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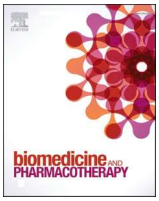

Review

Ferroptosis: A new view on the prevention and treatment of diabetic kidney disease with traditional Chinese medicine

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ABSTRACT

Diabetic kidney disease is one of the complications of diabetes mellitus, which can eventually progress to end-stage kidney disease. The increasing prevalence of diabetic kidney disease has brought huge economic burden to society and seriously jeopardized public health. Ferroptosis is an iron-dependent, non-apoptosis-regulated form of cell death. The regulation of ferroptosis involves different molecular mechanisms and multiple cellular metabolic pathways. In recent years, ferroptosis has been proved to be closely related to the occurrence and development of diabetic kidney disease, and can interact with pathological changes such as fibrosis, inflammation, oxidative stress, and disorders of glucose and lipid metabolism, destroying the structure, form and function of the inherent cells of the kidney, and promoting the progression of the disease. Traditional Chinese medicine has a long history of treating diabetic kidney disease with remarkable curative effect. Current scholars have shown that the oral administration of traditional Chinese medicine and the external treatment of Chinese medicine can regulate GPX4, Nrf2, ACSL4, PTGS2, TFR1 and other key signaling molecules, curb ferroptosis, and prevent the progressive deterioration of diabetic kidney disease. In this paper, the mechanism of ferroptosis and diabetic kidney disease and the prevention and treatment of traditional Chinese medicine are analyzed and summarized, in order to provide new ideas and new plans for the treatment of diabetic kidney disease.

1. Introduction

Diabetic kidney disease (DKD) is the most common and serious microvascular complication of diabetes mellitus (DM). It is chronic kidney damage caused by persistent hyperglycemia. The lesions can involve the whole kidney (including glomerulus, renal tubules, renal interstitium and renal vessels). The clinical characteristics are mainly persistent proteinuria and/or progressive decline of eGFR, which can progress to end-stage kidney disease (ESRD) [1]. According to the data released by International Diabetes Federation (IDF) in 2021, about 537 million adults worldwide have diabetes, and 20~40% of DM patients can be combined with DKD [2]. With the increasing number of DM patients in the world and the rising incidence rate, DKD has become the primary cause of ESRD [3].

Ferroptosis is a form of cell death that differs from traditional necrosis, apoptosis, and autophagy (Table 1). It is characterized by the accumulation of fatal lipid reactive oxygen species (ROS) that rely on iron catalysis, but this process can be inhibited by iron chelators, lipid peroxidation inhibitors, and lipophilic antioxidants [4]. In terms of cell morphology, mitochondrial volume decreases, double-layer membrane density increases, mitochondrial ridge decreases or disappears, but the cell membrane is intact and the nucleus size is normal. Biochemical manifestations include depletion of intracellular glutathione (GSH) and loss of glutathione peroxidase 4 (GPX4) activity, leading to abnormal lipid peroxide metabolism. Fe^{2+} oxidizes lipids through the Fenton reaction and produces a large amount of ROS to promote iron phosphorylation, inducing cell death. Genetically, it is manifested as multiple genes jointly regulating, mainly involving genetic changes in iron homeostasis and lipid peroxidation[5–7]. Recent studies have shown that ferroptosis is involved in the occurrence and development of a variety of kidney diseases and plays an important role in the DKD process [8]. This article will sort out and summarize the mechanism of ferroptosis in DKD and Chinese medicine treatment, and provide new ideas and new plans for clinical prevention and treatment of DKD.

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2. The origin of ferroptosis

Erastin is a novel compound. In 2003, Dolma found that Erastin was selectively lethal and irreversible to cells overexpressed by the ST oncoprotein and H-RasV_{12} oncogene, but the nuclear morphology of the cells did not change [9]. Therefore, this is a novel non apoptotic cell death program. In 2007, Yagoda discovered that Erastin induces oxidative cell death by inducing the release of oxides from mitochondria, which is a completely different form of death from cell apoptosis, necrosis, and autophagy. Its characteristics include damage to mitochondrial structure, changes in mitochondrial outer membrane permeability and so on [10]. In 2008, Yang showed that Erastin induced cell death is related to oxidation level and iron content, and it promotes ROS production and iron absorption by regulating cell oxidation and iron metabolism, and finally initiates cell death process [5]. In 2012, Dixon officially named Erastin-induced cell death "ferroptosis" and demonstrated that Erastin-induced cell death has unique morphological, biochemical, and genetic characteristics [6].

3. The mechanism of ferroptosis

Ferroptosis is regulated by various metabolic factors and signaling pathways, such as amino acid metabolism, iron metabolism, lipid metabolism and so on (Fig. 1).

3.1. Cystine/glutamate reverse transporter (System Xc-)

System Xc- is an amino acid antitransporter widely found in the phospholipid bilayer. It is a heterodimer of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2) [11]. SLC7A11 is responsible for transporting cysteine (Cys) and glutamic acid (Glu), while SLC3A2 is responsible for regulating the transport and expression of SLC7A11 [12], which together regulate System Xc- activity. System Xc- controls the intracellular and extracellular exchange of Cys and Glu in a 1:1 ratio [11]. Intracellular Cys is reduced to cysteine, which affects GSH synthesis, and GSH maintains the dynamic balance of cell redox by activating GPX4. Studies have shown that Erastin inhibits System Xc- activity, hinders cell uptake of Cys, leads to GPX4 inactivation, ROS accumulation, and ultimately induces cell oxidative damage and ferroptosis [13].

GPX4 belongs to the glutathione peroxidase family and is a selenoprotein whose active site contains selenocysteine (Sec) and requires GSH catalytic activation. Therefore, there is a positive correlation between GPX4 activity and GSH content, and GSH depletion can lead to GPX4 inactivation. GPX4 is a key factor limiting intracellular hydrogen peroxide (H_2O_2) content [14]. High concentrations of H2O2 can promote the generation of ROS and rapidly oxidize fatty acids (FAs) and arachidonic acid (AA), ultimately producing a large amount of lipid toxic substances. GPX4 not only converts GSH into glutathione disulfide (GSSG), decreases esterified oxidized fatty acids and cholesterol hydroperoxide, but also converts toxic lipid hydroperoxides (L-OOH) into non-toxic lipid hydroxyl derivatives (L-OH) to resist oxidative damage [15]. Research has shown that Erastin either directly inactivates GPX4 or indirectly inhibits GPX4 activity by upregulating activating transcription factor 3 (ATF3), thereby impacting cell antioxidant capacity and inducing ferroptosis [16]. Therefore, GPX4 is considered an important regulatory factor for ferroptosis, playing a negative regulatory role.

3.2. P53

P53 gene is a key factor in regulating physiological and pathological processes such as cell growth, aging, and apoptosis[17]. Some studies have found that p53 is involved in regulating the ferroptosis process, but the specific mechanism of action is not yet clear. H1299 cells with wild-type p53 gene silencing did not experience cell death under ROS stimulation, but activation of p53 can lead to a large number of cell death. Interestingly, ferroptosis inhibitors can significantly reduce cell death rate[18]. In addition, the p53 acetylation-deficient mutant $p53^{3KR}$ inhibits SLC7A11 expression by binding to the SLC7A11 promoter, ultimately reducing GPX4 activity and initiating the ferroptosis program [19]. Other studies have shown that p53 indirectly activates

Table 1
Morphological and biochemical characteristics of different types of cell death.

Cell death forms	Cell membrane	Cytoplasm	Cell nucleus	Biochemical Features	Key signaling molecule
Ferroptosis	Cell membranes burst and blister	Mitochondrial volume decreases, body ridges decrease or disappear, membrane density increases, and outer membrane ruptures	Normal nucleus	Intracellular accumulation of iron and reactive oxygen species; The increase of iron-dependent lipid peroxides; Inhibition of system Xc- with decreased cystine uptake; Release of arachidonic acid mediators	SLC7A11, Nrf2, GPX4, p53, TFR1, ACSL4, LOXs, NCOA4, ALOX12, FPN
Necroptosis	Rupture of plasma membrane	Swelling of cytoplasmic and organelle	Partial condensation of chromatin	Drop in ATP levels; Activation of RIP1, RIP3 and MLKL; Release of DAMPs;	RIP1, RIP3, MLKL
Apoptosis	Formation of apoptotic bodies and cytoskeletal disintegration	Cell volume decreases, but there is no significant change in mitochondrial structure	Nuclear contraction; Chromatin condensation;	DNA is cleaved into small fragments by endogenous endonucleases; Phosphatidylserine eversion; Mitochondrial transmembrane potential decreased;	Caspase, Bcl-2, Bax, p53
Autophagy	Normal cell membrane	Formation of autophagosomes with a bilayer membrane structure, including macroautophagy, microautophagy and chaperone mediated autophagy	Normal nucleus	Increased lysosomal activity	ATG5, ATG7, LC3, Beclin-1, TFEB

*ATP: adenosine triphosphate, ATG5: autophagy protein 5, ATG7: autophagy-related 7, ACSL4: acyl-CoA synthetase long-chain family member 4, ALOX12: arachidonate lipoxygenase 12, Bax: BCL2-associated X protein, Bcl-2: B-cell lymphoma-2, DAMPs: damage-associated molecular patterns, FPN: ferroportin, FSP1: ferroptosis suppressor protein 1, FTH1: ferritin heavy chain 1, GPX4: glutathione peroxidase 4, GSH: glutathione, LC3: microtubule-associated protein 1 light chain 3, LOXs: arachidonate lipoxygenase, MLKL: mixed lineage kinase domain-like protein, NCOA4: nuclear receptor coactivator 4, Nrf2: nuclear factor erythroid 2-related factor 2, PTGS2: prostaglandin-endoperoxide synthase 2, RIP1: receptor-interacting protein 1, RIP3: receptor-interacting protein 3, ROS: reactive oxygen species, SLC7A11: solute carrier family 7 member 11, SLC3A2: solute carrier family 3 member 2, System Xc-: cysteine/glutamate transporter receptor, TFR1: transferrin receptor 1, TFEB: transcription factor EB.

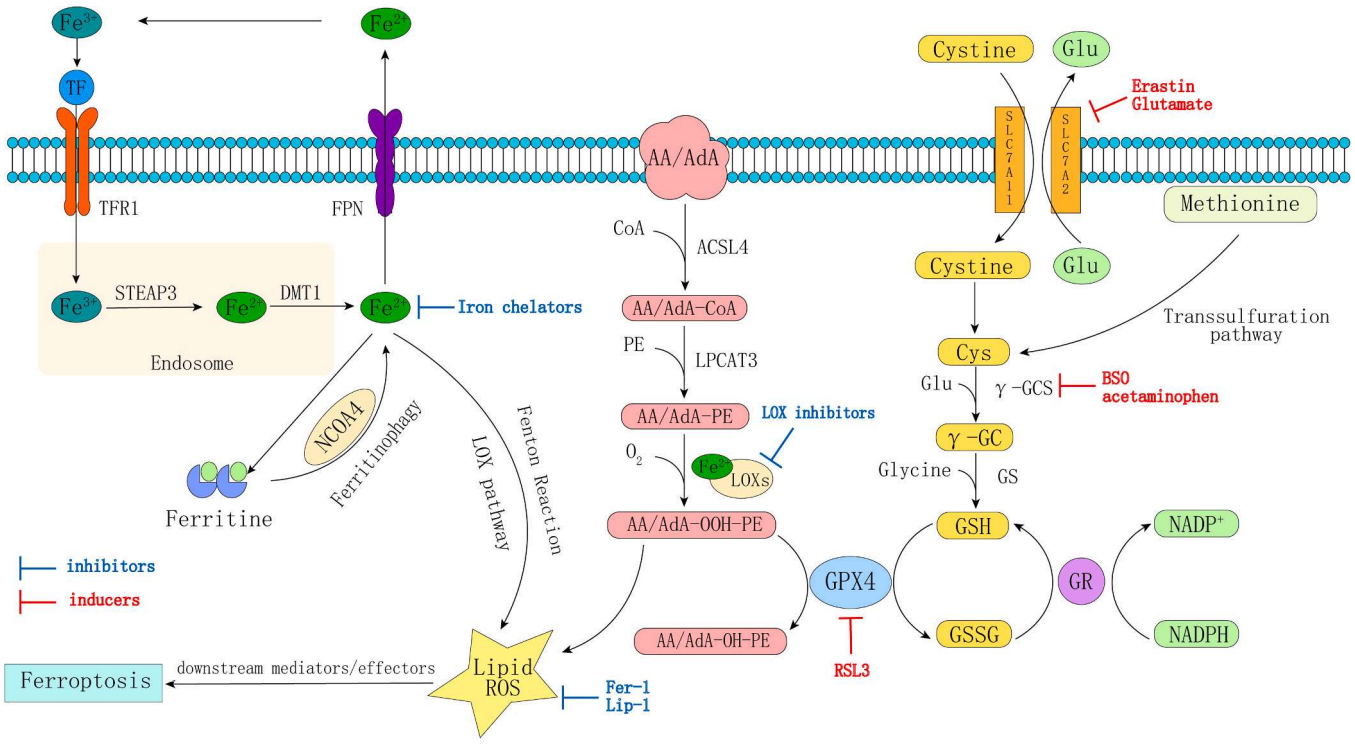

Fig. 1. Molecular mechanism of ferroptosis. Fe^{3+} is reduced to Fe^{2+} through TFR1, and some Fe^{2+} is released into unstable iron pools under the regulation of factors such as DMT1, forming free iron ions. Free iron can interact with ROS to form free radicals, and rapidly react with oxygen through Fenton reaction to form lipid peroxides. Thus, iron import, export, storage, and turnover impact ferroptosis sensitivity. Lipid peroxidation is also a sign of ferroptosis. Phosphatidyl ethanolamines containing AA or AdA are key membrane phospholipids that can form phospholipid hydroperoxides through non enzymatic reactions such as free radical lipid peroxidation or Fenton chemistry, inducing ferroptosis. This process involves the regulatory effects of ACSL4 and LPCAT3. In addition, lipid peroxides and their degradation products are also controlled by the redox reaction of glutathione. System Xc− imports cystine, which is reduced to cysteine and used to synthesize glutathione. And then GPX4 can reduces membrane phospholipid hydroperoxides to suppress ferroptosis.

arachidonate-12-lipoxygenase (ALOX12) by inhibiting the expression of SLC7A11, inducing ferroptosis of cells, and this process does not change the GSH content and GPX4 activity [20]. Unlike the above research findings, Xie and Tarangelo's study showed that p53 gene expression can inhibit ferroptosis of cell [21,22]. From this, it can be seen that the mechanism of action of the p53 gene in ferroptosis is is very complex and may have a bidirectional regulatory effect, which may be related to changes in the p53 domain or cell type.

3.3. Iron metabolism

Iron is one of the important trace elements in the human body, and abnormal distribution or content of iron can affect the normal physiological activities of the body. At present, iron is considered the central medium of ferroptosis. The Fe^{2+} formed through intestinal absorption or red blood cell degradation is oxidized by ceruloplasmin to Fe^{3+}. Fe^{3+}binds to transferrin (TF) to form TF-Fe^{3+}, which then enters the cell through transferrin receptor 1 (TFR1) and is reduced to Fe^{2+} under the action of reductase. Some Fe^{2+} is released into unstable iron pools or ferritin storage through the regulation of divalent metal transporter 1 (DMT1) or zinc iron regulatory protein family 8/14 (ZIP8/14), The remaining Fe^{2+} is further oxidized by ferroportin (FPN) to form Fe^{3+} [23]. This cycling mode strictly controls intracellular iron homeostasis. There are research reports that silencing the TFRC gene encoding TFR1 can suppress Erastin induced ferroptosis [24], while heat shock proteins β1 (HSPB1) has an inhibitory effect on TFR1 expression [25], so HSPB1 inhibits ferroptosis by reducing intracellular iron concentration. Other studies have shown that iron sulfur cluster biosynthetic enzyme (NFS1) absorbs sulfur elements through cysteine, increasing the total amount of iron sulfur clusters, thereby inhibiting the excessive release of Fe^{2+} by iron storage molecules [26]. In addition, heme oxygenase-1 (HO-1) is considered a positive regulatory factor for iron death, which can accelerate the release of Fe^{2+} [27]. In summary, iron metabolism is regulated by multiple signaling molecules, and existing research has not elucidated the dominant pathway of action. However, the accumulation of Fe^{2+} promotes the development of ferroptosis, which cannot be denied.

In addition, the oxidative damage caused by hydroxyl radicals (OH) generated by unstable Fe^{2+} during the iron cycle through Fenton reaction is also one of the important pathways leading to ferroptosis. Fe^{2+} catalyzes H_2O_2 to produce OH through Fenton reaction, resulting in intracellular ROS overload. Systems such as superoxide dismutase and catalase can clear ROS and prevent oxidative stress-induced ferroptosis [28]. When ROS clearance and generation are out of balance, oxidative stress occurs, promoting the release of Fe^{2+} from iron-containing substances, and excessive Fe^{2+} exacerbates oxidative stress through Fenton reaction, ultimately forming a vicious cycle [29]. The nuclear factor-erythroid 2 related factor 2 (Nrf2) is a key factor in maintaining cellular redox homeostasis and a negative regulatory factor for ferroptosis. Activating Nrf2 can upregulate the expression level of GPX4, reduce cell oxidative damage, and inhibit ferroptosis [30]. Other studies have shown that Nrf2 blockade of ferroptosis is related to its activation of NADH dehydrogenase quinone 1 (NQO1) and ferritin heavy chain 1 (FTH1) gene transcription [31]. It can be seen that the interaction between iron metabolism disorder and oxidative stress promotes the process of ferroptosis together.

3.4. Lipid metabolism

Lipid peroxidation is a driver of iron death, which leads to the insertion of oxygen into the C-H bonds of oxidizable free polyunsaturated fatty acids (PUFAs), participating in all pathways of

ferroptosis. Studies have shown that phosphatidylethanolamines (PEs) containing AA or adrenal acid (AdA) are key phospholipids in lipid peroxidation induced ferroptosis [32]. Acyl CoA synthase long chain member 4 (ACSL4) and lysophosphatidyl acyltransferase 3 (LPCAT3) participate in the biosynthesis and remodeling of PEs, activate PUFAs, and regulate their transmembrane properties, which are key lipid metabolism enzymes [33,34]. In addition, lipoxygenases (LOXs) can directly oxidize PUFAs or lipids containing PUFAs, and knocking out the LOXs gene can inhibit the induction effect of Erastin [35]. In conclusion, ferroptosis induced by lipid peroxidation is regulated by several signaling molecules, and PUFAs oxidation is the central link in this process.

4. DKD and ferroptosis

Renal intrinsic cells are an important component of maintaining normal physiological activity in the kidneys. Study has shown that pathological changes such as fibrosis, inflammation, oxidative stress and lipid metabolism disorder may lead to iron retention and induce ferroptosis of intrinsic cells in the kidney, which in turn can aggravate renal histopathological changes[8]. Therefore, exploring the molecular mechanisms of intrinsic cells in the kidney and ferroptosis is of great significance for the prevention and treatment of DKD (Fig. 2).

4.1. Renal tubular epithelial cells

Research has shown that ferrostatin 1 (Fer-1) up-regulates the expression levels of SLC7A11 and GPX4, thereby increasing GSH concentration and improving renal tubule injury in db/db mice. In addition, Fer-1 can inhibit the induction of transforming growth factor β1 (TGF-β1) and reduce the mortality of renal tubular epithelial cells[36]. From this, it can be seen that TGF-β1 activation can cause signal crosstalk, leading to System Xc- inactivation and ferroptosis of cell. Secondly, TGF-β1 is recognized as an important participant in renal fibrosis[37], so fibrotic lesions may lead to secondary cell ferroptosis. Other studies have shown that advanced glycation end products (AGEs) can affect iron metabolism and System Xc- activity, initiating the ferroptosis program. AGEs induce downregulation of SLC7A11 and GPX4 protein levels, upregulation of TFR1 and ACSL4 protein levels, leading to accumulation of Fe^{2+} and ROS, and decreased activity of renal tubular epithelial cells. But Fer-1 can weaken the effect of AGEs[38]. In addition, high glucose stimulation not only inhibited the protein expression of cell membrane ferroportin FP1 (SLC40A1), blocked the transport of Fe^{2+} from intracellular to extracellular, and induced iron retention. It can also down-regulate the protein expression of SLC7A11 and GPX4, increase the content of malondialdehyde (MDA), and finally accelerate cell death [39]. Therefore, the disturbance of glucose metabolism can destroy iron homeostasis, promote lipid peroxidation and induce ferroptosis in renal tubular epithelial cells, and involve the regulation of multiple signaling molecules. Zhou et al.[40]. found that the expression of GPX4 in the kidney tissue of UUO model mice was significantly reduced, while the protein expressions of fibronectin (FN), α-smooth muscle actin (α-SMA) and monocyte chemotactic protein 1 (MCP-1) were enhanced, which was basically consistent with the trend of GPX4 inhibitor (RSL3) inducing NRK-52E cells. Therefore, ferroptosis may lead to the release of pro-inflammatory factors and fibrosis mediators from renal tubular epithelial cells, which in turn recruit macrophages or lymphocytes to aggregate and drive interstitial inflammation and fibrosis. In summary, the occurrence of ferroptosis in renal tubular epithelial cells is mainly regulated by iron metabolism and amino acid metabolism. Fibrosis, glucose metabolism disorders, AGEs and other pathological damages interact with ferroptosis in renal tubular epithelial cells, jointly promoting the development of DKD. This process involves cross talk of multiple signals, and the mechanism of action is very complex. Ferroptosis may be in a critical position.

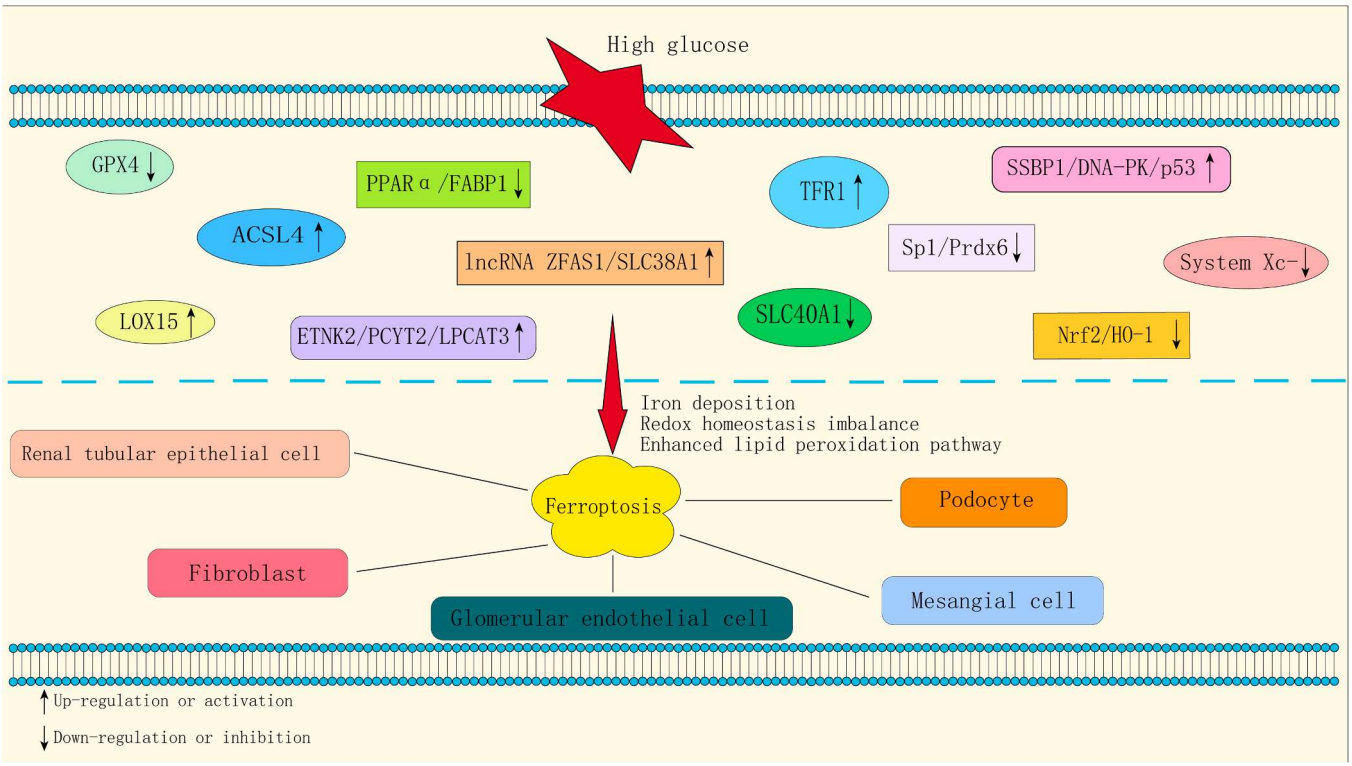

Fig. 2. Key regulators and signaling pathways of ferroptosis in diabetic kidney disease. Nrf2/HO-1, SLC3A2/SLC7A11/GPX4, ACSL4, TFR1 and other signal pathways regulate iron deposition, lipid peroxidation and so on in the body, and then interfere with the ferroptosis of podocytes, renal tubular epithelial cells, endothelial cells and other intrinsic renal cells, affecting the occurrence and development of diabetic kidney disease.

4.2. Podocyte

Research has found that high sugar can inhibit the mRNA expression of prostaglandin-endoperoxide synthase 2 (PTGS2) in prostaglandins, down-regulate the protein levels of GPX4 and ACSL4, resulting in ROS accumulation and podocin reduction, resulting in structural disorders and decreased vitality of podocytes. In addition, transmission electron microscopy showed mitochondrial shrinkage and disappearance of somatic crest in podocytes[41]. Therefore, long-term hyperglycemia can drive ferroptosis in podocytes and induce oxidative stress. Another study suggests that the single-stranded DNA-binding protein 1 (SSBP1)/p53 signaling pathway may be one of the important mechanisms by which high glucose induces System Xc- inactivation and leads to podocyte ferroptosis. High glucose stimulation of SSBP1 overexpression enhances DNA-dependent protein kinase (DNA-PK) activity, thereby promoting p53 S15 phosphorylation activation and downregulating SLC7A11 protein levels, resulting in the disappearance of mitochondrial cristae in podocytes[42]. In addition, Zhang et al.[43]. found that high glucose inhibited the expression of specificity protein 1 (Sp1) and peroxiredoxin 6 (Prdx6), thereby reducing the content of SLC7A11 and GPX4 and the protein levels of podocin and nephrin, resulting in podocin damage and excessive secretion of inflammatory factors and fibrotic mediators. From this, it can be seen that hyperglycemia induces podocyte ferroptosis by disrupting System Xc- activity, exacerbating pathological damage in DKD. This process involves the regulatory role of PTGS2/GPX4, SSBP1/DNA-PK/p53 and Sp1/Prdx6 signaling pathways.

4.3. Glomerular endothelial cells

A research team has shown that hyperhomocysteinemia (HHcy) can promote glomerular lesions and worsen renal damage. This is related to HHcy upregulating the mRNA expression of ethanolamine kinase 2 (ETNK2), ethanolamine-phosphate cytidylyltransferase 2 (PCYT2), and LPCAT3, promoting PE accumulation and activating PUFA. Not only that, the glycolytic disorder caused by B cell activation is also a key node in HHcy mediated endothelial cell ferroptosis, exacerbating renal pathological damage. B cell derived anti-beta-2-Glycoprotein I (β2GPI) induces increased expression of ACSL4 and LOX15, while weakened expression of SLC7A11 and GPX4, leading to increased levels of lipid peroxides (LPO) and MDA, promoting lipid peroxidation in endothelial cells. The use of rituximab to consume B cells can improve endothelial cell damage, which is basically consistent with the therapeutic effect of Fer-1 [44]. Therefore, targeting B cells to regulate the release of anti β2GPI may be an important pathway for maintaining lipid metabolism balance, inhibiting endothelial cell ferroptosis, and delaying the progression of DKD. Other studies have shown that Fer-1 upregulates the expression of SLC7A11 and GPX4, reduces mitochondrial ROS levels, and ultimately inhibits high glucose induced mitochondrial oxidative stress, reducing endothelial cell damage [45]. In addition, hydrogen sulfide (H_2S) may also be an important substance mediating endothelial cell ferroptosis and improving oxidative damage. In the kidney tissue of AKI model mice can be seen the protein expression of cystathionine-γ-lyase (CSE) and GPX4 is weakened, TF protein expression is enhanced, and Fe^{2+} deposition, which is similar to the experimental results of LPS induced endothelial cells. However, exogenous H_2S intervention can reverse the above results [46]. In summary, ferroptosis of endothelial cells can accelerate the pathological changes of kidney. However, it is still unknown whether ferroptosis of endothelial cells interacts with pathological processes such as fibrosis, inflammation and hemodynamic changes.

4.4. Fibroblast

Solute carrier family 38 member 1 (SLC38A1) is a target gene of miR-150, and the transcription of miR-150 is regulated by lncRNA ZFAS1. Study has shown that TGF-β1 induces lncRNA ZFAS1 overexpression, inhibits miR-150 transcriptional activation, thereby up-regulating the expression level of SLC38A1 and down-regulating the protein expression of GPX4, resulting in increased levels of α-SMA, FN, interleukin6 (IL-6), and interleukin1β (IL-1β) [47]. Therefore, the lncRNA ZFAS1/miR-150/SLC38A1 signaling pathway is an important molecular mechanism that mediates fibroblast activation and induces lipid peroxidation, which can further affect fibrosis and inflammatory pathological changes. Other studies have found that high glucose stimulation can down-regulate the expression levels of SLC7A11 and GPX4, increase the concentrations of ROS and MDA, and ultimately induce ferroptosis in fibroblasts and reduce cell viability. In vivo experiments further hint that the inactivation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway may be one of the molecular mechanisms by which ferroptosis impacts on the anti-inflammatory ability [45]. In summary, ferroptosis of fibroblast is involved in the pathological process of inflammatory response, exacerbating inflammatory damage in the body. However, existing research has failed to elucidate the specific regulatory mechanism, which is regrettable.

4.5. Glomerular mesangial cells

Fatty acid binding protein 1 (FABP1) is the downstream target of peroxisome proliferator-activated receptor α (PPARα). A study has shown that galactose-deficient IgA1 (Gd-IgA1) can inhibit the expression of PPARα and FABP1, down-regulate GPX4 protein level, and up-regulate ACSL4 protein level in mesangial cells, and leads to ROS accumulation, GSH level is decreased, and mitochondrial structure disorder. However, inducing PPARα overexpression can improve cell damage and reduce mortality [48]. Therefore, the PPARα/FABP1 signal axis mediates ferroptosis in mesangial cells by regulating redox balance and PUFA activity. In addition, the activation of the Nrf2/HO-1 pathway may also be an important mechanism for regulating amino acid metabolism and preventing ferroptosis. High glucose stimulation inhibits Nrf2 expression, downregulates GPX4 and HO-1 protein levels, promotes ROS production, and reduces mesangial cell survival rate [49]. It can be seen that oxidative damage is an important factor inducing ferroptosis in mesangial cells.

In summary, the occurrence of ferroptosis in renal intrinsic cells can participate in pathological and physiological processes such as AGEs, fibrosis, inflammation, oxidative stress, and glucose metabolism disorders, and jointly promote the DKD process through interactions. Unfortunately, there is limited research on fibroblasts and mesangial cells, and it is not yet known whether signal crosstalk is formed between cells.

5. Traditional Chinese medicine etiology and pathogenesis

Although DKD belongs to the concept of modern medicine, its etiology, pathogenesis, and symptoms have been recorded in ancient Chinese medicine books, such as *Huang Di Nei Jing (Huangdi's Internal Classic), Gu Jin Yan Fang Lu, Zhu Bing Yuan Hou Lun (General Treatise on Causes and Manifstations of All Diseases)* and so on. It can be traced back to the Warring States period (475 BC-221 BC) and is called "Xiaodan", "Shenxiao", "Edema" and so on. Most doctors believe that DKD is caused by prolonged illness of DM, which consumes qi and damages yin over time, ultimately resulting in deficiency of both qi, blood, yin and yang, and a mixture of phlegm dampness, blood stasis and turbid toxins. The basic pathogenesis of this disease is the deficiency in origin and excess in superficislity. This deficiency in origin is divided into lung qi deficiency, spleen stomach qi yin deficiency, spleen kidney yang deficiency and kidney yin yang deficiency. This excess in superficiality is divided into water dampness, blood stasis and turbid toxicity. However, there are also doctors who have different opinions on this. Professor Lv Renhe proposed the pathogenesis theory of "miniature zheng jia", believing that during the development of DKD, the body may experience changes such as heat stagnation, qi stagnation, phlegm accumulation and blood stasis. The cementation and entanglement of these products can further

form tangible and symptomatic pathological changes in the kidneys, affecting visceral function and the balance of yin and yang in the body [50]. Chinese medicine master Zhou Zhongying believes that the deficiency of qi, blood, yin and yang in the organs can lead to dampness, dryness and phlegm heat stagnation, which over time becomes heat stagnation and worsens the condition of DKD. Therefore, stasis heat is not only a pathological factor but also a pathogenesis, thus proposing the "stasis heat theory" [51]. Professor Nan Zheng puts forward the theory of "poison damages the kidney collaterals, and pathogens lie behind between the pleura and diaphragm". It is believed that DKD is caused by insufficient body endowment and excessive consumption of greasy food, which leads to the dysfunction of the spleen, stomach and tissue surrounding the spleen, and the invasion of poison and pathogens, which lies in the membrane, damages the kidney collaterals, and causes significant damage to the kidney qi. Therefore, toxin and evil are the main causes and pathogenesis of DKD[52]. In conclusion, the pathogenic factors of DKD are diverse, and multiple factors can promote the development of the disease together.

6. Traditional Chinese medicine treatment

6.1. Effective ingredients or extracts of traditional Chinese medicine

6.1.1. Resveratrol

Natural resveratrol is mainly derived from the Chinese medicine *Polygonum cuspidatum* and is a non flavonoid polyphenol compound. Research has shown that resveratrol can regulate lipid peroxidation, inhibit iron deposition, and prevent interstitial fibrosis. Resveratrol upregulates GPX4 expression, thereby reducing Fe^{2+} and ROS levels, ultimately improving mitochondrial damage and reducing collagen deposition [53]. In addition, resveratrol can activate heat shock factor 1 (HSF1), thereby upregulating the protein expression of GPX4 and SLC7A11, reducing the levels of lactate dehydrogenase (LDH) and MDA, ultimately inhibiting ferroptosis, and improving pathological damage caused by chronic hyperglycemia[54]. Not only that, resveratrol can mediate Nrf2-GPX4 signaling crosstalk, up-regulate the levels of superoxide dismutase (SOD) and GSH, alleviate oxidative stress, and inhibit ferroptosis of epithelial cells [55]. In summary, resveratrol may alleviate renal injury in DKD by regulating iron death, and GPX4 activity is the key to resveratrol's intervention in ferroptosis. Other studies have found that resveratrol downregulates the protein expression of ubiquitin-specific protease 19 (USP19) and Beclin-1, upregulates the protein expression of GPX4 and FTH1, and ultimately reduces Fe^{2+} and MDA levels [56]. It can be seen that there may be an interaction between autophagy and ferroptosis, and resveratrol regulates autophagy activity by regulating the USP19/Beclin-1 signaling axis, thereby inhibiting cell ferroptosis.

6.1.2. Saikosaponin

Saikosaponin is the main active ingredients of Chinese medicine *Radix bupleuri*, which have anti-inflammatory, antioxidant and other pharmacological effects. Research has found that saikosaponin A upregulates the expression level of GPX4, downregulates the expression level of ACSL4, increases the content of SOD and GSH, thereby alleviating endothelial cell oxidative damage and inhibiting ferroptosis [57]. Other studies have shown that saikosaponin B2 down-regulates the protein expression of Toll-like receptor 4 (TLR4) and nuclear factor kappa-B (NF-κB), up-regulates the expression levels of SLC7A11 and GPX4, and finally decreases the levels of Fe^{2+}, ROS, IL-6 and IL-1β. In addition, knockdown of GPX4 increased the protein expression of ATF6 and XBP1, and Ca^{2+} concentration, while saikosaponin B2 attenuated the effect of shGPX4 [58]. Therefore, TLR4/NF-κB–SLC7A11/GPX4 signal crosstalk is an important molecular mechanism that inflammation induces ferroptosis and further activates endoplasmic reticulum stress, and GPX4 is the central link that saikosaponin B2 blocks the vicious cycle of inflammation-ferroptosis-endoplasmic reticulum stress. However, there are many types of saikosaponins, and it is not clear whether other types have regulatory effects on iron death. In the future, research should be expanded to improve and perfect the pharmacological mechanism of saikosaponins targeting ferroptosis to prevent and treat DKD.

6.1.3. Leonurine

Leonurine is the main pharmacological substance of *motherwort*, which can upregulate the expression levels of Nrf2, NQO1 and HO-1, reduce the accumulation of Fe^{2+} and ROS in the kidneys, and reduce the levels of MDA and kidney injury molecule 1 (KIM-1), but siNrf2 reversed the above effects [59]. Therefore, leonurine maintains redox balance by activating Nrf2 signals, regulates iron metabolism disorders, and alleviates renal tubular injury. Study has shown that p62 may be an important participant in activating the Nrf2 antioxidant pathway, preventing ferroptosis in renal tubular epithelial cells. Leonurine promotes p62 expression, accelerates Nrf2 translocation into the nucleus, upregulates protein expression of HO-1 and GPX4, and ultimately increases GSH content [60]. In summary, regulating the Nrf2 signaling pathway is an important molecular mechanism by which leonurine targets ferroptosis, and alleviates renal damage in DKD.

6.1.4. Salvia miltiorrhiza extract

Salvia miltiorrhiza is a Chinese herbal medicine that promotes blood circulation and dissipates blood stasis, mainly containing lipid soluble diterpenoids and water-soluble phenolic acids. Research has found that tanshinone IIA can regulate lipid metabolism, reduce oxidative damage, and curb ferroptosis. Tanshinone IIA inhibits p53 expression, upregulates the expression levels of GPX4 and SLC7A11, ultimately reducing ROS production and lowering serum triacylglycerol (TG) and total cholesterol (TC) levels [61]. In addition, dihydrotanshinone I can activate Nrf2/HO-1 signal transduction, reduce Fe^{2+}, ROS, MDA levels, and improve mitochondrial function [62]. From this, it can be seen that the diterpenoid components of *Salvia miltiorrhiza* can improve antioxidant capacity, reduce iron poisoning, and prevent ferroptosis. Salvianolic acid is a water-soluble phenolic acid component. Study has shown that salvianolic acid B improves lipid peroxidation, inhibits ferroptosis, and reduces the levels of collagen type I (Col-I) and collagen type III (Col-III) by activating the Nrf2/GPX4 signal axis, alleviating renal fibrosis [63]. To sum up, the Chinese medicine *Salvia miltiorrhiza* blocks the process of iron death, thereby intervening the pathophysiological processes of lipid metabolism disorder, oxidative stress and fibrosis, and delaying the progression of DKD.

6.1.5. Licorice extract

Licorice has the effects of tonifying the middle and supplementing qi, clearing heat and detoxifying, dispelling phlegm and relieving cough, and relieving pain. It can be used to treat various diseases. Study has shown that isoliquiritigenin can inhibit the expression of high mobility group protein B1 (HMGB1) and nuclear receptor coactivator 4 (NCOA4), upregulate GPX4 protein levels, restore System Xc- activity, thereby improving renal tubular mitochondrial damage and reducing iron deposition. Not only that, in vivo, renal collagen deposition and reduced inflammatory infiltration were also observed [64]. Therefore, isoliquiritigenin regulates ferritin autophagy and further affects lipid peroxidation by regulating HMGB1/NCOA4 signaling pathway, and finally alleviates renal fibrosis and inflammation. Other studies have found that glabridin mediates vascular endothelial growth factor (VEGF)/AKT/extracellular regulated protein kinases (ERKs)–SLC7A11/SLC3A2 signal crosstalk, thereby downregulating TFR1 protein expression, reducing KIM-1 and neutropil gelatinase-associated lipocalin (NGAL) levels, ultimately inhibiting ferroptosis, and alleviating DKD renal injury [65]. Both isoliquiritigenin and glabridin belong to flavonoids, so flavonoids may be the main effective components of *Licorice* to regulate ferroptosis and prevent the progressive aggravation of pathological damage of DKD.

6.1.6. Salidroside

Salidroside mainly comes from the Chinese medicine *Rhodiola*, and has pharmacological effects such as antioxidant, anti-inflammatory, and hypoglycemic effects. Research has found that salidroside inhibits TFR1 expression, upregulates FPN1 and FTH1 protein levels, thereby reducing renal iron load and inhibiting TGF-β1 activating and improving renal interstitial fibrosis [66]. Other studies have shown that salidroside can reduce Fe^{2+} and ROS deposition, reduce the levels of tumor necrosis factor α (TNF-α), IL-6 and IL-1β by activating the Nrf2/SLC7A11/GPX4 signaling pathway, and ultimately reduce inflammatory response and inhibit ferroptosis of epithelial cells [67]. In conclusion, salidroside may prevent ferroptosis by regulating iron metabolism and inhibiting lipid peroxidation, and then interfere with the pathological process of DKD fibrosis and inflammation.

6.1.7. Quercetin

Quercetin is a flavonoid alcohol compound that can exist in various medicinal plants, such as *Cacumen biotae*, *Alpinia officinarum*, *Flos farfarae*, *Loranthus parasiticus* and *Panax notoginseng*. Study has found that quercetin can inhibit PTGS2 expression, restore System Xc- activity, upregulate GSH and SOD levels, and ultimately block pancreatic islet β cell ferroptosis, stabilizing pancreatic function, regulating glucose metabolism disorders [68]. In addition, quercetin inhibits ATF3 expression, activates the SLC7A11/SLC3A2/GPX4 signaling pathway, reduces MDA and ROS levels, thereby inhibiting renal tubular iron deposition and reducing the release of inflammatory factors [69]. Other studies have shown that quercetin regulates Nrf2/HO-1–SLC7A11/GPX4 signal crosstalk, downregulates TFR1 protein levels, inhibits ferroptosis, and alleviates renal tubular fibrosis [70]. Taken together, regulation of System Xc- activity is a key link for quercetin to block ferroptosis and ameliorate the pathological damage of DKD.

6.1.8. Astragalus extract

Astragalus membranaceus is a commonly used tonifying medicine in clinical practice. Through modern pharmacological research and analysis, it has been found that the various active ingredients (polysaccharides, saponins, flavonoids and so on) contained in *Astragalus membranaceus* have significant therapeutic effects in preventing and treating DKD. Research shows that astragaloside IV can up-regulate the expression levels of Nrf2 and GPX4, prevent the activation of TGF-β1/Smads pathway, reduce the levels of Col-I, Col-III and ROS, and finally inhibit ferroptosis and improve fibrosis [71]. Silent information regulator 1 (SIRT1) is a target gene of miR-138 and a positive regulatory factor of Nrf2. Study has shown that astragaloside IV regulates the miR-138/SIRT1 signaling pathway, promotes Nrf2 activation, upregulates GPX4 protein levels, enhances epithelial antioxidant capacity, and suppresses high glucose induced ferroptosis [72]. From this, it can be seen that the Nrf2/GPX4 signal axis is an important molecular mechanism for astragaloside IV to regulate ferroptosis. In addition, astragalus polysaccharides regulate the Nrf2/HO-1 signaling pathway, down-regulate PTGS2 mRNA expression, inhibit iron deposition, and prevent epithelial cell ferroptosis [73]. Taken together, astragaloside and astragalus polysaccharides may maintain redox homeostasis by targeting Nrf2 and hinder ferroptosis to induce pathological damage in DKD. However, it is still unknown whether the flavonoids contained in *Astragalus membranaceus* have similar functions. In the future, the potential connection between flavonoids and ferroptosis should be explored, and the pharmacological mechanism of *Astragalus membranaceus* regulating ferroptosis and preventing DKD should be improved.

6.1.9. Asiatic acid

Asiatic acid is one of the main effective ingredients of the Zhuang medicine *Centella asiatica*, which has anti-inflammatory, antioxidant and other pharmacological effects. Study has found that asiatic acid regulates Kelch-like ECH-associated protein 1 (Keap1) /Nrf2 signaling axis to trigger a cascade reaction to reduce iron load and alleviate kidney injury. Asiatic acid inhibited Keap1 expression and up-regulated Nrf2 protein level, thereby activating NQO1 transcription, promoting the activation of SLC7A11/GPX4 pathway, and finally enhancing the activities of glutathione peroxidase (GSH-Px), catalase (CAT) and SOD [74]. Other studies have shown that iron overload can induce the transformation of macrophages to M1 phenotype, and asiatic acid may restore GPX4 activity by blocking PI3K/AKT signal transduction, prevent the polarization of M1 macrophages, and reduce inflammatory response [75]. It can be seen that the molecular mechanism of asiatic acid regulating ferroptosis prevention and treatment DKD is complex, involving the cross dialogue of multiple signal pathways, and GPX4 signal molecule may be the key node of this regulatory network.

6.1.10. Curcumin

Curcumin is a diketone compound that can be extracted from Chinese herbal medicines such as *Radix curcumae*, *Rhizoma curcumae longae*, *Curcuma zedoary* and *Calamus*. Study has shown that curcumin inhibits tubular cell ferroptosis and relieves kidney inflammation by blocking TLR4/NF-κB/ERK signaling pathway and then activating Nrf2 signaling. Curcumin down-regulates the mRNA expression of TLR4, inhibits the phosphorylation of NF-κB and ERK, thereby up-regulates the expression of Nrf2 and HO-1 protein, and finally decreases the levels of 4-hydroxynonenal (4-HNE), MCP-1 and TNF-α [76]. In addition, curcumin activates the Nrf2/HO-1 signaling pathway to upregulate the expression levels of GPX4 and SLC7A11, reduce Fe^{2+} accumulation, and inhibit high glucose induced oxidative damage and ferroptosis in epithelial cells [77]. Other studies have found that curcumin inhibits TFR1 protein expression, upregulates FTH1 protein levels, thereby regulating iron metabolism disorders, reducing ROS levels, and preventing epithelial cell ferroptosis [78]. In conclusion, curcumin inhibits inflammation and hyperglycemia induced ferroptosis by regulating TLR4/NF-κB/ERK, Nrf2/HO-1 and TFR1/FTH1 signaling pathways, thereby delaying the progression of DKD.

6.1.11. Ophiopogon japonicus extract

Ophiopogon japonicus has the effects of nourishing yin and moistening the lungs, benefiting the stomach and promoting fluid production, clearing the heart and eliminating troubles, and can be used to treat cardiovascular, endocrine, and respiratory system diseases. Study has shown that ophiopogonin D regulates the ACSL4/cyclooxygenase 2 (COX2), TFR1/FTH1 and SLC7A11/GPX4 signaling pathways, upregulates GSH-Px levels, reduces Fe^{2+} and ROS content, and inhibits myocardial cell ferroptosis [79]. Another study found that *Ophiopogon japonicus* water extract inhibited the expression of Rev-erbα and Rev-erbβ, then activated SLC7A11/HO-1 signaling pathway, increased GSH content, and finally prevented ferroptosis process and alleviated kidney injury [80]. Throughout the above research, *Ophiopogon japonicus* has regulatory effects on multiple signaling molecules of ferroptosis, which can regulate iron metabolism, lipid peroxidation, and inhibit the development of iron death. Therefore, *Ophiopogon japonicus* is expected to become a new method for preventing ferroptosis in renal intrinsic cells, and delaying the process of DKD.

6.1.12. Ginsenoside

Ginsenoside belongs to triterpenoid glycosides and is important active ingredients of Chinese medicine *Panax ginseng*. They have antioxidant, anti-inflammatory and blood sugar regulating effects. Study has shown that ginsenoside Rg3 promotes the activation of Nrf2/HO-1 pathway, inhibits PTGS2 expression, enhances GPX4 activity, ultimately reduces Fe^{2+}, ROS and MDA levels, and inhibits the release of pro-inflammatory factors [81]. In addition, ginsenoside Rg1 upregulates the protein expression of ferroptosis suppressor protein 1 (FSP1) and GPX4, reduces the levels of KIM-1 and NGAL, prevents ferroptosis in renal tubular epithelial cells, and alleviates renal injury [82]. It can be

seen that ginsenoside inhibits the progression of ferroptosis and alleviates pathological damage in DKD by regulating key signals such as Nrf2/HO-1 and GPX4.

6.1.13. *Schisandra Chinensis extract*

Schisandra chinensis has the effects of astringency, qi tonifying and fluid promoting. Schisandrin A and schisandrin B are effective components of *Schisandra chinensis*. Schisandrin B upregulates the expression levels of Nrf2, HO-1 and GPX4, enhances the activity of SOD and GSH-Px, inhibits ferroptosis, and thus prevents complications caused by DM [83]. In addition, schisandrin B promotes the phosphorylation and inactivation of glycogen synthase kinase 3β (GSK3β), inhibits GSK3β expression, activates Nrf2/GPX4 signaling axis, down-regulates TFR1 and ACSL4 protein levels, and ultimately reduces lipid peroxidation and inflammatory injury in renal tubules [84]. Therefore, schisandrin B can intervene in ferroptosis and delay the progression of DKD by regulating Nrf2/GPX4 signal transduction.Other studies have shown that schisandrin A mediates signal crosstalk between adiponectin receptor 1 (AdipoR1)/AMP-activated protein kinase (AMPK)/Nrf2 and thioredoxin-interacting protein (TXNIP)/NOD-like receptor thermal protein domain associated protein 3 (NLRP3), reduces iron concentration, inhibits ROS accumulation, and reduces inflammatory factor secretion, thereby affecting the interaction between ferroptosis and inflammation and improving renal disorder in DKD [85]. In conclusion, *Schisandra chinensis* can regulate ferroptosis through multiple molecular pathways and exert therapeutic effects on DKD.

6.1.14. *Berberine*

Berberine is a quaternary ammonium alkaloid that can be isolated and extracted from the Chinese medicine *Coptis chinensis*. Study has found that berberine activates the Nrf2/HO-1/GPX4 signaling pathway, downregulates the expression levels of ACSL4 and PTGS2, thereby inhibiting high glucose induced ferroptosis in podocytes [41]. Not only that, berberine promotes GPX4 activation to reduce Fe^{2+} and ROS deposition, block ferroptosis of pancreatic islets β cells, regulate glucose metabolism disorders, and prevent DM from progressing to DKD [86]. In conclusion, berberine enhances the antioxidant capacity of the body by restoring GPX4 activity, inhibits the development of ferroptosis, protects the structure and function of renal intrinsic cells, and potentially preventing sustained hyperglycemia induced DKD kidney damage.

6.1.15. *Ginkgo Biloba extract*

Terpene lactones and flavonoids are the main active components of *Ginkgobiloba*. Study has shown that ginkgolide B upregulates the protein expression of GPX4 and FTH1, and downregulates the protein expression of TFR1, thereby reducing ROS and α-SMA levels, inhibits podocytes ferroptosis, improves renal fibrosis [87]. Other studies have found that ginkgetin enhances Nrf2 expression, activates the SLC7A11/GPX4 signaling axis, thereby downregulating COX2 and 4-HNE protein levels, and preventing endothelial cells from initiating ferroptosis programs [88]. From this, it can be seen that *Ginkgobiloba* protects renal intrinsic cells and alleviates pathological changes in DKD by mediating ferroptosis.

In short, the active ingredients or extracts of traditional Chinese medicine mainly intervene in the physiological and pathological processes of oxidative stress, iron metabolism, and lipid metabolism by regulating signaling pathways such as SLC7A11/SLC3A2/GPX4, Nrf2/HO-1, ACSL4, PTGS2 and TFR1/FTH1, thereby blocking the process of ferroptosis, and further affecting DKD inflammation and fibrosis. (Table 2).

6.2. *Traditional Chinese medicine compound preparation*

Persistent inflammation of the circulatory system and renal tissue is an important pathophysiological basis for the progression of DKD. Studies have shown that pro-inflammatory factors such as IL-6, TNF-α,

Table 2
Molecular mechanism of regulating ferroptosis by traditional Chinese medicine extracts.

Name	Target	Role	Reference
Astragaloside IV	PTGS2↓, NOX2↓, NOX4↓, TGF-β1↓, Smad2↓, Smad3↓, GPX4↑, Nrf2↑	Inhibiting ferroptosis, and improving fibrosis	[71]
	miR-138↑, SIRT1↑, GPX4↑, Nrf2↑	Improving antioxidant capacity, and inhibiting ferroptosis	[72]
Astragalus polysaccharide	HO-1↑, Nrf2↑, PTGS2↓	Reducing the release of inflammatory factors, and inhibiting ferroptosis	[73]
Asiatic acid	Keap1↓, Nrf2↑, NQO1↑, GPX4↑, SLC7A11↑	Reducing oxidative damage, and inhibiting ferroptosis	[74]
	PI3K↓, AKT↓, GPX4↑	Relieving iron load, and inhibiting M1 macrophage polarization	[75]
Berberine	ACSL4↓, PTGS2↓, Nrf2↑, HO-1↑, GPX4↑	Inhibiting ferroptosis in podocyte	[41]
	GPX4↑	Reducing iron load, and regulating glucose metabolism disorders	[86]
Curcumin	TLR4↓, NF-κB↓, ERK↓, HO-1↑, Nrf2↑	Inhibiting ferroptosis in epithelial cell, and reducing inflammatory response	[76]
	Nrf2↑, HO-1↑, GPX4↑, SLC7A11↑	Reducing iron deposition, and inhibiting oxidative damage to epithelial cell	[77]
	TFR1↓, FTH1↑, GPX4↑, SLC7A11↑	Regulating iron metabolism disorder, and reducing inflammatory response	[78]
Dihydrotanshinone I	GPX4↑, HO-1↑, Nrf2↑	Protecting mitochondrial function, and inhibiting iron deposition	[62]
Ginkgetin	Nrf2↑, GPX4↑, SLC7A11↑, COX2↓, p53↓	Inhibiting lipid peroxidation, and reducing iron deposition	[88]
Ginkgolide B	TFR1↓, FTH1↑, GPX4↑	Inhibiting ferroptosis in podocyte, and improving fibrosis	[87]
ginsenoside Rg1	FSP1↑, GPX4↑	Inhibitiing ferroptosis in epithelial cell	[82]
ginsenoside Rg3	PTGS2↓, Nrf2↑, HO-1↑, GPX4↑	Reducing iron deposition, and improving oxidative stress	[81]
Glabridin	GPX4↑, SLC7A11↑, SLC3A2↑, TFR1↓, VEGF↓, Akt↓, ERK↓	Regulating glucose metabolism disorders, improving oxidative stress, and inhibiting ferroptosis	[65]
Isoliquiritigenin	HMGB1↓, NCOA4↓, GPX4↑	Maintaining mitochondrial biogenesis, and reducing lipid peroxidation damage	[64]
Leonurine	Nrf2↑, NQO1↑, HO-1↑	Inhibiting iron deposition, protecting mitochondrial function, and reducing oxidative damage	[59]
	Nrf2↑,GPX4↑, p62↑, HO-1↑	Inhibitiing ferroptosis in epithelial cell	[60]

(*continued on next page*)

Table 2 (*continued*)

Name	Target	Role	Reference
ophiopogonin D	ACSL4↓, COX2↓, NOX1↓, TFR1↓, FTH1↑, GPX4↑	Improving iron load, and reducing oxidative damage	[79]
Ophiopogon japonicus water extract	Rev-erbα↓, Rev-erbβ↓, HO-1↑, SLC7A11↑	Inhibiting ferroptosis	[80]
Quercetin	PTGS2↓, GPX4↑	Regulating glucose metabolism disorders, improving lipid peroxidation, and inhibiting iron deposition	[68]
	SLC7A11↑, SLC3A2↑, GPX4↑, ATF3↓	Inhibiting ferroptosis, and alleviating inflammatory damage	[69]
	HO-1↑, Nrf2↑, SLC7A11↑, FTH1↑, GPX4↑, TFR1↓	Improving lipid peroxidation, and inhibiting iron deposition	[70]
Resveratrol	GPX4↑, NQO1↑, Nrf2↑, FTH1↑, p53↓	Protecting mitochondrial function, reducing lipid peroxidation, and inhibiting interstitial fibrosis	[53]
	HSF1↑, GPX4↑, SLC7A11↑	Regulating iron homeostasis, and reducing cell damage	[54]
	GPX4↑, HO-1↑, Nrf2↑	Reducing oxidative damage, and inhibiting ferroptosis	[55]
	USP19↓, GPX4↑, FTH1↑	Regulating autophagy activity, and inhibiting ferroptosis	[56]
Salidroside	GPX4↑, FPN1↑, FTH1↑, ACSL4↓, TFR1↓, TGF-β1↓	Inhibiting iron deposition, and improving fibrosis	[66]
	GPX4↑, SLC7A11↑, Nrf2↑	Inhibiting ferroptosis, and alleviating inflammatory damage	[67]
Salvianolic acid B	GPX4↑, Nrf2↑	Inhibiting ferroptosis, and improving fibrosis	[63]
Saikosaponin A	GPX4↑, ACSL4↓	Improving oxidative stress, and inhibiting ferroptosis in endothelial cell	[57]
Saikosaponin B2	SLC7A11↑, FTH1↑, GPX4↑, Nrf2↑, ACSL4↓, TFR1↓, TLR4↓, NF-κB↓	Improving endoplasmic reticulum stress, reducing inflammatory factor release, and inhibiting iron deposition	[58]
Schisandrin A	TXNIP↓, NLRP3↓, AdipoR1↑, AMPK↑, Nrf2↑, HO-1↑	Reducing the release of inflammatory factors, improving oxidative stress, and inhibiting ferroptosis	[85]
Schisandrin B	Nrf2↑, HO-1↑, GPX4↑	Reducing iron deposition and oxidative damage	[83]
	ACSL4↓, GSK3β↓, TFR1↓, Nrf2↑, GPX4↑	Inhibiting lipid peroxidation, and reducing inflammatory reactions	[84]
Tanshinone IIA	SLC7A11↑, FTH1↑, GPX4↑, p53↓	Regulating lipid metabolism, and inhibiting lipid peroxidation	[61]

↑: upregulation or promotion, ↓: downregulation or inhibition

IL-1β and IL-18 levels increase with the development of the disease and are independently related to urinary albumin excretion [89,90]. Shaoyao Gancao Decoction can inhibit the release of IL-6 and TNF-α and reduce the inflammatory reaction by enhancing the expression of GPX4, destroying the ferroptosis process and reducing the production of ROS [91]. In addition, the active ingredients of Shaoyao Decoction can interact with GPX4 molecules, promote GPX4 activation, thereby reducing iron concentration, inhibiting ferroptosis, and ultimately alleviating epithelial cell inflammatory damage [92]. Another study shows that Wenqingyin can trigger a cascade reaction by activating Nrf2 signal, restore the activity of System Xc-, regulate iron metabolism disorder and inhibit the secretion of proinflammatory factors [93]. From this, it can be seen that traditional Chinese medicine prescriptions may suppress ferroptosis by regulating key signaling molecules such as GPX4 and Nrf2, thereby interfering with the cross-dialogue between ferroptosis and inflammation, and delaying the progression of DKD. The mononuclear phagocytic system is an important part of maintaining renal homeostasis, and its role can extend to the stages of renal injury and prognosis [94]. Monocyte macrophage is a member of the system. It has been found that Qingxin Jieyu Granule can activate SLC7A11/SLC3A2/GPX4 signal pathway, inhibit ferroptosis of mononuclear macrophage and improve the inflammatory state of the body [95]. Therefore, targeting ferroptosis with traditional Chinese medicine compound can maintain renal homeostasis and prevent the progressive aggravation of inflammatory damage.

Fibrosis is a progressive and irreversible pathological feature of DKD. Ferroptosis leads to persistent renal fibrosis by triggering the death of tubular epithelial cells or aggravating the damage of proximal tubular cells [40,96]. Study has found that Shenlong decoction downregulates the expression of interleukin-3 mediated nuclear factor (NFIL3), inhibits the interaction of NFIL3 and FSP1 signals, thereby reducing ferroptosis damage and inhibiting the transformation of fibroblasts into myofibroblasts [97]. In addition, Taohong Siwu Decoction can reduce the level of transferrin by regulating p53/Nrf2 signaling pathway, and then inhibit the activation of TGF-β1, down-regulate the protein expression of FN and Col-I, and relieve renal fibrosis [98]. Another study showed that Buyang Huanwu Decoction promoted the activation of SLC7A11/GPX4 pathway, down-regulated the expression of TFR1 and ACSL4 proteins, and reduced the levels of MDA, ROS and 4-HNE, which finally reduced the collagen deposition in kidney [99]. Therefore, traditional Chinese medicine compound formulations can regulate the key signal molecules such as SLC7A11/GPX4, p53/Nrf2, FSP1, ACSL4, inhibit the ferroptosis of renal intrinsic cells, and block the fibrosis process of DKD.

Mitochondrial dysfunction is an important pathogenic factor in the progression of DKD. In the course of DKD, mitochondrial damage occurs earlier than proteinuria and renal histological changes [100], and the ferroptosis program initiated by renal cells will destroy the structure and function of mitochondria [36,41,45,48]. Study has shown that Qishen Yiqi Dripping Pills can inhibit the mRNA expression of PTGS2 and ACSL4 by activating SLC7A11/GPX4 signal axis, thereby up-regulating the protein levels of mitofusin 2 (MFN2) and peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α), finally inhibiting ferroptosis, repairing mitochondrial structure and maintaining mitochondrial biogenesis [101]. Other studies have found that the Didang Decoction upregulates hypoxia inducible factor 1α (HIF-1 α), GPX4 protein expression, reduces ROS production, prevents endothelial cell ferroptosis, and reduces mitochondrial damage [102]. The above research datas indicate that traditional Chinese medicine compound formulations can inhibit mitochondrial damage induced by ferroptosis. Therefore, targeting ferroptosis to maintain mitochondrial homeostasis may be a new way for traditional Chinese medicine to prevent and treat DKD, and targeted research should be carried out in the future to explore the molecular mechanisms involved.

The disorder of lipid metabolism is not only an important pathological factor of DKD, but also a driver of ferroptosis. Wu et al.[103]. found that the Huayu Qutan Formula upregulates the expression level of GPX4, enhances System Xc- activity, inhibits liver lipid deposition, and blocks the process of ferroptosis. The research team also found that Sijunzi Decoction inhibited the expression of NADPH oxidase 1 (NOX1) and PTGS2, and increased the expression level of ferritin light chain (FTL), which ultimately reduced the level of ROS and prevented

ferroptosis induced by lipid peroxidation [104]. Another study showed that Zexie Decoction activated Nrf2/HO-1 signaling pathway, which promoted GPX4 activation, inhibited ACSL4 mRNA expression, and finally improved hyperlipidemia [105]. In addition, Jiawei Erzhi Pill promotes the activation of SLC7A11/GPX4 pathway, inhibits the expression of NOX1 and COX2, and then increases GSH content, inhibits lipid peroxidation and reduces lipid accumulation [106]. In a word, traditional Chinese medicine compound formulations can regulate lipid metabolism disorders, reduce oxidative damage, and inhibit ferroptosis. In recent years, traditional Chinese medicine research on lipid metabolism has mostly focused on the liver, neglecting the importance of lipid metabolism disorders for chronic kidney disease. Clinically, DKD patients often have dyslipidemia [107], thus, regulating lipid metabolism is indispensable in the treatment plan of DKD. In the future, it is necessary to expand the related research on regulating renal lipid by targeting ferroptosis with traditional Chinese medicine compound formulations, so as to further improve the mechanism of traditional Chinese medicine compound formulations in preventing and treating DKD.

To sum up, traditional Chinese medicine compound formulations regulate SLC7A11/SLC3A2, HIF-1/GPX4, PTGS2, ACSL4, p53/Nrf2/HO-1 and other signaling pathways to intervene in ferroptosis, thus improving the mitochondrial damage, inflammatory reaction and fibrosis of DKD kidney. (Table 3).

Table 3
Molecular mechanism of traditional Chinese medicine compound preparations regulating ferroptosis.

Prescription	Pharmaceutical ingredient	Target	Role	Reference
Buyang Huanwu decoction	Astragalus, Angelica sinensis, Red paeony root, Pheretima, Szechuan lovage rhizome, Peach seed, Safflower	TFR1↓, ACSL4↓, SLC7A11↑, GPX4↑	Regulating iron metabolism, and reducing oxidative damage	[99]
Didang decoction	Hirudo, Gadfly, Peach seed, Rhubarb	HIF-1α↑, GPX4↑	Protecting mitochondrial function, improving lipid metabolism, and inhibiting endothelial cell ferroptosis	[102]
Huayu Qutan formula	Pilose asiabell root, Gynostemma pentaphyllum, Astragalus, Poria, Turmeric root-tuber, Pinellia tuber, Salvia miltiorrhiza, Szechuan lovage rhizome, Acori tatarinowii rhizoma	p53↓, GPX4↑	Reducing lipid peroxidation, and inhibiting ferroptosis	[103]
Jiawei-Erzhi pill	Glossy privet fruit, Shorthorned epimedium herb, Ecliptae herba	SCL7A11↑, GPX4↑, FTH1↑, p53↓, COX2↓, NOX1↓	Regulating iron homeostasis, and reducing lipid peroxidation	[106]
QiShenYiQi dripping pill	Astragalus, Salvia miltiorrhiza, Notoginseng, Rosewood heart wood	PTGS2↓, ACSL4↓, SLC7A11↑, GPX4↑, Nrf1↑, PGC-1α↑	Inhibiting ferroptosis, and improving mitochondrial dynamic homeostasis and biogenesis	[101]
Qingxin Jieyu Granule	Astragalus, Salvia miltiorrhiza, Szechuan lovage rhizome, Cablin potchouli herb, Coptis root	SLC7A11↑, GPX4↑	Reducing the secretion of inflammatory factors, and inhibiting macrophage ferroptosis	[95]
Taohong Siwu decoction	Angelica sinensis, Prepared rehmannia root, Szechuan lovage rhizome, Paeoniae radix alba, Peach seed, Safflower	p53↓, p21↓, TGF-β1↓, Nrf2↑	Inhibiting ferroptosis, and improving fibrosis	[98]
Sijunzi decoction	Ginseng, Largehead atractylodes rhizome, Poria, Radix glycyrrhizae preparata	FTL↑, p53↓, PTGS2↓, NOX1↓	Regulating lipid metabolism disorders, and inhibiting ferroptosis	[104]
Shenlong decoction	Astragalus, Adenophora stricta, Angelica sinensis, Szechuan lovage rhizome, Prepared rehmannia root, Pheretima,	NFIL3↓	Preventing excessive cell ferroptosis, and inhibiting fibroblast myofibroblast transformation	[97]

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7. Traditional Chinese medicine external treatment

7.1. Acupuncture

Acupuncture is one of the main means of external treatment of traditional Chinese medicine. Electroacupuncture therapy is a combination of traditional acupuncture and modern electrical stimulation, which can continuously stimulate acupoints and be used to treat various acute and chronic diseases. Recent study has shown that selecting acupoints such as Zhongwan, Xuehai, Taichong, Guanyuan, and Zusanli for electroacupuncture treatment can effectively improve renal function and alleviate microcirculation disorders in early DKD patients [108]. Li et al.[109]. found that electroacupuncture stimulation of acupoints (Baihui, Shuigou, bilateral Sanyinjiao, bilateral Neiguan) can regulate the TFR1/FTH1 signaling axis, promote GPX4 activation, upregulate SOD and GSH levels, ultimately protect mitochondrial structure and function, and prevent oxidative stress induced ferroptosis. In addition, electroacupuncture stimulation of bilateral Zusanli acupoints can activate the SLC7A11/GPX4 signaling pathway, upregulate FTH1 expression levels, reduce Fe^{2+} and ROS accumulation, inhibit epithelial cell ferroptosis, and alleviate inflammatory reactions [110]. To sum up, electroacupuncture therapy can regulate amino acid and iron metabolism disorder, reduce lipid peroxidation damage, and is expected to become an important therapeutic means to prevent and treat DKD by targeting ferroptosis.

7.2. Moxibustion

Moxibustion is the heat generated by Chinese medicine *Artemisia argyi* leaves to stimulate acupuncture points or specific parts of the human body, and adjust the disordered physiological functions of the human body by stimulating the activity of qi in meridians, so as to achieve the purpose of preventing and treating diseases. Moxibustion of acupoints (Shenshu, Pishu, Guanyuan, Zusanli and Sanyinjiao) can regulate renal hemodynamics, improve blood lipid abnormalities in patients, and protect residual renal function [111,112]. In addition, moxibustion on Shenshu acupoint can also reduce transferrin levels, relieve proteinuria, and curb renal fibrosis [113]. Another study shows that moxibustion at Shenshu and Zusanli can enhance the expression of p53, promote the activation of SLC7A11/GPX4 pathway, reduce the level of ROS, and finally inhibit ferroptosis and alleviate inflammatory damage [114].

Table 3 (*continued*)

Prescription	Pharmaceutical ingredient	Target	Role	Reference
	Licorice and so on			
Shaoyao Gancao decoction	Paeoniae radix alba, Radix glycyrrhizae preparata	GPX4↑	Reducing inflammatory reactions and oxidative damage, and inhibiting ferroptosis	[91]
Shaoyao decoction	Paeoniae radix alba, Betelnut, Rhubarb, Baikal skullcap root, Coptis root, Angelica sinensis, Cinnamon, Licorice, Costus root	GPX4↑	Inhibiting iron accumulation and alleviating epithelial inflammatory damage	[92]
Wenqingyin	Coptis root, Amur corktree bark, Baikal skullcap root, Gardenia, Prepared rehmannia root, Angelica sinensis, Szechuan lovage rhizome, Paeoniae radix alba	Nrf2↑, SLC7A11↑, HO-1↑, GPX4↑	Regulating iron metabolism disorder, and reducing inflammatory response	[93]
Zexie decoction	Oriental waterplantain rhizome, Largehead atractylodes rhizome,	Nrf2↑, HO-1↑, GPX4↑, CoQ10↑, ACSL4↓	Improving oxidative stress, and inhibiting ferroptosis	[105]

↑: upregulation or promotion, ↓: downregulation or inhibition

Although the above studies have shown that acupuncture and moxibustion may delay the process of DKD by interfering with ferroptosis, there are many external treatment methods in traditional Chinese medicine, besides the above two methods, there are acupoint massage, herbal fumigation, Chinese herb acupoint application, umbilical therapy, acupoint catgut embedding, medicinal thread moxibustion, auricular points plaster therapy and so on. Clinical studies have shown that the combination of oral administration of drugs and external treatment of traditional Chinese medicine or a variety of external treatment methods can better improve the renal function of patients [115–117], thus, the basic research on external treatment of traditional Chinese medicine can not be ignored. Exploring the molecular mechanism of external treatment of traditional Chinese medicine targeting ferroptosis to intervene renal lesions in DKD can provide a new scheme for global prevention and treatment of DKD.

8. Conclusion

Ferroptosis, as a new form of cell death, has become a research hotspot in the field of kidney diseases in recent years. Throughout the above research, ferroptosis plays an important role in the occurrence and development of DKD, which can form cross-talk with pathophysiological processes such as fibrosis, AGEs, inflammation, oxidative stress, glucose metabolism disorder, and jointly promote the disease process.

Traditional Chinese medicine has a long history. According to existing literature research, traditional Chinese medicine can activate the SLC7A11/SLC3A2/GPX4, Nrf2/HO-1, HIF-1 signaling pathways, or inhibit the activation of ACSL4, PTGS2, TFR1, thereby disrupting the ferroptosis process. Not only that, traditional Chinese medicine can also block signal transduction such as TLR4/NF-κB, PI3K/AKT, thereby intervening its in signal crosstalk with ferroptosis regulatory factors and inhibiting the process of ferroptosis. Therefore, traditional Chinese medicine can regulate ferroptosis through multiple pathways and further affect pathological changes such as fibrosis, inflammation, and oxidative damage, delaying the progression of DKD. However, there are still many shortcomings in the study of targeted ferroptosis prevention and treatment of DKD by traditional Chinese medicine. First, most of the existing research is basic research, and the research object is limited to cells and animals, lacking clinical verification. Secondly, the research on traditional Chinese medicine is mostly limited to the treatment of single traditional Chinese medicine or extract, and there are few studies on traditional Chinese medicine compound prescriptions, proprietary Chinese medicines and external treatment methods of traditional Chinese medicine. Thirdly, most studies only explore the molecular mechanism of ferroptosis regulated by traditional Chinese medicine through a single way, without considering the cross dialogue of multiple signal pathways. Finally, traditional Chinese medicine intervention in ferroptosis affects renal lesions, mainly focusing on fibrosis and inflammation, without exploring aspects such as AGEs, glucose metabolism disorders, autophagy, endoplasmic reticulum stress and so on.

In the future, we should combine the clinical practice of traditional Chinese medicine with basic research, and explore the molecular mechanism of traditional Chinese medicine regulating ferroptosis from multiple channels and angles. In addition, we should dig deep into the traditional Chinese medicine compound prescriptions, proprietary Chinese medicines and external treatment of traditional Chinese medicine with remarkable clinical effects, and explore the specific mechanism of preventing and treating DKD by targeting ferroptosis, so as to provide new schemes and new ideas for the clinical treatment of DKD.

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CRediT authorship contribution statement

Wang Huiling: Writing – review & editing. **Zhang Zechao:** Writing – review & editing. **Xu Yitan:** Writing – review & editing. **Shen Xiaonan:** Writing – review & editing. **Chen Yu:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Qin Ting:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Huang Guodong:** Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

All authors have agreed to submit and publish this manuscript. The author of the thesis guarantees that there is no dispute about the signature of the manuscript. If there is any dispute about the signature, the author shall bear the responsibility. The author guarantees that the manuscript is original, and there is no problem of one manuscript being delivered to multiple journals at the same time. No conflict of interest exits in the submission of this manuscript by all authors for publication.

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