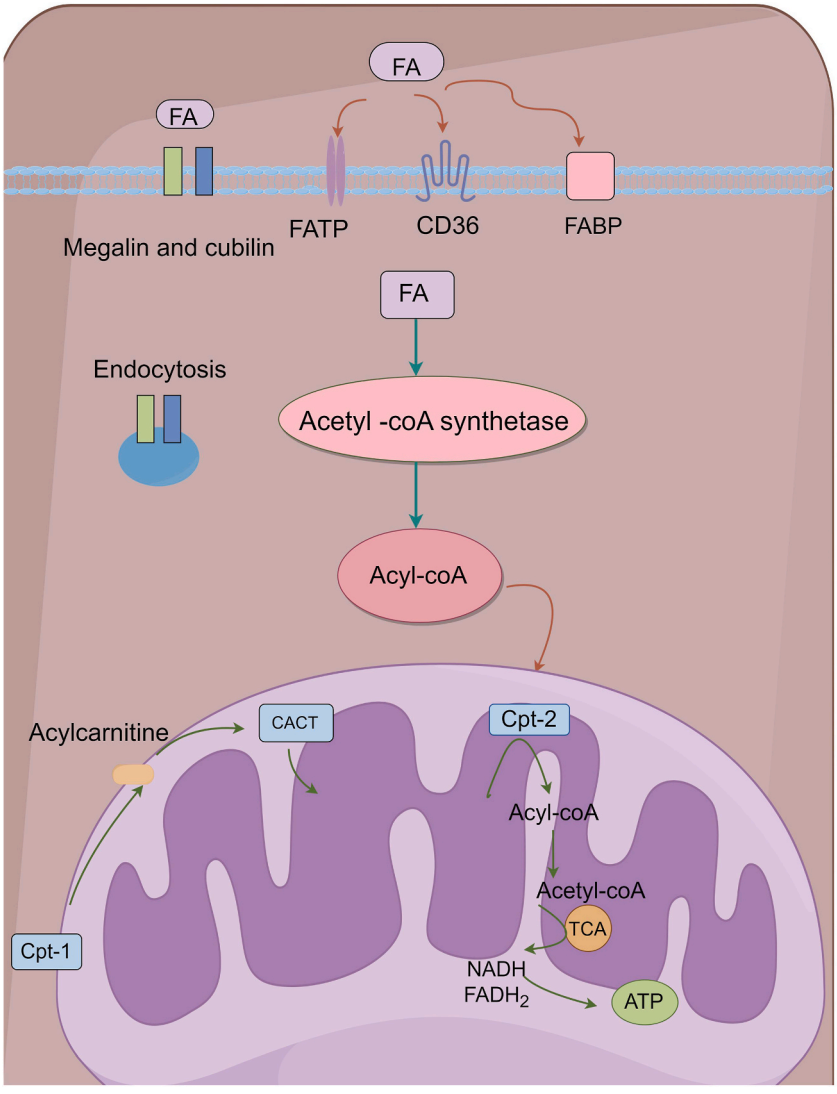

Fig. 2. Processes of lipid-energy metabolism in the kidney. Cpt, Carnitine palmitoyltransferase; FA, fatty acid; FABP, fatty acid binding protein; FATP, fatty acid transport proteins; CACT, carnitine-acylcarnitine translocase; ceramides.

5 CKD had increased levels of saturated C16-C20 FFAs and long polyunsaturated composite lipids compared to those in the early stages [72]. A retrospective cohort study investigating the association between serum NEFA concentration and cardiovascular disease (CVD) mortality in CKD patients found that NEFAs could predict CVD mortality [73]. Chen et al. found increased levels of FFAs, glycerolipids, and glycerophospholipids in CKD patients [74]. Czumaj et al. [75] analyzed serum FA composition in 191 CKD patients of varying severity and 30 healthy controls, finding that MUFA content increased and n-3 and n-6 PUFA content decreased with worsening CKD severity. Increased serum MUFA in CKD patients also increased the risk of cardiovascular diseases. The study demonstrated that a higher dietary intake of polyunsaturated FAs (n-3 FA and n-6 FA) could prevent the progression of CKD [76]. CKD can progress to uremia, and hemodialysis (HD) is a common strategy for treating uremia [77]. For the investigation of the effect of HD on uremia-associated lipid metabolism, Wang et al. used the lipidomic ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS) to collect plasma samples from a total of 87 pre-, post-, and healthy plasma samples, and healthy plasma samples. They found that the sums of FFA, saturated FAs and eicosanoids in the pre-HD patients, as well as the sums of lyso-phosphatidyl inositol and lyso-phosphatidyl ethanolamine, and the sums of FFA 16: 1/FFA 16:0 and FFA 18:1/FFA 18:0 were markedly higher in pre-HD patients than in controls, whereas they were markedly lower in post-HD patients than in controls [78].

3.2. Glyceride lipids in Lipidomic studies of CKD

Glycerides are mainly produced by the activation of intracellular protein kinases, which phosphorylate several substrate proteins to generate the corresponding metabolites [79,80]. Glycerides formed by the esterification of 1, 2 or 3 fatty acyl groups with glycerol are known as monoacylglycerols, diacylglycerols and triacylglycerols (TAG) [81,82]. Numerous studies indicate increased TAG content in CKD patients [83–85]. Higher TAG/HDL ratios have been found to increase the risk of CKD occurrence and progression [86,87]. Glyceride intake for 3 months [88] reduced abdominal fat levels in HD patients and altered glycerol monostearate levels, reducing very low-density lipoprotein serum levels and increasing HDL levels at 3 months. In 44 end-stage renal disease (ESRD) patients receiving HD treatment, an increase in medium-chain length (52–56) TAG and decreased shorter TAG (42–48) were found compared to healthy controls [89]. Yang et al. [90] found that long-chain FA, phosphatidylcholine (PC), phosphatidylethanolamine (PE) and other lipids were significantly elevated in serum of mice, while TAG (12:0/16:1/18:2, 18:0/18:1/18:1, 12:0/16:0/18:2, 14:0/16:0/18:1) was also up-regulated; it was speculated that TAG formation was mainly affected by lipid accumulation and accompanied by drug-induced nephrotoxicity. These studies suggest that TAG may be a potential biomarker for predicting and monitoring the development of CKD.

3.3. Phospholipid lipidomics in CKD

Reportedly, phospholipids are markers of chronic glomerulonephritis, chronic renal failure (CRF), IgA nephropathy and diabetic nephropathy (DN) [22]. Phospholipids are categorized as sphingolipids and glycerophospholipids and include PE, PC, phosphatidylserine, phosphatidic acid, and phosphatidylinositol [91]. It's found that patients with CKD have higher levels of PC 30:1, 34:1, and 38:2, which are substantially related to all-cause mortality [92]. Braun et al. [93] observed a downregulation of PC and a significant increase in lysophosphatidylcholine (LPC) in renal samples of DN rat models when compared to healthy controls. Research has reported lower plasma PC and LPC levels in HD patients compared to non-dialyzed CKD patients [94]. A population-based longitudinal cohort study found that serum SM C18:1 and PC aa C38:0 can predict the development of CKD development in patients with baseline normal renal function and hyperglycemia [95]. Marczak et al. [96] found that CKD was characterized by upregulated TAGs and downregulated cholesterol/cholesterol esters, sphingolipids, PE, PC, and ceramides (Cer) compared to the CVD group and controls. The POKO mouse model (early lipid nephrotoxicity model) showed a significant increase in PE (36:4e), PC (36:5e), and PE (38:7e) Cer in the kidneys of POKO mice [97]. Pang et al. [98] developed a rapid, specific analytical method using reversed-phase high--performance LC-MS/MS to simultaneously measure and quantify seven major classes of phospholipids in human blood, finding most phospholipid concentrations decreased with the progression of DN. Compared with the control group, the levels of several phospholipids (C-30:0) in DN patients were significantly reduced, suggesting that phospholipids, particularly PC and PE, may serve as predictors for CKD [99]. Additionally, macrophages expressing CD36 can detect internal lipid ligands, including oxidized phospholipids and ox-LDL, which are implicated in their phagocytosis and trafficking [100]. CD36-mediated fatty acid uptake can induce podocyte apoptosis through an oxidative stress pathway [101]. CD36 also can promotes podocyte injury by engaging the NLRP3 inflammasome. Conversely, reducing NLRP3 inflammation and alleviating podocyte injury by increasing autophagy inhibition [102]. These studies have demonstrated the predictive property of phospholipids, especially PC and PE, in CKD disease.

3.4. Sphingolipid lipidomics in CKD

Developments in lipidomics technology have resulted in the identification of over 600 sphingolipids in humans [103], including sphingosine (Sph), Cer, sphingomyelin (SM), and others [104]. Here we concentrate on the application of Cer and SM in lipidomics. Cer is the central metabolite in sphingolipid metabolism, convertible to SM by sphingomyelin synthase [105]. SM can revert to Cer while retaining the acylated fatty acid chain via sphingomyelinase [106]. A prospective cohort study of CKD patients revealed a significant correlation between high HDL abundance of Cer, SM with long acylated fatty acids, and saturated and monounsaturated PC and increased risk of all-cause mortality [92]. Studies pointed out that lower eGFR correlates with higher plasma concentrations of various sphingolipids and higher proteinuria [107,108]. Compared with patients without CKD, plasma Cer (d18:1/16:0), (d18:1/18:0), (d18:1/20:0), and (d18:1/24:0) in CKD patients significantly increased [109]. In the renal cortex of aging mice, the

levels of Cer and SM were significantly reduced, and there was no significant difference in the medulla [110]. To investigate the relationship between increased albuminuria and the Cer and SM content of HDL in CKD patients, Lidgard et al. [111] investigated 490 CKD patients based on a targeted lipidomics approach, and showed that when albuminuria was greater, the absolute abundance of total Cer and medium- and long R-chain sphingomyelins, Cer 22:0 and 24:1, capryloyl Cer 16:0, and SM 16:0 was higher. Studies have demonstrated that plasma total ceramide levels are substantially increased in mice who have a high-fat diet (HFD) as compared to a low-fat diet (LFD). Moreover, the HFD-induced increase in plasma ceramide levels is significantly attenuated by the acid sphingomyelinase inhibitor amitriptyline [112].

3.5. Sterol lipidomics in CKD

Sterols, involved in cell membrane synthesis and affecting membrane permeability and fluidity, play a role as signaling molecules and hormones in various physiological processes. Cholesterol is the most predominant sterol in the human body [113]. There is relatively limited research on sterol lipids in CKD. Renal samples from obese patients with CKD were found to have elevated levels of cholesterol and phospholipids compared to healthy controls, possibly due to phospholipid accumulation in proximal TECs, impeding cholesterol efflux [114].The by-products of cholesterol metabolism are bile acids (BAs). The liver synthesises BAs, which account for a significant proportion of daily human cholesterol turnover [115]. BAs have been found to act as endogenous signaling molecules coupled with BA receptors, affecting lipid and energy homeostasis [116]. Some studies have indicated a potential role for BAs in CKD, with increased serum BA levels and decreased urinary BA excretion in CRF patients [117]. Using a targeted metabolomic approach (UPLC-MS/MS), Li et al. determined changes in serum BA between patients with end-stage renal disease (n = 77) and healthy volunteers (n = 30) and found a significant difference in BA levels between patients with and without end-stage renal disease, suggesting that changes in serum bile acid profile might be associated with adverse consequences in patients with end-stage renal disease [118]. Deoxycholic acid (DCA), a secondary BA that is derived from BAs, was found by Frazier et al. [119] to have a non-linear association with mortality, progression to end-stage kidney disease (ESKD), atherosclerotic events, and heart failure mortality. Jovanovich et al. [120] demonstrated that elevated DCA is a new mechanism and potential biomarker for the development of vascular calcification in CKD.

4. Targeting natural products for CKD Lipid treatment

Over the past 30 years, data collection methods based on MS technology have continuously improved. Due to advancements in these technologies and increased data analysis capabilities, they provide new opportunities to address real-world clinical problems. Lipidomics has been extensively applied in CKD research. Studies in lipidomics provide new biomarkers to leverage disease progression or drug treatment effects. The application of lipidomics and research methods in this field help identify disordered metabolites

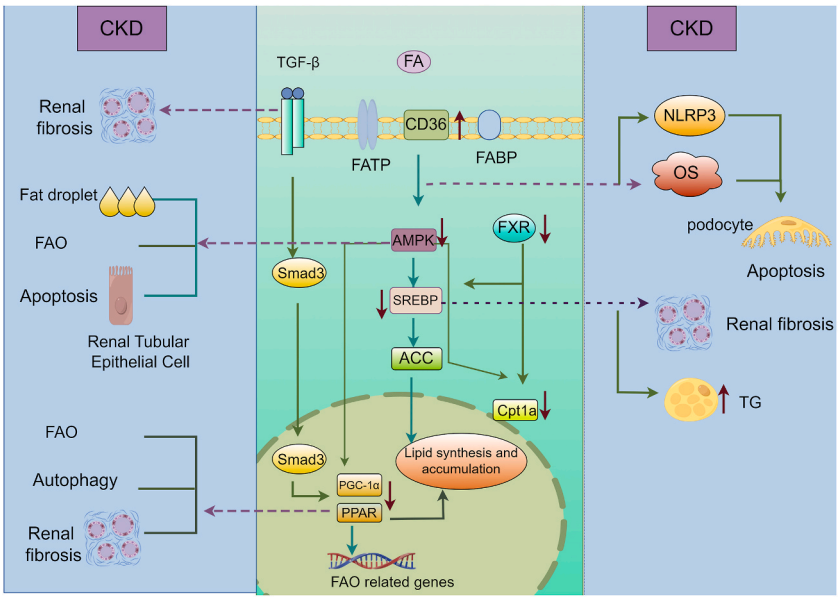

Fig. 3. Schematic representation of key factors of renal lipid metabolism and their impact on CKD patients. The image is divided into two main sections. The middle part focuses on the key proteins, key enzymes, transcription factors, and signaling pathways involved in FA uptake, synthesis, and oxidative defects. Including CD36, FABP, FATP, AMPK, SPEBP, PPAR, FXR and so on. Both sides described their effects on CKD patients, including oxidative stress, inflammatory response, renal fibrosis, lipid accumulation. ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; FAO, fatty acid oxidation; FXR, farnesoid X receptor; PPAR, Peroxisome proliferator-activated receptor; PGC-1α, PPARγ coactivator-1α; SREBP, sterol regulatory element-binding protein.

in the state of CKD, offering new perspectives for the prediction and treatment of CKD. The history of natural products used to treat human diseases dates back over 3000 years [121]. From a historical perspective, natural products from plants and animals have been the source of almost all pharmaceutical formulations. Recently, natural products have continued to enter clinical trials or provide clues for compounds entering clinical trials [122]. However, exploring the role of natural products in the treatment of CKD from a lipidomic perspective is unclear. This article next describes CKD lipid therapy with targeted natural products. The key factors of the real dyslipidemia discussed in the following section and their impact on CKD are shown in Fig. 3.

4.1. Coptis Chinensis and its main components

Coptis Chinensis (CC) is widely used in traditional Chinese medicine and contains various natural products such as berberine (BBR), coptisine, palmatine, jatrorrhizine, and epiberberine [123,124]. BBR is known for various effects like lowering blood glucose and lipids [125], reducing uric acid [126], anti-inflammation [127], anti-fibrosis [128], antioxidant [129], and anti-cancer activities [130]. Zhu et al. [131] used BBR (50,100, or 200 mg/kg) in a streptozotocin (STZ, 65 mg/kg body weight)-induced DN rat model and found that BBR ameliorated STZ-induced renal injury, inflammation, and HG-induced podocyte apoptosis by inactivation of the TLR4/NF-κB pathway. The AMP-activated protein kinase (AMPK) is a crucial sensor of the energy status of the cell [132]. Mice with renal tubular epithelial cell-specific AMPKα deficiency displayed more severe renal injury and tubular epithelial cell apoptosis after ischemia/reperfusion, with accumulation of lipid droplets, Cer, and FFAs in the tubules after ischemic reperfusion injury [133]. Studies showed that BBR stimulates basal lipolysis in mature adipocytes by enhancing the upregulation of adipose triglyceride lipase through mechanisms related to the AMPK pathway [134]. This indicated that BBR can promote fat breakdown by targeting the AMPK pathway: lipid droplets, Cer, and FFAs. BBR can significantly alleviate mitochondrial over-fragmentation, dysfunction, and excessive reactive oxygen species (ROS) production, protecting podocytes from apoptosis and detachment, thereby significantly impeding the pathological progression of DN [135]. Additionally, BBR prevents lipid accumulation, excessive mitochondrial reactive ROS generation, mitochondrial dysfunction, and insufficient fatty acid oxidation (FAO) in DN mice models and cultured podocytes by activating PPARγ coactivator-1α (PGC-1α), promoting mitochondrial energy homeostasis and FAO [136]. BBR also protects renal TECs from hypoxia/HG-induced apoptosis by activating HIF-1α in the PI3K/Akt signaling pathway, suggesting BBR as a potential drug for treating DN [137]. Recent research indicated that BBR protects podocytes from FFA-induced injury and apoptosis by modulating Drp1-mediated mitochondrial function [138]. BBR has been shown to prevent PA-induced podocyte apoptosis, and inhibiting ROS-dependent ER stress might be a key mechanism of BBR's protective action [139]. All the above studies have supported the effectiveness of CC and its major constituents in kidney diseases and lipid metabolism.

4.2. Astragalus Membranaceus and its main components

Modern research shows that Astragalus Membranaceus (AM) has various medicinal benefits, for example improving heart function [140], regulating blood sugar [141], lowering blood lipids [142], anti-tumor [143], and enhancing immunomodulatory activity. The main active components of AM include natural products such as polysaccharides, flavonoids, and saponins [144,145]. Using lipidomics combined with network pharmacology, Li et al. found that SMPD1, Cpt1a, and LCAT might be the lipid-connection targets of AM against nephrotic syndrome in an adriamycin-induced rat model of kidney disease, with glycerophospholipids, sphingolipids, and fatty acids metabolism are identified as key pathways [146]. Ge et al. [147] also considered cholesterol and sphingolipids biosynthesis, and glycerophospholipids metabolism as the principal pathways in AM's regulation of lipid metabolism. AM (0.1 mL/5g) can improve blood lipid levels in HFD fed mice by suppressing lipid genesis, and by stimulating lipid breakdown, and β-oxidation [148]. Astragaloside IV (AS-IV), a natural saponin derived from AM, was shown by Ji et al. to prevent indoxyl sulfate (IS)-induced tubulointerstitial injury by ameliorating oxidative stress [149]. AS-IV improves cisplatin-induced acute kidney injury (AKI) by affecting inflammatory response, oxidative stress, and energy metabolism [150]. TGF-β is a critical upstream regulator of the metabolism of FAs [151]. As a major driver of renal fibrosis, TGF-β has been shown to disrupt FAO by reducing the expression of PGC-1α, a gene involved in determining mitochondrial biogenesis, in a Smad3-dependent pathway [152,153]. AS-IV was found to delay renal fibrosis in diabetic KKAy mice fed a HFD (40 mg/(kg/d)), by affecting the TGF-β/Smads signaling pathway and downregulating TGF-β1, Smad2/3, and α-SMA expression [154]. Activation of PPARγ and PGC-1α increases FAO to reduce FA accumulation [155,156]. Studies have shown that the protective mechanism of AS-IV against type 2 diabetic cardiac injury involves regulation of abnormal energy and lipid metabolism, modulation of PGC-1α and nuclear respiratory factor 1 release, reversal of high glucose-induced oxidative stress and autophagy, and amelioration of cardiac lipid accumulation [157,158]. These findings underscore the significant impact of AM and its main active component, AS-IV, on renal health and lipid metabolism.

4.3. Alismatis Rhizoma and its main components

Alismatis Rhizoma (AR), as a natural product, is renowned for its anti-hyperlipidemic, anti-atherosclerotic, renal, anti-diabetic, and diuretic properties [159]. AR effectively regulates lipid metabolism [160], and possesses anti-inflammatory [161], anti-oxidative stress [162], and anti-fibrotic effects [163]. Using pharmacological and UPLC-HDMS lipidomics methods, Dou et al. studied AR's lipid-lowering and renal tubulointerstitial fibrosis effects in adenine-induced CKD rats. Results showed significant reductions in three polyunsaturated FAs (8,9-EET, EPA, and DHA) and increases in TG (46:6), TG (60:14), TG (64:9), and TG (68:12) in adenine-induced CKD rats, with considerable decreases in DG (44:6), DG (40:9), DG (35:1), DG (46:6), and DG (42:4). These changes were reversed after treatment with AR at a dose of 130 mg/kg [164]. In a high-fructose beverage-induced metabolic syndrome mouse model treated with

AR (0.75 g/kg/d/1.50 g/kg/d), AR extract was found to reduce glycerophospholipids and ceramide synthesis and improve bile acid secretion, with the higher dose group showing better effects [165]. After AR treatment, the serum, liver cholesterol, and TG of hyperlipidemic mice significantly decreased, while serum HDL cholesterol increased [166]. Research has demonstrated that triterpenes in AR contribute to its lipid-lowering effect in HFD-induced hyperlipidemia. Li et al. again validated the efficacy of the triterpene compounds in AR using a characteristic chemical profile supported vector machine model based on multiple reaction monitoring [167]. FXR plays a renal protective role in various diseases [168]. A series of studies suggested that FXR activation exerts a protective effect in renal disease by suppressing the expression of sterol regulatory element-binding protein-1 (SREBP-1) [169,170]. In addition, the SREBPs are a family of transcription factors recognised for their crucial role in lipid homeostasis [171] and regulate the biosynthesis of cholesterol, FAs, TG, and phospholipids [172]. Luan et al. [173] showed that Alisol B 23-acetate (Ali-B 23) prevented ischaemic AKI in an FXR-dependent manner, as demonstrated by enhanced renal function, reduced tubular cell apoptosis, inhibited the expression of inflammatory factors, and ameliorated oxidative stress.

4.4. Rhubarb and its main components

Rhubarb shows various pharmacological activities, such as anti-fibrosis [174,175], anti-inflammatory [176], modulating gut microbiota [177,178], and anti-cancer properties [179]. It contains various compounds, including anthraquinones, anthrones, tannins, and stilbenes [180]. Zhang et al. [181] found that ethyl acetate extract (EA) and butanol extract (BU) of Rhubarb reversed increases in plasma PE (38:4), PE (44:6), TG (55:1), and decreases in plasma TG (53:0), DG (38:9), and LPC (15:0) to normal levels in CRF rats, with EA extract reversing the decrease in PE (38:4). These comments suggest that Rhubarb extracts can improve certain adenine-induced CRF-related glycerophospholipids metabolic abnormalities. In an adenine-induced CKD rat model, Rhubarb extract (EA extract (200 mg/kg), PE extract (800 mg/kg), and BU extract (600 mg/kg)) reversed increases in LPC (18:1), MG (18:3), palmitic acid, stearic acid, and linoleic acid to normal levels [182]. Comparing Rhein with simvastatin, Gao et al. studied Rhein's regulatory and protective effects on renal injury and lipid abnormalities in db/db mice with DN, showing that both Rhein and simvastatin regulated lipid abnormalities [183]. Research has found that HFD-induced rats treated with emodin had significantly reduced blood glucose, total cholesterol, TG, and low-density lipoprotein [184]. HFD-induced rats treated with emodin had significantly reduced blood glucose, total cholesterol, TG, and low-density lipoprotein. The natural product targeted therapy for CKD lipid abnormalities mentioned above is shown in Table 2 and Fig. 4.

4.5. Other natural products therapies

Chitooligosaccharide is a natural product derived from the ocean. Lipidomics analysis indicated that 31 lipids are regarded as potential lipid biomarkers in Chitooligosaccharide therapy [185]. Lipidomic studies indicated that Curcuma aromatica can regulate abnormalities in sphingolipids, glycerophospholipids, and glycerolipids metabolism, thereby improving blood lipid levels [186]. Honokiol is a biphenolic compound found in the bark of the magnolia tree. As a natural product, it has been proven to reverse increases in PC, PE, Cer, and TAG classes in CKD rats and improve FAO in the kidneys of CKD rats when administered at a dose of 5 mg/kg/day via gavage [187]. Morroniside, a primary compound isolated from Cornus officinalis, has been shown in our research to upregulate the expression of PGC-1α, ABCG1, ABCA1, LXR, and ApoE, thereby reducing cholesterol accumulation [188]. Research showed that Salvia miltiorrhiza (0.675g/1.35g/2.70 g/kg/d) can lower levels of TGs, diglycerides, cardiolipins UPLC-Q-TOF/MS, UHPLC, ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry;, and Cer in obese rats, regulating lipid metabolism without dose dependency [189]. Triterpenoid compounds, the main active ingredients in the Magnolia genus, have shown lipid-lowering effects by adjusting sphingolipids and glycerophospholipids metabolism and through activation of the AMPK pathway, with rotundic acid being one example [190]. Fan et al. [191]found that leonurine modulates the abundance of lipid molecules associated with both FAs and glycerophospholipids, such as TxB3, carnitine C12-OH, carnitine C18:1-OH and LPC (20:3/0:0). Studies showed that treatment with bitter melon extract modulates lipid metabolism and significantly reduces PC, PE and fibrinolytic ethanolamine levels [192]. A lipidomic correlation analysis demonstrated that ginseng polysaccharides can be therapeutic by modulating differential lipid expression [193]. All these examples demonstrate the effectiveness and significance of natural products in treating renal diseases and lipid metabolism issues.

5. Discussion

Lipids are ubiquitous in the human body, playing crucial parts as constituents of cell membranes and hormones, as well as mediators of energy storage and cellular signaling pathways [194]. Increasing evidence supports the significant impact of lipids on the development and progression of disease and on patient health. CKD leads to various lipid abnormalities, predominantly hypertriglyceridemia and low levels of HDL cholesterol. Mitochondrial FAO is a major source of ATP production in the kidney, especially in the proximal renal tubules. Damage to FAO is associated with ATP depletion-induced AKI, lipotoxicity, and long-term sequelae leading to CKD [195]. CD36, various transcription factors, key enzymes and signaling pathways involved in lipid metabolism in CKD play a key role in this regard.

Advancements in MS have led to significant developments in lipidomics, allowing for the analysis of new lipid mediators or disease biomarkers using cutting-edge MS techniques. Lipidomics has also been extensively applied in the study of CKD. In this review, we summarized some applications of lipidomics in CKD, observing metabolic change2s such as increased levels of MUFA, decreased PUFA, elevated TAG, downregulated PC, increased Cer, decreased SM, and elevated BA. The changes in these lipid biomarkers will help us

Table 2
Targeted natural products for CKD lipid management.

Chinese Herbal Medicine	Primary monomer or compound	Model	*In vivo/in vitro*	Dosages	References
Coptis Chinensis	Berberine;	Streptozotocin-induced DN rat model	*In vivo*	50,100 or 200 mg/kg	[131]
		db/db diabetic mice model	*In vivo*	8 mg/kg/d	[135]
		NRK-52E; HK-2	*In vitro*	30 μM	[137]
		db/db mice; Podocyte.	*In vivo/in vitro*	*In vivo*: 8 mg/kg/d *in vitro*:0.4μmol/L	[138]
Astragalus Membranaceus	Saponins; Flavonoids and polysaccharides; Astragaloside-IV.	Sprague-Dawley rats	*In vivo*	1.5 g/kg	[146]
		High-fat diet-induced six- to eight-week-old male C57BL/6J mice	*In vivo*	10.0 mL/5g/d	[148]
		Mouse model of renal tubulointerstitial injury induced by indophenol sulfate	*In vivo*	10 mg/kg or 20 mg/kg	[149]
		Cisplatin-induced Sprague-Dawley rats	*In vivo*	75 mg/kg/d	[150]
Alismatis Rhizoma	AR extract; Triterpenoid Alisol B-23 acetate	Rat model of CKD	*In vivo*	6 mg/kg	[164]
		High fructose beverage induced metabolic syndrome in a mouse model	*In vivo*	0.75 g/kg/d or 1.5/kg	[166]
		Wild-type and FXR knockout mice	*In vivo*	60 mg/kg	[173]
Rhubarb	PE extract:800 mg/kg; EA extract: 200 mg/kg; BU extract:600 mg/kg.	A model of adenine-induced chronic tubulointerstitial nephropathy	*In vivo*		[181]
		Adenine-induced rat model of CKD	*In vivo*	PE extract:800 mg/kg; EA extract: 200 mg/kg; BU extract:600 mg/kg.	[182]
		db/db diabetic mouse model	*In vivo*	150 mg/kg/d	[183]
		High-fat diet-induced rat model	*In vivo*	25,100 mg/kg/d	[184]

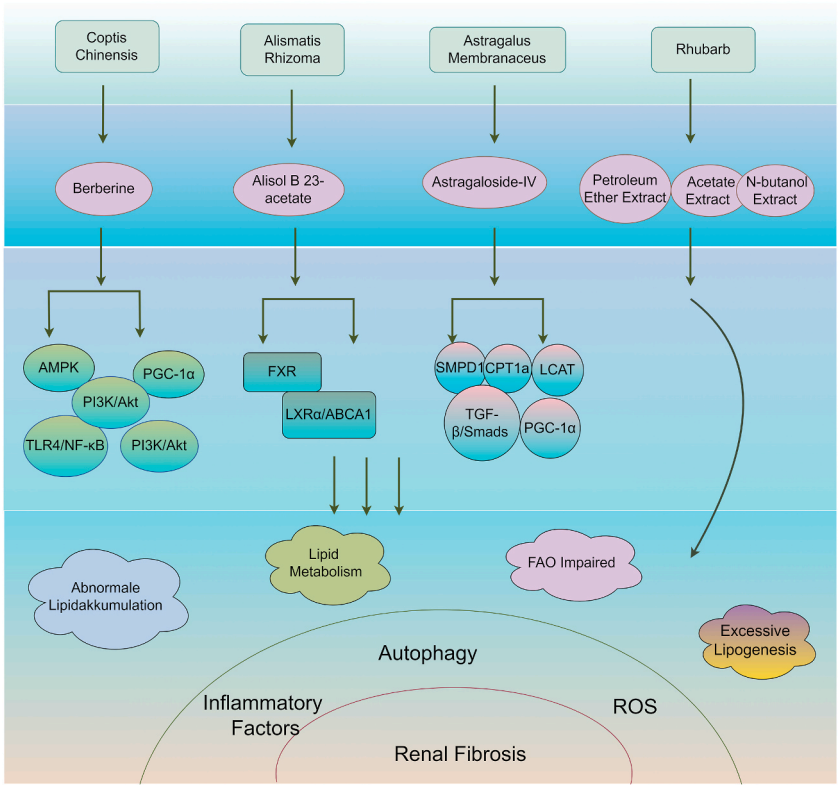

Fig. 4. Mechanisms of Chinese medicines and their main components in the treatment of CKD disease. ROS, reactive oxygen species.

better understand CKD and provide new targets for the treatment of CKD. The addition of omics enables us to study drugs and natural products from a more detailed perspective, rather than being limited to a specific type of lipid, thus making our targets more precise. Our review introduces the therapeutic effects of natural products in CKD, targeting the lipid structure in CKD patients to alter different lipid components, improve lipid accumulation, and elucidate the pathogenesis of CKD formation. For example, the article summarizes that natural products can regulate lipid metabolism and fat production through AMPK, TGF - β, FXR, etc. Consequently, they can regulate inflammation, autophagy, oxidative stress, and renal fibrosis. As a powerful research tool, lipidomics can help us discover disordered lipid metabolites in the state of CKD, offering new perspectives for predicting and treating CKD. The utilization of lipidomic approaches provides us with new perspectives and methods for treating CKD from natural products.

Of course, there are still some flaws in the articles we have summarized in our current research. Firstly, CKD is a complex disorder, and the adjustment of lipid structure by natural products is not completely consistent for different types and stages. More data validation and search for unified standards are still required. Secondly, we did not introduce the application of clinical lipidomics platforms here, which is a limitation of ours and more information is needed to enrich our content. Despite significant progress, lipidomics remains a young field still in its infancy. Challenges in sample sources, instrumentation, lipid separation methods, and variability in data analysis and processing continue to pose significant challenges in lipidomic technology. However, advancements in MS provide new opportunities to address these challenges. The application of lipidomics with other 'omics' platforms, in particular metabolomics, proteomics, and genomics, can maximize its utility. Moreover, lipidomic studies based on clinical samples, particularly targeted lipidomics, represent a possible future trend. To evaluate the clinical utility of proposed biomarkers, extensive clinical outcome studies are required. This will also provide us with a broader and more refined therapeutic concept for the treatment of CKD from the perspective of natural products.

CRediT authorship contribution statement

Rui Zhang: Writing – original draft. **Jingjing Wang:** Writing – original draft. **Chenguang Wu:** Writing – original draft. **Lifan Wang:** Conceptualization. **Peng Liu:** Writing – review & editing, Supervision, Conceptualization. **Ping Li:** Writing – review & editing, Supervision, Conceptualization.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] K. Kalantar-Zadeh, et al., Chronic kidney disease, Lancet 398 (10302) (2021) 786–802.
[2] T.K. Chen, D.H. Knicely, M.E. Grams, Chronic kidney disease diagnosis and management: a review, JAMA 322 (13) (2019) 1294–1304.
[3] A.S. Levey, et al., Measured and estimated glomerular filtration rate: current status and future directions, Nat. Rev. Nephrol. 16 (1) (2020) 51–64.
[4] A. Reis, et al., Top-down lipidomics of low density lipoprotein reveal altered lipid profiles in advanced chronic kidney disease, J. Lipid Res. 56 (2) (2015) 413–422.
[5] R. Minutolo, et al., Risk of ESRD and death in patients with CKD not referred to a nephrologist: a 7-year prospective study, Clin. J. Am. Soc. Nephrol. 9 (9) (2014) 1586–1593.
[6] L. De Nicola, et al., [Epidemiology of chronic kidney disease in Italy: current state and contribution of the CARHES study], G. Ital. Nefrol. 28 (4) (2011) 401–407.
[7] S.F. Rapa, et al., Inflammation and oxidative stress in chronic kidney disease-potential therapeutic role of minerals, vitamins and plant-derived metabolites, Int. J. Mol. Sci. 21 (1) (2019).
[8] X. Li, L. Cui, H. Xu, Association between systemic inflammation response index and chronic kidney disease: a population-based study, Front. Endocrinol. 15 (2024) 1329256.
[9] A. Sureshbabu, S.W. Ryter, M.E. Choi, Oxidative stress and autophagy: crucial modulators of kidney injury, Redox Biol. 4 (2015) 208–214.
[10] S. Ruiz, et al., Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease, Kidney Int. 83 (6) (2013) 1029–1041.
[11] S. Panizo, et al., Fibrosis in chronic kidney disease: pathogenesis and consequences, Int. J. Mol. Sci. 22 (1) (2021).
[12] A. Mitrofanova, S. Merscher, A. Fornoni, Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease, Nat. Rev. Nephrol. 19 (10) (2023) 629–645.
[13] A. Mitrofanova, S. Merscher, A. Fornoni, Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease, Nat. Rev. Nephrol. 19 (10) (2023) 629–645.
[14] C.J. Ferro, et al., Lipid management in patients with chronic kidney disease, Nat. Rev. Nephrol. 14 (12) (2018) 727–749.
[15] H. Noels, et al., Lipoproteins and fatty acids in chronic kidney disease: molecular and metabolic alterations, Nat. Rev. Nephrol. 17 (8) (2021) 528–542.
[16] A. Kontush, M. Lhomme, M.J. Chapman, Unraveling the complexities of the HDL lipidome, J. Lipid Res. 54 (11) (2013) 2950–2963.
[17] J. Graessler, et al., Top-down lipidomics reveals ether lipid deficiency in blood plasma of hypertensive patients, PLoS One 4 (7) (2009) e6261.
[18] R. Wang, et al., Integration of lipidomics and metabolomics for in-depth understanding of cellular mechanism and disease progression, J Genet Genomics 47 (2) (2020) 69–83.
[19] C.H. Johnson, J. Ivanisevic, G. Siuzdak, Metabolomics: beyond biomarkers and towards mechanisms, Nat. Rev. Mol. Cell Biol. 17 (7) (2016) 451–459.
[20] J. Ivanisevic, A. Thomas, Metabolomics as a tool to understand pathophysiological processes, Methods Mol. Biol. 1730 (2018) 3–28.
[21] F. Afshinnia, et al., Lipidomics and biomarker discovery in kidney disease, Semin. Nephrol. 38 (2) (2018) 127–141.
[22] Y.Y. Zhao, N.D. Vaziri, R.C. Lin, Lipidomics: new insight into kidney disease, Adv. Clin. Chem. 68 (2015) 153–175.
[23] J.E. Kyle, et al., Interpreting the lipidome: bioinformatic approaches to embrace the complexity, Metabolomics 17 (6) (2021) 55.
[24] E. Fahy, et al., Update of the LIPID MAPS comprehensive classification system for lipids, J. Lipid Res. 50 (Suppl) (2009) S9–S14. Suppl.
[25] Y. Liu, et al., Evaluation of changes in egg yolk lipids during storage based on lipidomics through UPLC-MS/MS, Food Chem. 398 (2023) 133931.
[26] X. Han, R.W. Gross, The foundations and development of lipidomics, JLR (J. Lipid Res.) 63 (2) (2022) 100164.
[27] M. Wolk, P. Prabutzki, M. Fedorova, Analytical toolbox to unlock the diversity of oxidized lipids, Acc. Chem. Res. 56 (7) (2023) 835–845.
[28] L.G. Yang, et al., Apolipoprotein E in lipid metabolism and neurodegenerative disease, Trends in Endocrinology & Metabolism 34 (8) (2023) 430–445.
[29] J. Brandts, K.K. Ray, Novel and future lipid-modulating therapies for the prevention of cardiovascular disease, Nat. Rev. Cardiol. 20 (9) (2023) 600–616.
[30] X. Jin, et al., A metastasis map of human cancer cell lines, Nature 588 (7837) (2020) 331–336.
[31] Y. Wu, et al., Therapeutic effects of alisma orientale and its active constituents on cardiovascular disease and obesity, AmJ Chin Med 51 (3) (2023) 623–650.
[32] T. Xu, et al., Recent advances in analytical strategies for mass spectrometry-based lipidomics, Anal. Chim. Acta 1137 (2020) 156–169.
[33] X. Han, K. Yang, R.W. Gross, Multi-dimensional mass spectrometry-based shotgun lipidomics and novel strategies for lipidomic analyses, Mass Spectrom. Rev. 31 (1) (2012) 134–178.
[34] S.J. Blanksby, T.W. Mitchell, Advances in mass spectrometry for lipidomics, Annu. Rev. Anal. Chem. 3 (2010) 433–465.
[35] S. Salihovic, et al., Recent advances towards mass spectrometry-based clinical lipidomics, Curr. Opin. Chem. Biol. 76 (2023) 102370.
[36] L. Yetukuri, et al., Informatics and computational strategies for the study of lipids, Mol. Biosyst. 4 (2) (2008) 121–127.
[37] P.E. Del, et al., ADViSELipidomics: a workflow for analyzing lipidomics data, Bioinformatics 38 (24) (2022) 5460–5462.
[38] A.D. Southam, et al., A complete workflow for high-resolution spectral-stitching nanoelectrospray direct-infusion mass-spectrometry-based metabolomics and lipidomics, Nat. Protoc. 12 (2) (2016) 310–328.
[39] H.C. Lee, T. Yokomizo, Applications of mass spectrometry-based targeted and non-targeted lipidomics, Biochem. Biophys. Res. Commun. 504 (3) (2018) 576–581.
[40] M. Horing, et al., Benchmarking one-phase lipid extractions for plasma lipidomics, Anal. Chem. 94 (36) (2022) 12292–12296.
[41] M. Letertre, G. Dervilly, P. Giraudeau, Combined nuclear magnetic resonance spectroscopy and mass spectrometry approaches for metabolomics, Anal. Chem. 93 (1) (2021) 500–518.
[42] W.J. Griffiths, Y. Wang, Mass spectrometry: from proteomics to metabolomics and lipidomics, Chem. Soc. Rev. 38 (7) (2009) 1882–1896.
[43] E.M. Harrieder, et al., Current state-of-the-art of separation methods used in LC-MS based metabolomics and lipidomics, J Chromatogr B Analyt Technol Biomed Life Sci 1188 (2022) 123069.
[44] O. Nunez, et al., State-of-the-art in fast liquid chromatography-mass spectrometry for bio-analytical applications, J Chromatogr B Analyt Technol Biomed Life Sci 927 (2013) 3–21.
[45] M.R. Hager, A.D. Narla, L.R. Tannock, Dyslipidemia in patients with chronic kidney disease, Rev. Endocr. Metab. Disord. 18 (1) (2017) 29–40.
[46] M.C. Bulbul, et al., Disorders of lipid metabolism in chronic kidney disease, Blood Purif. 46 (2) (2018) 144–152.
[47] V. Jha, et al., Chronic kidney disease: global dimension and perspectives, Lancet 382 (9888) (2013) 260–272.
[48] A. Pirillo, et al., Global epidemiology of dyslipidaemias, Nat. Rev. Cardiol. 18 (10) (2021) 689–700.

[49] M. Sundaram, Z. Yao, Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion, Nutr. Metab. 7 (2010) 35.
[50] J.P. Segrest, The role of non-LDL:non-HDL particles in atherosclerosis, Curr Diab Rep 2 (3) (2002) 282–288.
[51] N.D. Vaziri, Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences, Am J Physiol Renal Physiol 290 (2) (2006) F262–F272.
[52] B.C. Kwan, et al., Lipoprotein metabolism and lipid management in chronic kidney disease, J. Am. Soc. Nephrol. 18 (4) (2007) 1246–1261.
[53] P.O. Attman, O. Samuelsson, Dyslipidemia of kidney disease, Curr. Opin. Lipidol. 20 (4) (2009) 293–299.
[54] Y. Fujino, et al., Limited effects of systemic or renal lipoprotein lipase deficiency on renal physiology and diseases, Biochem. Biophys. Res. Commun. 620 (2022) 15–20.
[55] M.R. Taskinen, C.J. Packard, J. Boren, Emerging evidence that ApoC-III inhibitors provide novel options to reduce the residual CVD, Curr Atheroscler Rep 21 (8) (2019) 27.
[56] A. You, et al., Association between renal dysfunction and low HDL cholesterol among the elderly in China, Front Cardiovasc Med 8 (2021) 644208.
[57] A. Kuchta, et al., Plasma levels of prebeta1-HDL are significantly elevated in non-dialyzed patients with advanced stages of chronic kidney disease, Int. J. Mol. Sci. 20 (5) (2019).
[58] K. Yang, et al., LCAT- targeted therapies: progress, failures and future, Biomed. Pharmacother. 147 (2022) 112677.
[59] M. Bermudez-Lopez, et al., New perspectives on CKD-induced dyslipidemia, Expert Opin. Ther. Targets 21 (10) (2017) 967–976.
[60] F. Duranton, et al., The CKD plasma lipidome varies with disease severity and outcome, J Clin Lipidol 13 (1) (2019) 176–185.e8.
[61] H. Li, et al., Role of fatty acid transport protein 4 in metabolic tissues: insights into obesity and fatty liver disease, Biosci. Rep. 42 (6) (2022).
[62] M. Gekle, et al., Transforming growth factor-beta1 reduces megalin- and cubilin-mediated endocytosis of albumin in proximal-tubule-derived opossum kidney cells, J Physiol 552 (Pt 2) (2003) 471–481.
[63] A.L. Negri, Proximal tubule endocytic apparatus as the specific renal uptake mechanism for vitamin D-binding protein/25-(OH) D3 complex, Nephrology 11 (6) (2006) 510–515.
[64] M.M. Adeva-Andany, et al., Mitochondrial beta-oxidation of saturated fatty acids in humans, Mitochondrion 46 (2019) 73–90.
[65] Q. Luo, et al., Role of ACSL5 in fatty acid metabolism, Heliyon 9 (2) (2023) e13316.
[66] N. Simon, A. Hertig, Alteration of fatty acid oxidation in tubular epithelial cells: from acute kidney injury to renal fibrogenesis, Front. Med. 2 (2015) 52.
[67] S.M. Houten, et al., The biochemistry and physiology of mitochondrial fatty acid beta-oxidation and its genetic disorders, Annu. Rev. Physiol. 78 (2016) 23–44.
[68] G. Peluso, et al., Differential carnitine/acylcarnitine translocase expression defines distinct metabolic signatures in skeletal muscle cells, J. Cell. Physiol. 203 (2) (2005) 439–446.
[69] R.J. Smeets, et al., A novel splice site mutation in neonatal carnitine palmitoyl transferase II deficiency, J. Hum. Genet. 48 (1) (2003) 8–13.
[70] M. Mazidi, et al., Association of dietary intakes and genetically determined serum concentrations of mono and poly unsaturated fatty acids on chronic kidney disease: insights from dietary analysis and mendelian randomization, Nutrients 14 (6) (2022).
[71] A. Mika, et al., Potential contribution of monounsaturated fatty acids to cardiovascular risk in chronic kidney disease, Pol. Arch. Intern. Med. 128 (12) (2018) 755–763.
[72] F. Afshinnia, et al., Impaired beta-oxidation and altered complex lipid fatty acid partitioning with advancing CKD, J. Am. Soc. Nephrol. 29 (1) (2018) 295–306.
[73] Z. Xiong, et al., Nonesterified fatty acids and cardiovascular mortality in elderly men with CKD, Clin. J. Am. Soc. Nephrol. 10 (4) (2015) 584–591.
[74] H. Chen, et al., Combined clinical phenotype and lipidomic analysis reveals the impact of chronic kidney disease on lipid metabolism, J. Proteome Res. 16 (4) (2017) 1566–1578.
[75] A. Czumaj, et al., Alterations of fatty acid profile may contribute to dyslipidemia in chronic kidney disease by influencing hepatocyte metabolism, Int. J. Mol. Sci. 20 (10) (2019).
[76] F. Lauretani, et al., Plasma polyunsaturated fatty acids and the decline of renal function, Clin. Chem. 54 (3) (2008) 475–481.
[77] Y. Wang, L. Gao, Inflammation and cardiovascular disease associated with hemodialysis for end-stage renal disease, Front. Pharmacol. 13 (2022) 800950.
[78] L. Wang, et al., Plasma lipidomics investigation of hemodialysis effects by using liquid chromatography-mass spectrometry, J. Proteome Res. 15 (6) (2016) 1986–1994.
[79] W. Raphael, L.M. Sordillo, Dietary polyunsaturated fatty acids and inflammation: the role of phospholipid biosynthesis, Int. J. Mol. Sci. 14 (10) (2013) 21167–21188.
[80] A.E. Decleves, et al., AMP-activated protein kinase activation ameliorates eicosanoid dysregulation in high-fat-induced kidney disease in mice, J. Lipid Res. 60 (5) (2019) 937–952.
[81] Y. Shi, D. Cheng, Beyond triglyceride synthesis: the dynamic functional roles of MGAT and DGAT enzymes in energy metabolism, Am. J. Physiol. Endocrinol. Metab. 297 (1) (2009) E10–E18.
[82] H.J. Ham, et al., Label-free measurement of the yeast short chain TAG lipase activity by ESI-MS after one-step esterification, J. Lipid Res. 58 (3) (2017) 625–631.
[83] S. Merscher, C.E. Pedigo, A.J. Mendez, Metabolism, energetics, and lipid biology in the podocyte - cellular cholesterol-mediated glomerular injury, Front. Endocrinol. 5 (2014) 169.
[84] W.F. Keane, J.E. Tomassini, D.R. Neff, Lipid abnormalities in patients with chronic kidney disease: implications for the pathophysiology of atherosclerosis, J Atheroscler Thromb 20 (2) (2013) 123–133.
[85] A.K. Elgakhow, et al., Prevalence of chronic kidney disease in nonalcoholic fatty liver disease patients, Saudi J Kidney Dis Transpl 33 (1) (2022) 201–209.
[86] S. Lv, et al., The effect of triglycerides to high-density lipoprotein cholesterol ratio on the reduction of renal function: findings from China health and retirement longitudinal study (CHARLS), Lipids Health Dis. 20 (1) (2021) 110.
[87] K. Tsuruya, et al., Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population, Atherosclerosis 233 (1) (2014) 260–267.
[88] T. Teramoto, et al., Significant effects of diacylglycerol on body fat and lipid metabolism in patients on hemodialysis, Clin Nutr 23 (5) (2004) 1122–1126.
[89] E.P. Rhee, et al., Metabolite profiling identifies markers of uremia, J. Am. Soc. Nephrol. 21 (6) (2010) 1041–1051.
[90] X. Yang, et al., Precision toxicology shows that troxerutin alleviates ochratoxin A-induced renal lipotoxicity, FASEB J 33 (2) (2019) 2212–2227.
[91] B. Wang, P. Tontonoz, Phospholipid remodeling in physiology and disease, Annu. Rev. Physiol. 81 (2019) 165–188.
[92] B. Lidgard, et al., High-density lipoprotein lipidomics and mortality in CKD, Kidney Med 5 (10) (2023) 100708.
[93] F. Braun, et al., Altered lipid metabolism in the aging kidney identified by three layered omic analysis, Aging (Albany NY) 8 (3) (2016) 441–457.
[94] F. Duranton, et al., The CKD plasma lipidome varies with disease severity and outcome, J Clin Lipidol 13 (1) (2019) 176–185.e8.
[95] J. Huang, et al., Machine learning approaches reveal metabolic signatures of incident chronic kidney disease in individuals with prediabetes and type 2 diabetes, Diabetes 69 (12) (2020) 2756–2765.
[96] L. Marczak, et al., Mass spectrometry-based lipidomics reveals differential changes in the accumulated lipid classes in chronic kidney disease, Metabolites 11 (5) (2021).
[97] C. Martinez-Garcia, et al., Accelerated renal disease is associated with the development of metabolic syndrome in a glucolipotoxic mouse model, Dis Model Mech 5 (5) (2012) 636–648.
[98] L.Q. Pang, et al., Simultaneous determination and quantification of seven major phospholipid classes in human blood using normal-phase liquid chromatography coupled with electrospray mass spectrometry and the application in diabetes nephropathy, J Chromatogr B Analyt Technol Biomed Life Sci 869 (1–2) (2008) 118–125.
[99] I.W. Wu, et al., Discovering a trans-omics biomarker signature that predisposes high risk diabetic patients to diabetic kidney disease, NPJ Digit Med 5 (1) (2022) 166.
[100] L. Zhao, et al., CD36 and lipid metabolism in the evolution of atherosclerosis, Br. Med. Bull. 126 (1) (2018) 101–112.
[101] W. Hua, et al., CD36 mediated fatty acid-induced podocyte apoptosis via oxidative stress, PLoS One 10 (5) (2015) e0127507.

[102] F. Lv, et al., CD36 aggravates podocyte injury by activating NLRP3 inflammasome and inhibiting autophagy in lupus nephritis, Cell Death Dis. 13 (8) (2022) 729.
[103] W.S. Chew, et al., Sphingolipidomics analysis of large clinical cohorts. Part 1: technical notes and practical considerations, Biochem. Biophys. Res. Commun. 504 (3) (2018) 596–601.
[104] M. Mei, et al., Sphingolipid metabolism in brain insulin resistance and neurological diseases, Front. Endocrinol. 14 (2023) 1243132.
[105] K. Hanada, Co-evolution of sphingomyelin and the ceramide transport protein CERT, Biochim. Biophys. Acta 1841 (5) (2014) 704–719.
[106] H. Xiang, et al., Physiological functions and therapeutic applications of neutral sphingomyelinase and acid sphingomyelinase, Biomed. Pharmacother. 139 (2021) 111610.
[107] V.P. Makinen, et al., Sphingomyelin is associated with kidney disease in type 1 diabetes (The FinnDiane Study), Metabolomics 8 (3) (2012) 369–375.
[108] J.J. Liu, et al., Profiling of plasma metabolites suggests altered mitochondrial fuel usage and remodeling of sphingolipid metabolism in individuals with type 2 diabetes and kidney disease, Kidney Int Rep 2 (3) (2017) 470–480.
[109] A. Mantovani, et al., Association between increased plasma ceramides and chronic kidney disease in patients with and without ischemic heart disease, Diabetes Metab. 47 (1) (2021) 101152.
[110] S.A. Noh, et al., Alterations in lipid profile of the aging kidney identified by MALDI imaging mass spectrometry, J. Proteome Res. 18 (7) (2019) 2803–2812.
[111] B. Lidgard, et al., High-density lipoprotein lipidomics in chronic kidney disease, Clin. Chem. 69 (3) (2023) 273–282.
[112] K.M. Boini, et al., Role of sphingolipid mediator ceramide in obesity and renal injury in mice fed a high-fat diet, J Pharmacol Exp Ther 334 (3) (2010) 839–846.
[113] T.A. Lagace, Phosphatidylcholine: greasing the cholesterol transport machinery, Lipid Insights 8 (Suppl 1) (2015) 65–73.
[114] E. Rampanelli, et al., Excessive dietary lipid intake provokes an acquired form of lysosomal lipid storage disease in the kidney, J. Pathol. 246 (4) (2018) 470–484.
[115] T. Li, J.Y. Chiang, Bile acid signaling in metabolic disease and drug therapy, Pharmacol. Rev. 66 (4) (2014) 948–983.
[116] P.B. Hylemon, et al., Bile acids as regulatory molecules, J. Lipid Res. 50 (8) (2009) 1509–1520.
[117] L. Chu, et al., Mechanism underlying an elevated serum bile acid level in chronic renal failure patients, Int. Urol. Nephrol. 47 (2) (2015) 345–351.
[118] R. Li, et al., Targeted metabolomics study of serum bile acid profile in patients with end-stage disease undergoing hemodialysis, PeerJ 7 (2019) e7145.
[119] R. Frazier, et al., Deoxycholic acid and risks of cardiovascular events, ESKD, and mortality in CKD: the CRIC study, Kidney Med 4 (1) (2022) 100387.
[120] A. Jovanovich, et al., Deoxycholic acid, a metabolite of circulating bile acids, and coronary artery vascular calcification in CKD, Am. J. Kidney Dis. 71 (1) (2018) 27–34.
[121] J.L. Huo, et al., Research advance of natural products in tumor immunotherapy, Front. Immunol. 13 (2022) 972345.
[122] A.L. Harvey, R. Edrada-Ebel, R.J. Quinn, The re-emergence of natural products for drug discovery in the genomics era, Nat. Rev. Drug Discov. 14 (2) (2015) 111–129.
[123] F.C. Meng, et al., Coptidis rhizoma and its main bioactive components: recent advances in chemical investigation, quality evaluation and pharmacological activity, Chin. Med. 13 (2018) 13.
[124] Y. Sun, et al., Berberine attenuates hepatic steatosis and enhances energy expenditure in mice by inducing autophagy and fibroblast growth factor 21, Br. J. Pharmacol. 175 (2) (2018) 374–387.
[125] Y. Wang, et al., Gut microbiota-mediated personalized treatment of hyperlipidemia using berberine, Theranostics 7 (9) (2017) 2443–2451.
[126] X. Li, et al., Macrophage HIF-2alpha suppresses NLRP3 inflammasome activation and alleviates insulin resistance, Cell Rep. 36 (8) (2021) 109607.
[127] M.S. Othman, et al., The potential effect of berberine in mercury-induced hepatorenal toxicity in albino rats, Food Chem. Toxicol. 69 (2014) 175–181.
[128] O.A. Ahmedy, et al., Insights into the role of P2X7R/DUSP6/ERK1/2 and SIRT2/MDM2 signaling in the nephroprotective effect of berberine against cisplatin-induced renal fibrosis in rats, Life Sci. 309 (2022) 121040.
[129] B. Wang, et al., Berberine improved aldo-induced podocyte injury via inhibiting oxidative stress and endoplasmic reticulum stress pathways both in vivo and in vitro, Cell. Physiol. Biochem. 39 (1) (2016) 217–228.
[130] Q. Liu, et al., Berberine for gastric cancer prevention and treatment: multi-step actions on the Correa's cascade underlie its therapeutic effects, Pharmacol. Res. 184 (2022) 106440.
[131] L. Zhu, et al., Berberine ameliorates diabetic nephropathy by inhibiting TLR4/NF-kappaB pathway, Biol. Res. 51 (1) (2018) 9.
[132] D.G. Hardie, F.A. Ross, S.A. Hawley, AMPK: a nutrient and energy sensor that maintains energy homeostasis, Nat. Rev. Mol. Cell Biol. 13 (4) (2012) 251–262.
[133] H. Ma, et al., Dephosphorylation of AMP-activated protein kinase exacerbates ischemia/reperfusion-induced acute kidney injury via mitochondrial dysfunction, Kidney Int. 101 (2) (2022) 315–330.
[134] D. Jiang, et al., Berberine increases adipose triglyceride lipase in 3T3-L1 adipocytes through the AMPK pathway, Lipids Health Dis. 15 (1) (2016) 214.
[135] X. Qin, et al., Berberine protects glomerular podocytes via inhibiting drp1-mediated mitochondrial fission and dysfunction, Theranostics 9 (6) (2019) 1698–1713.
[136] X. Qin, et al., Berberine protects against diabetic kidney disease via promoting PGC-1alpha-regulated mitochondrial energy homeostasis, Br. J. Pharmacol. 177 (16) (2020) 3646–3661.
[137] X. Zhang, et al., Protective effect of berberine on high glucose and hypoxia-induced apoptosis via the modulation of HIF-1alpha in renal tubular epithelial cells, AmJ Transl Res 11 (2) (2019) 669–682.
[138] X. Qin, et al., Berberine protects glomerular podocytes via inhibiting drp1-mediated mitochondrial fission and dysfunction, Theranostics 9 (6) (2019) 1698–1713.
[139] X.Y. Xiang, et al., Berberine alleviates palmitic acid-induced podocyte apoptosis by reducing reactive oxygen species-mediated endoplasmic reticulum stress, Mol. Med. Rep. 23 (1) (2021).
[140] X. Ma, et al., Extracts from Astragalus membranaceus limit myocardial cell death and improve cardiac function in a rat model of myocardial ischemia, J. Ethnopharmacol. 149 (3) (2013) 720–728.
[141] K. Zhang, et al., Biological active ingredients of traditional Chinese herb Astragalus membranaceus on treatment of diabetes: a systematic review, Mini Rev. Med. Chem. 15 (4) (2015) 315–329.
[142] L. Wang, et al., Mechanism of Astragalus membranaceus alleviating acquired hyperlipidemia induced by high-fat diet through regulating lipid metabolism, Nutrients 14 (5) (2022).
[143] R. Zhou, et al., Extract from Astragalus membranaceus inhibit breast cancer cells proliferation via PI3K/AKT/mTOR signaling pathway, BMC Complement Altern Med 18 (1) (2018) 83.
[144] B. Salehi, et al., Astragalus species: insights on its chemical composition toward pharmacological applications, Phytother Res. 35 (5) (2021) 2445–2476.
[145] G. Gong, et al., Pharmaceutical values of calycosin: one type of flavonoid isolated from Astragalus, Evid Based Complement Alternat Med 2021 (2021) 9952578.
[146] A.P. Li, et al., Uncovering the mechanism of Astragali Radix against nephrotic syndrome by intergrating lipidomics and network pharmacology, Phytomedicine 77 (2020) 153274.
[147] P.Y. Ge, et al., Potential mechanism of S. Baicalensis on lipid metabolism explored via network pharmacology and untargeted lipidomics, Drug Des Devel Ther 15 (2021) 1915–1930.
[148] L. Wang, et al., Mechanism of Astragalus membranaceus alleviating acquired hyperlipidemia induced by high-fat diet through regulating lipid metabolism, Nutrients 14 (5) (2022).
[149] C. Ji, et al., Effect of astragaloside IV on indoxyl sulfate-induced kidney injury in mice via attenuation of oxidative stress, BMC Pharmacol Toxicol 19 (1) (2018) 53.
[150] Y. Song, et al., Altered metabolic profiles and biomarkers associated with astragaloside IV-mediated protection against cisplatin-induced acute kidney injury in rats: an HPLC-TOF/MS-based untargeted metabolomics study, Biochem. Pharmacol. 183 (2021) 114299.
[151] H.M. Kang, et al., Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development, Nat Med 21 (1) (2015) 37–46.

[152] K. Saito, et al., Lipid accumulation and transforming growth factor-beta upregulation in the kidneys of rats administered angiotensin II, Hypertension 46 (5) (2005) 1180–1185.
[153] H. Yadav, et al., Protection from obesity and diabetes by blockade of TGF-beta/Smad3 signaling, Cell Metab 14 (1) (2011) 67–79.
[154] Y. Wang, et al., Astragaloside effect on TGF-beta1, SMAD2/3, and alpha-SMA expression in the kidney tissues of diabetic KKAy mice, Int. J. Clin. Exp. Pathol. 8 (6) (2015) 6828–6834.
[155] Q. Du, et al., PGC1alpha/CEBPB/CPT1A axis promotes radiation resistance of nasopharyngeal carcinoma through activating fatty acid oxidation, Cancer Sci. 110 (6) (2019) 2050–2062.
[156] E. Legchenko, et al., PPARgamma agonist pioglitazone reverses pulmonary hypertension and prevents right heart failure via fatty acid oxidation, Sci. Transl. Med. 10 (438) (2018).
[157] Z. Zhang, et al., Astragaloside IV alleviates myocardial damage induced by type 2 diabetes via improving energy metabolism, Mol. Med. Rep. 20 (5) (2019) 4612–4622.
[158] Z. Wang, et al., Protective effects of AS-IV on diabetic cardiomyopathy by improving myocardial lipid metabolism in rat models of T2DM, Biomed. Pharmacother. 127 (2020) 110081.
[159] H. Miao, et al., Urinary biomarker and treatment mechanism of Rhizoma Alismatis on hyperlipidemia, Biomed. Chromatogr. 31 (4) (2017).
[160] T. Tian, H. Chen, Y.Y. Zhao, Traditional uses, phytochemistry, pharmacology, toxicology and quality control of Alisma orientale (Sam.) Juzep: a review, J. Ethnopharmacol. 158 (Pt A) (2014) 373–387.
[161] X. Xue, et al., Effects of Alisma Decoction on lipid metabolism and inflammatory response are mediated through the activation of the LXRalpha pathway in macrophage-derived foam cells, Int. J. Mol. Med. 33 (4) (2014) 971–977.
[162] M.K. Jang, et al., Protective effects of alisma orientale extract against hepatic steatosis via inhibition of endoplasmic reticulum stress, Int. J. Mol. Sci. 16 (11) (2015) 26151–26165.
[163] Z. Shu, et al., Alisma orientale: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine, AmJ Chin Med 44 (2) (2016) 227–251.
[164] F. Dou, et al., An integrated lipidomics and phenotype study reveals protective effect and biochemical mechanism of traditionally used alisma orientale juzepzuk in chronic kidney disease, Front. Pharmacol. 9 (2018) 53.
[165] L. Jia, et al., Alismatis Rhizoma methanolic extract-Effects on metabolic syndrome and mechanisms of triterpenoids using a metabolomic and lipidomic approach, Front. Pharmacol. 13 (2022) 983428.
[166] H. Dan, et al., Hypolipidemic effects of Alismatis rhizome on lipid profile in mice fed high-fat diet, Saudi Med. J. 32 (7) (2011) 701–707.
[167] S. Li, et al., Identification of the lipid-lowering component of triterpenes from Alismatis rhizoma based on the MRM-based characteristic chemical profiles and support vector machine model, Anal. Bioanal. Chem. 411 (15) (2019) 3257–3268.
[168] D.H. Kim, et al., Farnesoid X receptor protects against cisplatin-induced acute kidney injury by regulating the transcription of ferroptosis-related genes, Redox Biol. 54 (2022) 102382.
[169] X.X. Wang, et al., The farnesoid X receptor modulates renal lipid metabolism and diet-induced renal inflammation, fibrosis, and proteinuria, AmJ Physiol Renal Physiol 297 (6) (2009) F1587–F1596.
[170] T. Jiang, et al., Farnesoid X receptor modulates renal lipid metabolism, fibrosis, and diabetic nephropathy, Diabetes 56 (10) (2007) 2485–2493.
[171] R.A. DeBose-Boyd, J. Ye, SREBPs in lipid metabolism, insulin signaling, and beyond, Trends Biochem. Sci. 43 (5) (2018) 358–368.
[172] D. Eberle, et al., SREBP transcription factors: master regulators of lipid homeostasis, Biochimie 86 (11) (2004) 839–848.
[173] Z.L. Luan, et al., A naturally occurring FXR agonist, alisol B 23-acetate, protects against renal ischemia-reperfusion injury, AmJ Physiol Renal Physiol 321 (5) (2021) F617–F628.
[174] HaoShang, et al., A comprehensive review of emodin in fibrosis treatment, Fitoterapia 165 (2023) 105358.
[175] X. Guo, et al., Exploring the mechanism of action of Chinese medicine in regulating liver fibrosis based on the alteration of glucose metabolic pathways, Phytother Res 38 (10) (2024) 4865–4876.
[176] H. Sha, et al., Rheinic acid ameliorates radiation-induced acute enteritis in rats through PPAR-gamma/NF-kappaB, Genes Genomics 41 (8) (2019) 909–917.
[177] C. Ji, et al., Rhubarb enema decreases circulating trimethylamine N-oxide level and improves renal fibrosis accompanied with gut microbiota change in chronic kidney disease rats, Front. Pharmacol. 12 (2021) 780924.
[178] S. Luo, et al., Rhubarb Peony Decoction ameliorates ulcerative colitis in mice by regulating gut microbiota to restoring Th17/Treg balance, J. Ethnopharmacol. 231 (2019) 39–49.
[179] F.P. Pan, et al., Emodin enhances the demethylation by 5-Aza-CdR of pancreatic cancer cell tumor-suppressor genes P16, RASSF1A and ppENK, Oncol. Rep. 35 (4) (2016) 1941–1949.
[180] F. Zhang, et al., Nephroprotective and nephrotoxic effects of Rhubarb and their molecular mechanisms, Biomed. Pharmacother. 160 (2023) 114297.
[181] Z.H. Zhang, et al., An integrated lipidomics and metabolomics reveal nephroprotective effect and biochemical mechanism of Rheum officinale in chronic renal failure, Sci. Rep. 6 (2016) 22151.
[182] Z.H. Zhang, et al., Rhubarb protect against tubulointerstitial fibrosis by inhibiting TGF-beta/smad pathway and improving abnormal metabolome in chronic kidney disease, Front. Pharmacol. 9 (2018) 1029.
[183] Q. Gao, et al., Rhein improves renal lesion and ameliorates dyslipidemia in db/db mice with diabetic nephropathy, Planta Med. 76 (1) (2010) 27–33.
[184] Y. Cao, et al., Emodin ameliorates high-fat-diet induced insulin resistance in rats by reducing lipid accumulation in skeletal muscle, Eur. J. Pharmacol. 780 (2016) 194–201.
[185] M. Zhou, et al., Anti-obesity effect and mechanism of chitooligosaccharides were revealed based on lipidomics in diet-induced obese mice, Molecules 28 (14) (2023).
[186] C. Fei, et al., Therapeutic mechanism of Curcuma aromatica Salisb. rhizome against coronary heart disease based on integrated network pharmacology, pharmacological evaluation and lipidomics, Front. Pharmacol. 13 (2022) 950749.
[187] X. Liu, et al., Lipidomics reveals the potential mechanism of honokiol against adenine-induced chronic kidney disease, Front. Pharmacol. 13 (2022) 1019629.
[188] J. Gao, et al., Morroniside promotes PGC-1alpha-mediated cholesterol efflux in sodium palmitate or high glucose-induced mouse renal tubular epithelial cells, BioMed Res. Int. 2021 (2021) 9942152.
[189] Z.L. Ai, et al., Salvia miltiorrhiza extract may exert an anti-obesity effect in rats with high-fat diet-induced obesity by modulating gut microbiome and lipid metabolism, World J. Gastroenterol. 28 (43) (2022) 6131–6156.
[190] W. Yang, et al., Triterpenoids from the genus Ilex attenuate free fatty acid-induced lipid accumulation in HepG2 cells by regulating lipid metabolism disorder and the AMPK signalling pathway, J. Ethnopharmacol. 302 (Pt A) (2023) 115845.
[191] W. Fan, et al., Leonurine inhibits hepatic lipid synthesis to ameliorate NAFLD via the ADRA1a/AMPK/SCD1 Axis, Int. J. Mol. Sci. 25 (19) (2024).
[192] S. Sur, et al., Inhibition of the key metabolic pathways, glycolysis and lipogenesis, of oral cancer by bitter melon extract, Cell Commun. Signal. 17 (1) (2019) 131.
[193] B. Jing, et al., Pharmacodynamic evaluation and mechanism of ginseng polysaccharide against nephrotoxicity induced by hexavalent chromium, Nutrients 16 (10) (2024).
[194] Z. Wu, et al., "Lipidomics": mass spectrometric and chemometric analyses of lipids, Adv. Drug Deliv. Rev. 159 (2020) 294–307.
[195] H.S. Jang, et al., Defective mitochondrial fatty acid oxidation and lipotoxicity in kidney diseases, Front. Med. 7 (2020) 65.