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Fucoidan attenuated diabetic kidney disease through liver-kidney crosstalk based on CXCL1

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ABSTRACT: As a major microvascular complication of diabetes, the incidence of diabetic kidney disease (DKD) is increasing progressively, especially in the elderly. Early intervention is essential for the prevention and treatment of DKD. Organ crosstalk has a strong association in the progression of DKD, while C-X-C motif chemokine ligand 1 (CXCL1), a chemokine plays a critical role in the liver-kidney axis. Our previous studies found that fucoidan interventions prevented the progression of long-term high-fat diet-induced DKD, while also improving liver damage. However, the precise mechanisms through which fucoidan influences CXCL1 associated with liver-kidney crosstalk in DKD are not yet fully understood. The purpose of this study was to investigate the possible mechanism of fucoidan on the high-fat diet-induced DKD. Sixty male C57BL/6J mice were randomly divided into control, DKD, metformin (MET), low dose fucoidan (LFC, 50 mg/kg/d), middle dose fucoidan (MFC, 100 mg/kg/d), and high dose fucoidan (HFC, 200 mg/kg/d) groups for 24 weeks. Compared to the DKD group, HFC significantly reduced the urine creatinine ((555.06 ± 87.67) μg/L vs. (429.62 ± 33.29) μg/L; $P < 0.05$) and glomerular hypertrophy ((61.46 ± 4.54) mmol/L vs. 54.86±2.66 mmol/L; $P < 0.05$). Moreover, HFC treatment significantly reduced the CXCL1 level in the liver ((37.51 ± 6.70) pg/ng prot vs. (63.64 ± 7.15) pg/ng prot; $P < 0.05$) and kidney ((38.77 ± 8.55) pg/ng prot vs. (56.76 ± 7.50) pg/ng prot; $P < 0.05$) compared to the DKD group. Fucoidan treatment inhibited macrophage recruitment ($P < 0.05$) and modulated the expression of IL-6 and TNF-α in the kidney of DKD mice. Moreover, the expression of cyclic GMP-AMP synthase, stimulator of interferon genes, and nuclear factor kappa-B in the HFC group was significantly lower compared with the DKD group. Collectively, these findings suggest that fucoidan exerts a protective effect against DKD induced by a high-fat diet through the crosstalk between the liver and kidney, based on CXCL1.

Keywords: Fucoidan, diabetic kidney disease, liver-kidney crosstalk, CXCL1

1. Introduction

Diabetic kidney disease (DKD) is one of the most frequent microvascular complications in both type 1 and type 2 diabetic patients. It is the leading cause of end-stage renal disease worldwide. Among patients with

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type 2 diabetes, approximately 40% develop DKD. DKD is more prevalent in elderly patients (≥60 years or ≥65 years) and is positively correlated with age[1]. There are five stages in the clinical stage of DKD and early intervention (I, II, and III stage)[2]. The disease will progress rapidly and become irreversible damage when diabetic kidney disease exceeds stage III. Therefore, early intervention is clinically valuable for preventing the risk of progression of DKD.

Recently, communication between organs has gradually become a new focus in the pathogenesis and progression of DKD. Liver secretes a series of hepatokines that affect other organs and human homeostasis[3]. It has been found that hepatic failure results in renal failure, and vice versa, kidney dysfunction leads to hepatic dyslipidemia[4-6]. Type 2 diabetes is often accompanied by lipid accumulation, further promoting the progression of chronic kidney disease[7]. Lipid accumulation in NAFLD aggravates hypertension, insulin resistance, and visceral obesity, which are associated with the progression of chronic kidney disease[8]. However, low-grade systemic inflammation is one of the contributing factors to CKD associated with fatty liver[7]. The role of hepatokines related to inflammation in liver-kidney crosstalk and DKD pathogenesis is rarely reported.

Human and mouse studies have demonstrated the accumulation of inflammatory cells in DKD[9-10], which further leads to renal inflammation and accelerates the development of DKD[11]. Chronic inflammation is responsible for the development of kidney injury[12]. It has been reported that interleukin 6, tumor necrosis factor alpha, and monocyte chemoattractant protein 1 exacerbate the progression of DKD. Moreover, chemokines and their receptors have a vital role in regulating immune cell infiltration and the inflammatory response. Therefore, targeting inflammatory cells, inflammatory cytokines, or chemokines would be a potential treatment for DKD. CXCL1 is a chemokine related to the inflammatory response, which plays a critical role in the crosstalk between the kidney and colon[13]. High-fat diets with excessive amounts of fat and simple sugars can lead to the release of CXCL1 and cause liver inflammation[14]. The increased CXCL1 content in hepatocytes promotes CXCL1 expression in tubular cells, which contributes to inflammation and cell infiltration in the kidney[15]. Renal function could be improved by suppressing the expression of CXCL1[16]. However, the role of CXCL1 in the crosstalk between the liver and kidney in DKD is still unclear.

Because of their low toxicity and side effects, as well as their clear medicinal effects, food and medicinal homological resources have been widely used in disease prevention and control in recent years [17-19]. Fucoidan is mainly composed of fucose and sulfate residues, which have a potential effect on systemic inflammation, gut microbiota, and glycolipid metabolism without any side effects[20]. In 2003, "Haikun Shenxi Capsule (Z20030052), mainly composed of fucoidan, was approved for the treatment of kidney. Therefore, fucoidan may have the potential to improve diabetic nephropathy. Recently, fucoidan from kelp was shown to attenuate streptozotocin-induced DKD in mice model [21]. However, streptozotocin destroys pancreatic B cells to indue diabetes mellitus[22], which is different from the pathogenesis of real type 2 diabetes. In our previous study, fucoidan treatment improved the DKD induced by a long-term high-fat diet[23]. Meanwhile, fucoidan treatment also suppressed liver injury in DKD mice[24]. The role of organ

crosstalk plays a crucial role in the progression of disease. It is unknown whether fucoidan affects the crosstalk between the liver and kidney and improves DKD. Therefore, the purpose of this study is to investigate the effect of fucoidan on the crosstalk between the liver and kidney in DKD mice and determine its potential mechanism. We explored the expression of CXCL1 in the liver and kidney as well as kidney function, to investigate the relationship between CXCL1 and kidney function after fucoidan treatment. Additionally, the protein expression related to CXCL1 in the liver and the infiltration of inflammatory cells in the kidney reveal the role of CXCL1 in the liver-kidney axis. This finding might offer a novel and efficacious approach to preventing chronic kidney disease induced by type 2 diabetes.

2. Materials and methods

2.1 Materials

Fucoidan powder with a molecular weight of 200-260 kDa was obtained from Qingdao Brightmoon Seaweed Group Co., Ltd (Qingdao, Shandong Province, China). Before the formal experiment, we characterize the raw materials. Results showed that the fucoidan mainly consists of L-fucose (22.66%), organic SO_4^{2-} (29.65%), galactose (17.62%), D-glucuronic acid (2.01%), mannose (0.66%), rhamnose (0.46%), and D-glucose (0.36%)). Carboxymethylcellulose sodium (CMC-Na) was obtained from Macklin Biochemical Co., Ltd. (Shanghai, China). Metformin was obtained from Beijing Solarbio Science & Technology Co., Ltd. (Beijing, China).

2.2 Animal experiments

Sixty 8-week-old male C57BL/6J mice were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd (Beijing, China). After one week of acclimatization, they were randomly divided into six groups. Mice in the normal control group were fed the standard diet (D12450J) and received a 0.5% CMC-Na solution by intragastric gavage. Mice in the model, positive, low dose fucoidan, middle dose fucoidan, and high dose fucoidan groups were given the high fat diet (D12492) and fed with 0.5% CMC-Na solution, 150 mg/kg/d metformin, 50 mg/kg/d, 100 mg/kg/d, 200 mg/kg/d for 24 weeks.

2.3 Measurement of oral glucose tolerance test and insulin tolerance

At the 24th week, the fasting blood glucose was measured after fasting for 8 hours. Blood glucose concentrations were tested after 30, 60, and 120 min of intragastric administration of a 50% glucose solution.

Fasting insulin was measured using an ELISA kit (Boster biological technology Co., Ltd., Wuhan, China). HOMA-IR was calculated by using Eq. (1):

$$\text{HOMA-IR} = \textit{fasting blood glucose level (mmol/L)} \times \textit{fasting insulin level (}\mu\textit{U/mL)}/22.5 \quad (1)$$

For the insulin tolerance test (ITT), blood glucose concentrations were tested after 30, 60, and 120 min of intragastric administration of insulin (0.5 U/kg of BW).

2.4 Measurement of biochemical indices in serum, tissues, and urine

The levels of lipopolysaccharides (LPS), CXCL1, IL-6 and IL-1β in serum or tissues (liver and kidney) were measured using commercial kits (Nanjing Jiancheng Technology Co., Ltd., Nanjing, Jiangsu, China).

The tissues were melted in RIPA lysis buffer with a phosphatase inhibitor, and then the protein concentration was determined using a BCA assay kit (Beyotime Biotechnology Industry, Shanghai, China). Urine creatinine was assayed according to the instructions of the Cr Assay kit (Nanjing Jiancheng Technology Co., Ltd., Nanjing, China).

2.5 Measurement of glomerular filtration rate

At the 22th week, the glomerular filtration rate (GFR) of DKD mice was determined using a fluorescence ratio assay according to a previous study[23]. Mice were anesthetized, fixed, and then had the hair on their back removed. The transdermal mini GFR monitor (Medibeacon, Germany) was fixed to the mice's back without hair. Then, fluorescent-labeled pharmaceutical ingredient (FITC-sinistrin) was injected via the tail vein after 2-5 min rest baseline period. The excretion kinetics of FITC-sinistin were recorded for 120 min and then the GFR was obtained.

2.6 Histological staining and immunohistochemistry

Renal tissues were paraffin-embedded and sliced into 5 μm sections, and then stained with hematoxylin and eosin, which were used to observe the kidney morphology. Staining for macrophages was performed on 7 μm paraffin-embedded sections. After blocking with horse serum, the primary antibody, rat anti-mouse F4/80 (70076T, 1:200, Cell Signaling Technology, Inc, USA) was applied and incubated for 60 min, It was then incubated with the secondary antibody biotinylated anti-rat IgG. Macrophage staining was determined using ImageJ.

2.7 Western blot analysis

The protein extracted from the kidney was quantified and used for western blot. The western blot was used in the method of a previous study. In this experiment, 8% separation gel and 10% stacking gel were applied for the separation of target protein. After transferring, PVDF membranes (0.45 μm) ware sealed using 5% BSA for 2 h, which then incubated with cGAS (31659S, 1:1000, Cell Signaling Technology, Inc, USA) or STING (13647S, 1:1000, CST, USA) at 4 ºC overnight.

2.8 Quantitative real-time Polymerase Chain Reaction

Total RNA from the liver and kidney were extracted using mixture solution (600 μL of trizol, 320 μL of isopropanol, 150 μL of chloroform, and 600 μL of 75% ethanol). The mRNA expression levels of TLR4 and CXCR2 were detected by real-time PCR using the specific primers.

2.9 Statistical analysis

All experimental data were analyzed using one-way ANOVA followed by Duncan's post hoc test (IBM SPSS Statistics 20). The results were expressed as mean ± standard deviations and two-sided P value < 0.05 was considered significant.

3. Results

3.1 Fucoidan improved the glucose metabolism

After an oral high-fat diet, the body weight significantly increased ($P < 0.05$). The body weight in the DKD group showed the highest value, whereas fucoidan treatment inhibited the increase in body weight (Fig. 1a). Additionally, there was no statistical difference in food intake between the DKD and fucoidan intervention groups ($P > 0.05$). This suggests that fucoidan does not affect body weight, regardless of food intake. Moreover, the renal organ index increased after a high-fat diet, while the middle dose and high dose of fucoidan reversed it (Fig. 1b). The fasting blood glucose in the DKD group was significantly increased compared to that of the control group. In contrast, HFC treatment inhibited the fasting blood glucose level (Fig. 1c). In addition, the fasting insulin levels in the DKD group were significantly higher than those in the control group (Fig.1d). Similarly, MFC and HFC significantly decreased fasting insulin and HOMA-IR compared with the DKD group (Fig. 1e). Compared with the DKD group, the OGTT in the HFC group was markedly decreased ($P < 0.05$) (Fig. 1f). There was no significant difference observed between the DKD and fucoidan treatment groups. Moreover, the ITT level in the DKD group was markedly higher than that in the control group, whereas fucoidan administration reversed this trend (Fig. 1g). Finally, fucoidan-treated mice did not have any side effects. Overall, these results indicate that fucoidan improves body weight and glucose intolerance in diabetic mice.

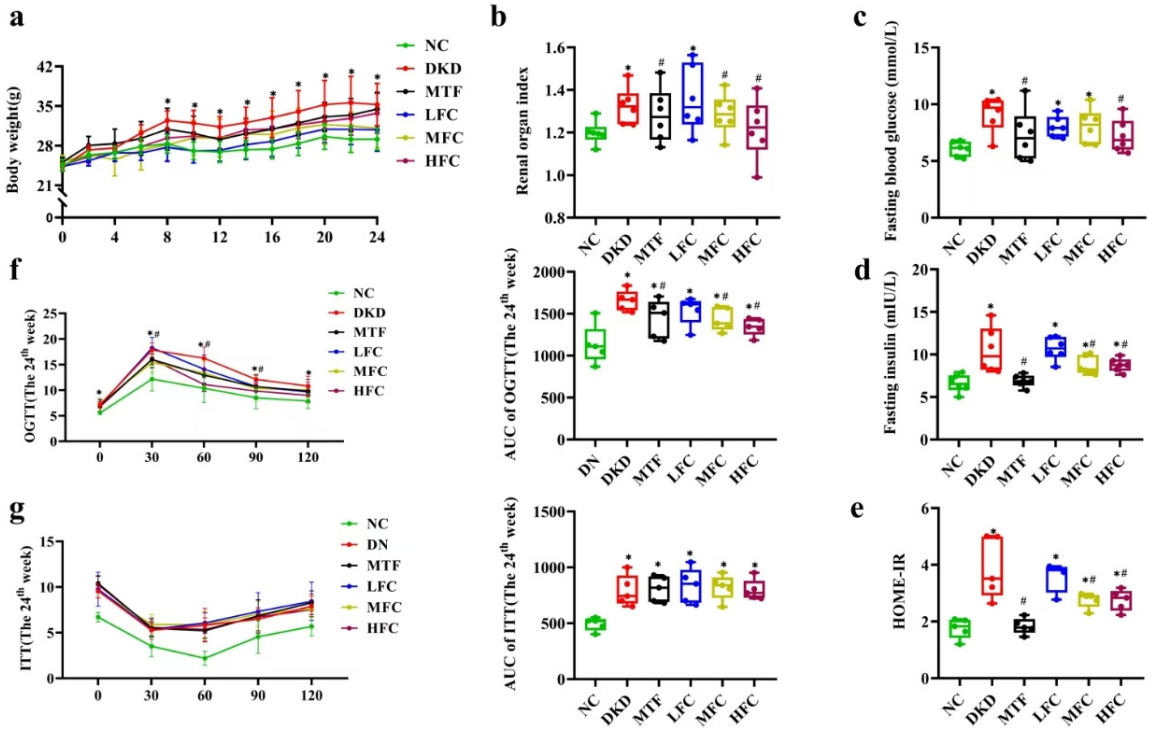

Fig. 1 The effect of fucoidan on body weight (a), renal organ index (b), fasting blood glucose (c), fast insulin (d), HOMA-IR (e), oral glucose tolerance test (OGTT) and AUC of OGTT (f), insulin tolerance test (ITT) and AUC of ITT (g). Data are presented ad mean ± SD (n ≥ 6), *$P < 0.05$ as compared with the CN group; #$P < 0.05$ as compared with the DKD group.

3.2 Fucoidan attenuated renal injury

As shown in Fig. 2a and b, the GFR and the level of urine creatinine were significantly increased in the DKD group compared to the control group. Moreover, there was no statistical difference between the DKD group and the control group in urinary albumin level (Fig. 2c). These results suggest that the mice were in the

first stage of DKD[2]. Fucoidan treatment inhibited the increased GFR and creatinine, indicating that fucoidan could ameliorate kidney injury induced by DKD. To further assess the effect of fucoidan on kidney function in mice, histologic examination was investigated. Renal dysfunction was correlated with structural changes in the kidney such as glomerular hypertrophy. Compared to the control group, glomerular hypertrophy occurred in the DKD group (Fig. 2d). However, fucoidan prevented glomerular hypertrophy induced in mice with diabetic nephropathy. Fucoidan-treated mice in the MFC and HFC groups showed a marked reduction in glomerular volume compared with the DKD group. Furthermore, inflammatory infiltration in the kidney tissues was observed in the DKD group. These results indicate that fucoidan could improve high- fat diet-induced DKD.

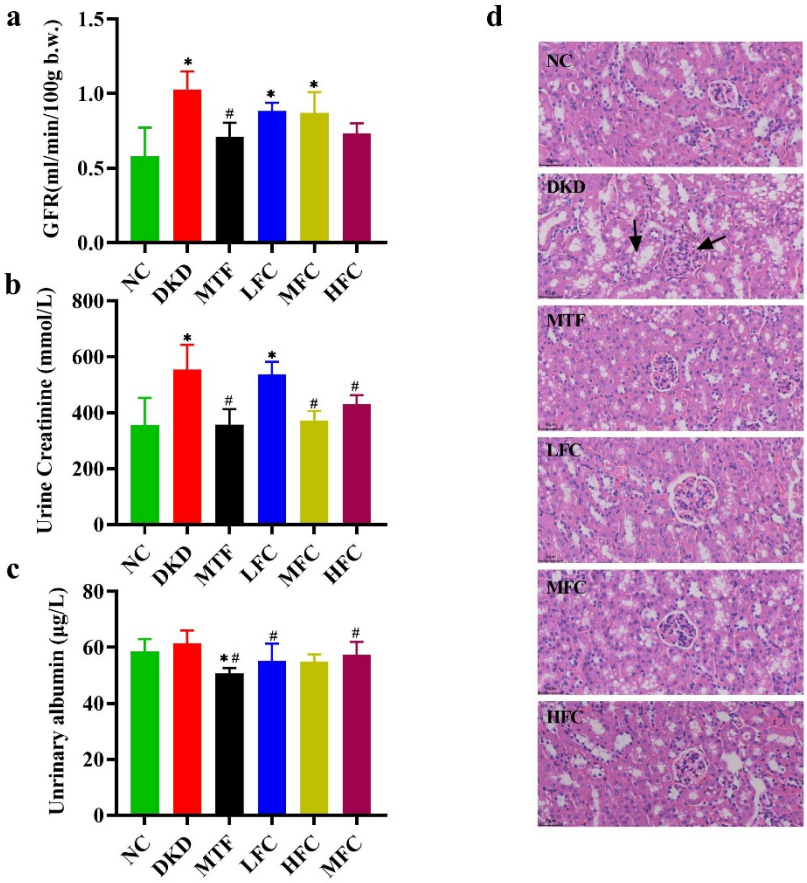

Fig. 2 Fucoidan improved kidney function. (a) Glomerular filtration rate (GFR) (n ≥ 3). (b) Levels of urine albumin (n = 6). (c) Levels of urine creatinine (n = 6). (d) Representative images of kidney tissues (n = 3). Data are presented ad mean ± SD, *P < 0.05 as compared with the CN group; #P < 0.05 as compared with the DKD group.

3.3 Fucoidan ameliorated liver injury

The presence of liver injury in diabetic patients is appreciated with a high incidence rate[25]. To evaluate liver damage in diabetic mice, HE stains, and liver function index were examined. As shown in Fig. 3a, the liver tissue in the control group is intact and the cells are densely arranged, whereas the hepatocytes in the DKD group are relatively loosely arranged. MFC and HFC treatments improved the morphology of liver tissue. Furthermore, the levels of ALT and AST in the serum of diabetic mice were significantly increased(P < 0.05). However, treatment with MFC and HFC restored these parameters (Fig. 3b and c).

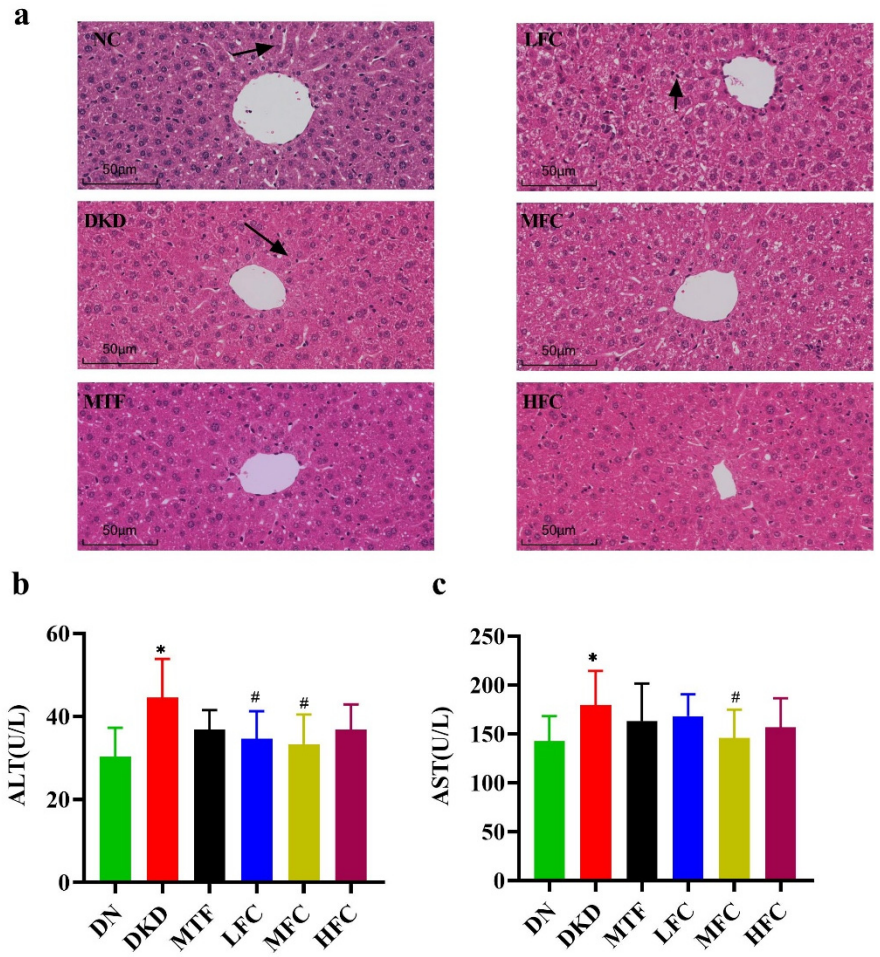

Fig. 3 Fucoidan improved liver function. (a) Representative histological staining of liver tissues (n = 3). (b) Levels of alanine aminotransferase (ALT) (n = 6). (c) Levels of aspartate transaminase (AST) (n = 6). Data are presented ad mean ± SD, *P < 0.05 as compared with the CN group; #P < 0.05 as compared with the DKD group.

3.4 Fucoidan improved the gut barrier and CXCL1 in liver

Intestinal barrier integrity is a vital factor for various metabolic diseases[7]. DKD is always accompanied by gut dysbiotic microbiota and metabolic disorders. Thus, we investigate the level of LPS that reflects the integrity of the intestinal barrier. Compared with the control group, the LPS level was significantly increased in diabetic mice (Fig. 4a). After fucoidan administration, the LPS level was inhibited, especially in the HFC group (P < 0.05). The result suggests that fucoidan protects the gut barrier function. Moreover, LPS derived from Gram-negative bacteria arrives at the liver, which could result in liver injury. High systemic LPS level could influence liver metabolites depending on its receptor (Toll-like receptor 4, TLR4). In the study, the expression level of TLR4 in the DKD group was obviously higher than that in the control group (Fig. 4b). In contrast, high-dose fucoidan treatment decreased the expression of TLR4 compared to the DKD group. Previous study has reported that LPS could upregulate CXCL1 expression through TLR4 in the liver[26]. As depicted in Fig. 4c, the expression of CXCL1 in the liver of the DKD group was significantly increased (P < 0.05), whereas the change was inhibited after fucoidan treatment. Fucoidan administration decreased the CXCL1 level in diabetic kidney disease mice.

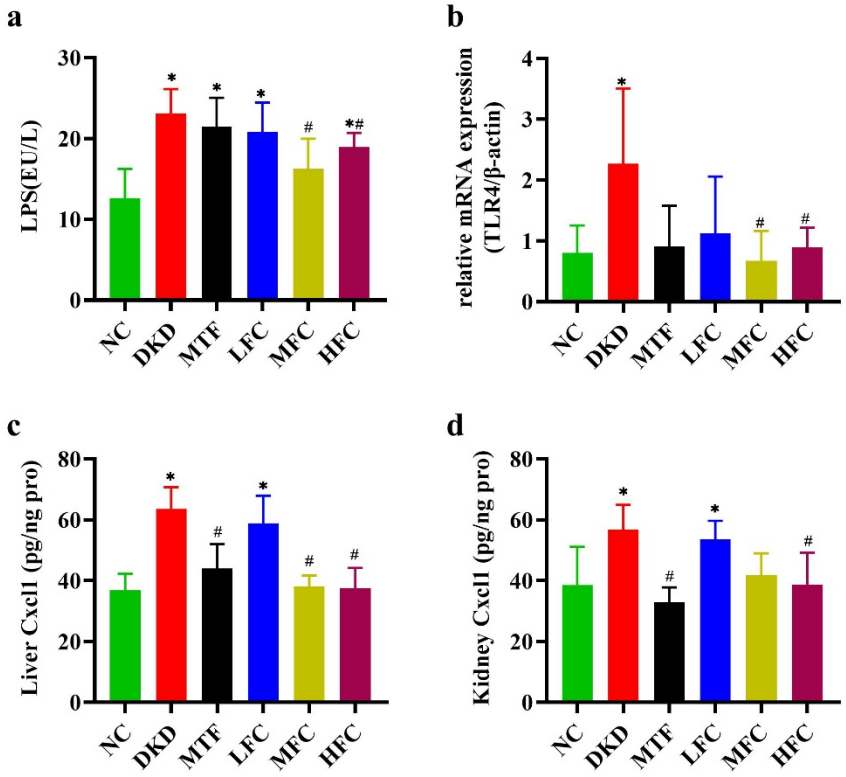

Fig. 4 The effect of fucoidan on serum LPS (a), relative expression of TLR4 in liver (b), CXCL1 (c), renal CXCL1 (d) (n = 6). Data are presented ad mean ± SD, **P* < 0.05 as compared with the CN group; #*P* < 0.05 as compared with the DKD group.

3.5 Fucoidan decreased macrophage infiltration and CXCL1 in kidney

It has been reported that the "liver-kidney axis" controls liver and kidney pathology. CXCL1 is crucial for recruiting immune cells, making it a crucial endocrine to affect the crosstalk between organs. To find the relationship between the liver and kidney, the levels of CXCL1 in the liver, CXCL1 and its receptor (CXCR2) in the kidney and macrophages in the kidney were tested. As shown in Fig. 4c, the liver CXCL1 level in diabetic mice was significantly enhanced compared with the mice of the control group, while fucoidan supplementation obviously reversed the trend ($P < 0.05$). In addition, fucoidan supplementation markedly decreased the expression of the CXCL1 receptor (CXCR2) in kidney (Fig. 5c). Similarly, the levels of renal CXCL1 in diabetic mice were obviously suppressed after fucoidan treatment (Fig. 4d). Moreover, a high level of macrophages was observed in diabetic mice compared to the mice in the control group. However, fucoidan reduced the level of macrophages (Fig. 5). Macrophages are strongly associated with immune response and disease progression[27]. These results suggest that fucoidan treatment ameliorates the macrophage recruitment in the kidney by inhibiting the CXCL1 levels.

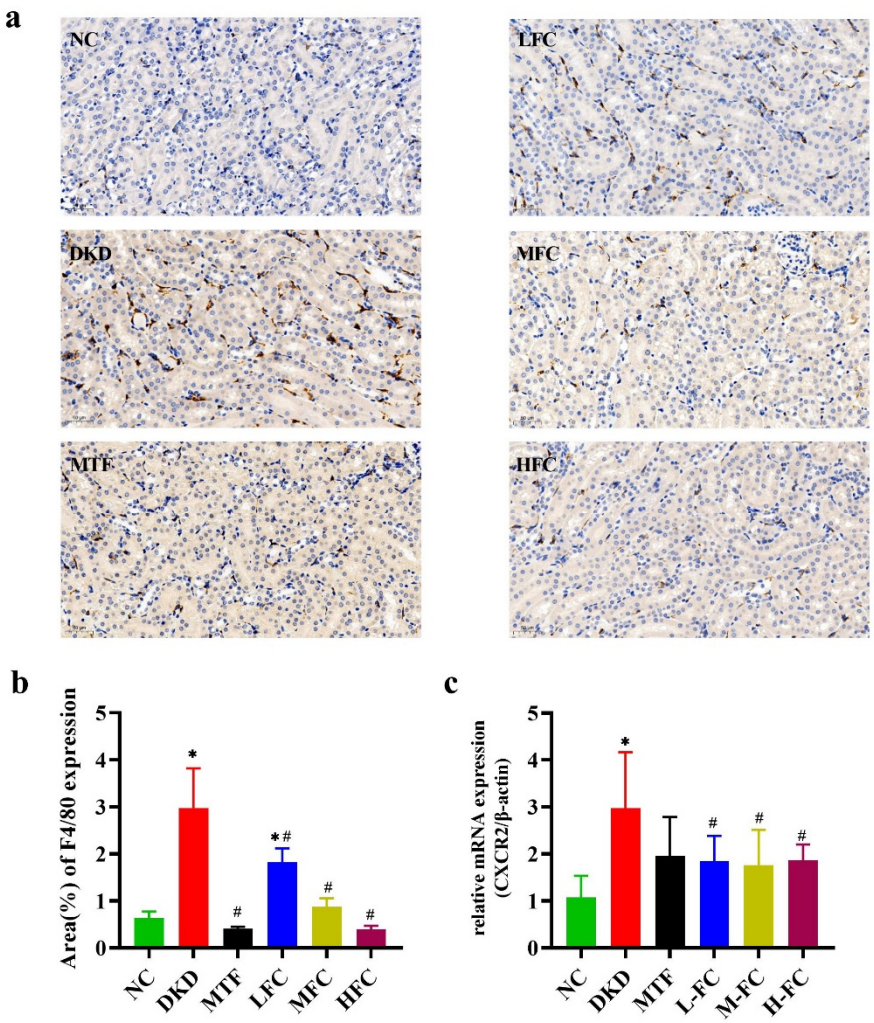

Fig. 5 (a-b) Immunohistochemical staining of macrophage makers in kidney tissues (n=3). (c) qRT-PCR examination of CXCR2 expression in kidney tissues (n=6). Data are presented ad mean ± SD, **P* < 0.05 as compared with the CN group; #*P* < 0.05 as compared with the DKD group.

3.6 Effect of fucoidan supplementation on inflammatory responses

To further explore the impact of fucoidan on inflammation responses, the cGAS-STING pathway was analyzed in the present study. As depicted in Fig. 6a, the mice with fucoidan treatment notably inhibited the expression of cGAS and STING, while it further inhibited the p-NF-*k*B/NF-*k*B compared with diabetic mice. We also investigated the level of IL-6 and IL-1β before and after fucoidan treatment. IL-6 and IL-1β were significantly elevated in renal tissues derived from diabetic mice. In contrast, fucoidan supplementation reduced the expression of IL-6 and IL-1β (Fig. 6b). Low-grade and chronic systemic inflammation is the major contributing factor to the pathogenesis of diabetic kidney disease.

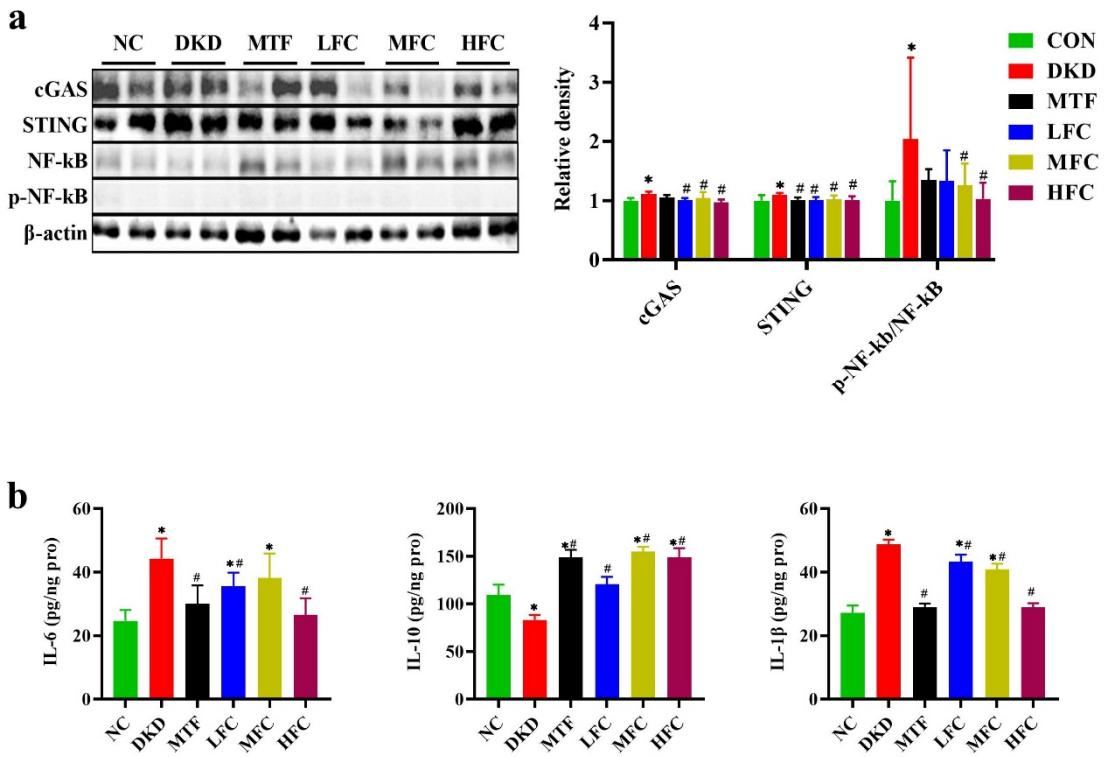

Fig. 6. Fucoidan alter inflammation response and its pathway. (a) Weatern blot results and density analysisof cGAS, Sting, pNFκB and NFκB (n = 4). (b) Levels of IL-6, IL-10 and IL-1β (n = 6). Data are presented ad mean ± SD, **P* < 0.05as compared with the CN group; #*P* < 0.05 as compared with the DKD group.

4. Discussion

Fucoidan, mainly composed of fucose residues and sulfate residues, has a potential effect on systemic inflammation, gut microbiota, and glycolipid metabolism without side effects[20]. Moreover, "Haikun Shenxi Capsule (Z20030052), mainly composed of fucoidan, was approved for the treatment of kidney. These studies imply that fucoidan has a potential therapeutic effect on kidney injury. In our study, we investigated the effect and potential mechanism of fucoidan on DKD induced by a long-term high-fat diet. Fucoidan treatment downregulated the serum LPS level and TLR4-dependent CXCL1 expression in the liver of diabetic mice. Subsequent CXCL1 expression in the kidney was significantly blocked after fucoidan administration. Moreover, the fucoidan supplement effectively inhibited the renal macrophage activation and cGAS-STING pathway. Based on all of the above results, fucoidan supplementation effectively improved diabetic kidney disease.

Previous studies have revealed that the crosstalk between organs is crucial for the function of the kidney. Most of these studies focus on how the gut-kidney axis improves kidney injury. Bacteria and bacterial product translocation resulted in systemic inflammation and kidney injury [28-29]. However, the liver secretes a series of hepatokines that affect other organs and human homeostasis[3]. The role of liver injury in diabetic kidney disease is rarely reported. Previous studies revealed the crosstalk between the liver and kidney organs via endocrine signaling. For instance, lipid accumulation in NAFLD can exacerbate hypertension, insulin resistance, and inflammation, potentially leading to the development of chronic kidney disease[8]. In addition, pro-inflammatory, pro-thrombotic, and profibrogenic factors in NAFLD might contribute to renal damage [30].

Till now, there is limited knowledge on the role of the liver-kidney axis in improving kidney function in DKD. In the present study, we found that a high-fat diet-induced DKD was accompanied by liver damage, and fucoidan treatment could restore it. Thus, we studied how fucoidan modulates the gut-liver-kidney axis to attenuate diabetic kidney disease. In the research, fucoidan administration decreased the serum LPS derived from Gram-negative bacteria. Bacteria-derived LPS was delivered to the liver and could stimulate TLR4 in macrophages to induce proinflammatory cytokines, which played a vital role in immune activation[31]. We discovered that the expression of TLR4 in the liver was notably diminished, accompanied by a decrease in blood LPS after fucoidan supplementation. Activation of TLR4 can lead to an abnormal immune response accompanied by excessive production of chemokines such as CXCL1, that exacerbate inflammatory responses[26]. In our research, fucoidan treatment reduced the level of CXCL1. CXCL1 is an important factor in organ crosstalk, which establishes a directed migration signaling network between different tissues through the secretion-receptor mechanism[32]. However, it remains unclear whether fucoidan improves DKD through the CXCL1-mediated hepatorenal axis. Therefore, we further analyzed the levels of CXCL1 and its receptor CXCR2 in the kidney. Consistently, our results confirmed that CXCL1 and CXCR2 were highly expressed in the kidney (Fig. 5c). These findings suggest that CXCL1 may have an important role in the fucoidan-mediated improvement of DKD in the liver-kidney axis.

Studies have shown that CXCL1 is involved in the inflammatory response by binding to CXCR2, which recruits macrophages [33]. In our research, fucoidan treatment reduced the level of CXCL1 in the liver, while fucoidan treatment decreased the expression of the CXCL1 receptor-CXCR2 and the macrophage infiltration in the kidney. Macrophage infiltration amplifies the inflammatory response through the NF-κB pathway [34-35]. Previous study has reported that fucoidan inhibits the release of pro-inflammatory cytokines by via modulating NF-κB and MAPK signaling[36]. Meanwhile, Jayasinghe et al. showed that fucoidan activates the PI3K/AKT/Nrf2 pathway and indirectly inhibits the inflammatory response of NF-κB through the antioxidant effect of Nrf2[37]. Therefore, we investigated the levels of NF-κB and the pro-inflammatory cytokines. The results showed that fucoidan treatment reduced the expression of NF-κB and pro-inflammatory cytokines in the kidney. Interestingly, recent studies show a strong relationship between STING activity and DKD, which is the upstream pathway of NF-κB. The cGAS/STING pathway was upregulated in the kidneys of humans and rats with type 2 diabetic kidney disease, with a more pronounced effect in older rats [38]. One human study found that substantial activity of fucoidan was observed in the liver, and low activity (< 5%) was observed in other organs[39], implying that fucoidan does not reach the kidney to perform its active functions. Thus, we deduced that fucoidan indirectly regulates the cGAS-STING-NF-κB pathway to alleviate DKD. Previous studies have reported that macrophage infiltration is closely related to renal cell damage[35]. In DKD and obesity-associated nephropathy, renal cell damage leads to an increased in mitochondrial membrane permeability and the leakage of mtDNA into the cytoplasm via Bcl-2-associated X protein[40]. MTDNA is efficiently recognized by cGAS because of its double-stranded structure, and cGAS binds to mtDNA through its N-terminal DNA-binding domain to form cGAMP[41]. The generated cGAMP binds to the STING protein,

triggers the TBK1-IRF3 and NF-κB pathways, and promotes the secretion of IFN-I and inflammatory factors[42]. Based on the above results, fucoidan treatment reduced the level of CXCL1 in the liver, which then decreased the expression of the CXCL1 receptor-CXCR2 and the macrophage infiltration in the kidney. Furthermore, renal cell damage driven by macrophage infiltration was inhibited, which further decreased the relative expression of cGAS, STING, and pNFκB/NFκB in DKD mice. Collectively, fucoidan mediates CXCL1 to regulate liver and kidney crosstalk, inhibits the cGAS-STING pathway, and alleviates DKD.

In addition, we found that the proinflammatory cytokines (IL-6 and IL-1β) produced by macrophages were high in DKD mice, while fucoidan treatment reduced them. Long-term chronic inflammation induces dysregulated tissue repair responses, leading to fibrosis[43]. Renal fibrosis eventually leads to the progression of chronic kidney disease to end-stage renal disease, and inhibition of renal fibrosis may reduce the rate of progression of chronic kidney disease. Consequently, fucoidan treatment has the potential to improve the high-fat diet-induced DKD by inhibiting inflammation. In future studies, a CXCL1 knockout or overexpressed mice model is necessary to analyze the causality of CXCL1 with or without fucoidan supplementation.

5. Conclusion

In conclusion, this study revealed that fucoidan could alleviate DKD by blocking the crosstalk between the liver and kidney through inhibiting the expression of CXCL1. Blocking the crosstalk between the liver and kidney suppressed macrophage cell recruitment and proinflammatory cytokines. The research uncovers the critical role of CXCL1 in mediating the liver-kidney axis and provides a novel and effective therapy in high-fat diet-induced diabetic nephropathy.

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.

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