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REVIEW

Traditional Chinese medicine for the treatment of immune-related nephropathy: A review

Pu Jiang[a,b], **Changliang Yao**[b], **De-an Guo**[a,b,*]

[a]*School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China*
[b]*Shanghai Research Center for Modernization of Traditional Chinese Medicine, National Engineering Research Center of TCM Standardization Technology, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China*

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Abstract Immune-related nephropathy (IRN) refers to immune-response-mediated glomerulonephritis and is the main cause of end-stage renal failure. The pathogenesis of IRN is not fully understood; therefore, treatment is challenging. Traditional Chinese medicines (TCMs) have potent clinical effects in the treatment of the IRN conditions immunoglobulin A nephropathy, lupus nephropathy, and diabetic nephropathy. The underlying mechanisms mainly include its inhibition of inflammation; improvements to renal interstitial fibrosis, oxidative stress, autophagy, apoptosis; and regulation of immunity. In this review, we summarize the clinical symptoms of the three IRN subtypes and the use of TCM prescriptions, herbs, and bioactive compounds in treating IRN, as well as the potential mechanisms, intending to provide a reference for the future study of TCM as IRN treatments.

*Corresponding author.
E-mail address: daguo@simm.ac.cn (De-an Guo).

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1. Introduction

Immune-related nephropathy (IRN) is a kind of glomerulonephritis with immunopathological characteristics. The main cause of IRN is an overactive immune response[1]. Immunological dysfunction results in a significant buildup of immune responses in the kidney, which damages native cells, causing inflammation, proteinuria, edema, and other symptoms[2]. Along with disease progression, end-stage renal disease (ESRD) may ultimately occur, which is a threat to human health[3]. Common subtypes of IRN include immunoglobulin A nephropathy (IgAN), lupus nephritis (LN), diabetic nephropathy (DN), Henoch-Schönlein purpura nephritis, membranoproliferative glomerulonephritis, and C3 glomerulopathy[4–9]. Although the pathophysiology varies among the above kidney illnesses, immune system dysfunction is a common link. The pathogenesis of IgAN mainly involves IgA1 and autoantibody production due to galactose deficiency. Up to 40% of patients experience ESRD for 20 years after diagnosis[7]. LN is a common complication of systemic lupus erythematosus (SLE) and a major risk factor for SLE morbidity and mortality. Its pathophysiology involves the aberrant stimulation of innate and adaptive immunological responses, including immune cells, cytokines, and inappropriate immune complex formation[8]. Approximately 30%−40% of diabetics develop DN, making it the most prevalent diabetes complication[9]. The associated persistent hyperglycemia releases proinflammatory factors that encourage innate immune response activity and result in the deposition of complement that aggravates DN progression[5].

Traditional Chinese medicine (TCM) is known to have biological activities *via* multiple pathways and targets[10]. Numerous clinical and animal studies have proven the therapeutic effects of TCM on IRN. TCM approaches for IRN treatment focus primarily on clearing heat and detoxification, controlling water and fluid metabolism to eliminate edema, regulating stomach and spleen function to improve overall immunity, and alleviating the proteinuria issue[11,12]. TCMs and formulas possessing such characteristics include Lycii Fructus, Huangkui capsules (HKC), Wenshen Jianpi recipe, and Huangqi Guizhi Wuwu decoction (HQGZWWD)[13–17], which have been demonstrated to improve the clinical symptoms and life quality of IRN patients.

The partial ineffective inhibition problem can be solved *via* the synergistic impact of combining personalized treatments (TCM view) and standardized treatments (Western medicine view). For instance, type 2 DN patients with normal blood pressure cannot avoid proteinuria with traditional angiotensin receptor blocker (ARB) treatments. However, the degree of proteinuria is dramatically alleviated when they are treated with ARB and Qidan Dihuang granules in combination due to their synergistic effect[18].

The prognosis of IRN has greatly improved as a result of advancements in diagnostic procedures, therapy plans, and novel immunosuppressants. The low toxicity and multicomponent synergistic properties of TCM demonstrate notable benefits in IRN treatment. Here, we mainly focus on the three major IRN subtypes (IgAN, DN, and LN), evaluate the efficacy of TCMs in IRN treatment, and discuss the primary mechanisms. This review intends to serve as a resource for further research.

2. Major IRN subtypes

2.1. IgAN

2.1.1. Epidemiology

IgAN is the most prevalent type of glomerulonephritis worldwide and was first described by Jean Berger in 1968[19]. The incidence of IgAN ranges from 45% to 50% in China, Japan, France, Germany, etc., but there are notable geographic patterns to IgAN development[20]. IgAN is more frequent in Asians than Caucasian individuals. A large-scale genome-wide association study indicated that Asian-Americans had the highest incidence of IgAN-related ESRD, followed by European-Americans, while African-Americans had the lowest incidence[21]. Even if the findings of medical tests carried out in various locations are inaccurate, there is an established correlation between IgAN and genetic lineage. Recent research has shown that IgAN aggregates within families, and the heritability of the aberrant glycosylation in the hinge region of circulating IgA1 (a major pathogenic factor of IgAN) is roughly 40%−50%[21]. Moreover, environmental triggers, including coronavirus disease 2019 immunization, are also connected to IgAN[22].

2.1.2. Pathophysiology/diagnosis

Individual clinical variations exist among IgAN patients. Most patients transform from being less symptomatic to diseased with recurrent macroscopic or microscopic hematuria, common symptoms that are typically brought on by upper respiratory and gastrointestinal tract infections[23]. Some patients also experience severe hypertension and renal failure[7]. Currently, the definitive diagnosis of IgAN is based on renal biopsy and supported by immunofluorescence or immunohistochemical examinations[24]. Under light microscopy, diffuse mesangial or focal segmental proliferative glomerulonephritis serves as a diagnosis indicator, whereas immunofluorescence can reveal dominant or codominant glomerular IgA deposits. However, because IgA immune complex deposition is not specific to IgAN, the use of serology may help clinicians differentiate the disease from other disorders that also exhibit IgA deposition[19]. Urine and renal function tests are further auxiliary methods used in determining the progression and prognosis of the illness. The histologic classification and clinical detection indicators of IgAN are shown in Fig. 1A.

2.1.3. Pathogenesis

IgA is the main immunoglobulin found at mucosal surfaces, where it participates in host defense functions. It accounts for 10%−20% of human serum immunoglobulins and includes two subtypes: IgA1 and IgA2. Compared to IgA2, IgA1 has a longer heavy-chain hinge segment that interacts with galactose[25]. The prevailing theory for IgAN development is the "four-hit hypothesis"[26], The monomeric IgA bears a typical antigen binding ability and effector poles separated by a hinge region. IgA is normally under *O*-glycosylation; however, disruption of this glycosylation process leads to the excessive production of IgA1-bearing galactose-deficient *O*-glycans (Gd-IgA1) in the circulation of IgAN patients (Hit 1). These aberrant immunoglobulins alone are not sufficient to cause renal impairment, but they are recognized as autoantigens by anti-Gd-IgA1 autoantibodies and accelerate disease progression (Hit 2). This recognition results in the formation of circulating nephritogenic immune complexes (Hit 3).

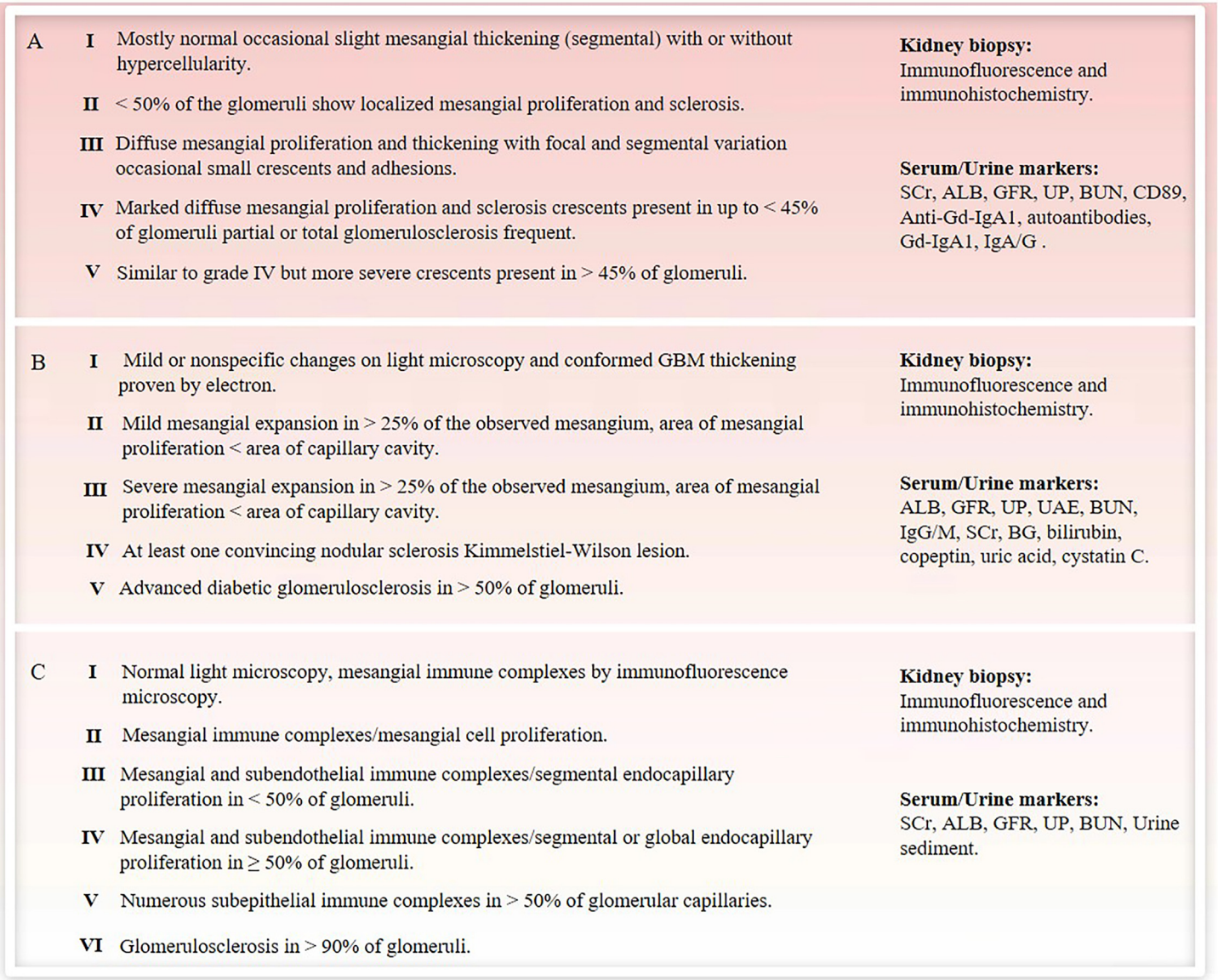

Figure 1 The histologic classification and clinical detection indicators of IRN. (A) IgAN, (B) DN, (C) LN.

Thereafter, the complexes are deposited in the glomerular mesangium, where they activate mesangial cells, increase extracellular matrix synthesis, and trigger the localized overproduction of cytokines, chemokines, and complement factors (Hit 4). Some of these cytokines also lead to podocyte and tubulointerstitial damage *via* mesangio−podocytic−tubular crosstalk[26].

IgAN mainly involves aberrant IgA1 formation that is due to defective galactosylation. There are nine potential attachment sites for *O*-glycans at the hinge region segment of the IgA1 heavy chain, and each hinge is 3−6 glycosylated. *N*-acetylgalactosamine (GalNAc) and galactose, which are the most common *O*-glycans attached to circulatory IgA1[27], are often accompanied with or without sialic acid. However, it was found that sialylated GalNAc cannot be galactosylated. The overproduction of the galactosyl-deficient IgA1 variant with terminal GalNAc or salivated GalNAc is often observed in IgAN patients, and these abnormalities may be related to changes in the activity of key glycosyltransferases (*e.g.*, core 1β1-3galactosyl transferase, α-*N*-acetylgalactosaminide, and α-2,6-sialoyltransferase)[28].

The formation of IgA and IgG autoantibodies is necessary for IgAN progression. These autoantibodies recognize Gd-IgA1 in a glycan-specific manner and form immune complexes. IgG is the most important of these antibodies; the serine of its heavy chain complementarity-determining region 3 is a necessary residue for Gd-IgA1 binding[29]. The deposition of immune complexes in the glomerular mesangium induces the infiltration of various immune cells, and the progressive kidney is infiltrated mainly by $\alpha\beta$T cells and $\gamma\delta$T cells. The proportions of circulating T helper (Th) cells Th2, Th17, Th22, T follicular helper (Tfh) cells, and the expression of toll-like receptor 4 (TLR4) are increased in patients[30]. T cells are involved in the entire progression of IgAN. Tumor growth factor-beta 1 (TGF-β1) secreted by $\gamma\delta$T and $CD4^+$ T cells induces an IgA1 isotype switch in B cells[31]. Several cytokines are also involved in the regulation of key glycosyltransferases. For instance, interleukin 4 ([IL-4], Th2 type interleukin), IL-17 (Th17 type interleukin), and TGF-β reduce the expression of C1GALT1 and its chaperone (C1GALT1C1), while IL-6 increases the expression of ST6GALNAC2 and decreases that of C1GALT1[29].

There are no reports of substantive pathological findings in patients in the early stage of IgAN. As the disease progresses, immune complexes form and are deposited in the mesangial glomeruli, and this is accompanied by a proliferation of mesangial cells, extracellular matrix synthesis, macrophages, monocytes, and T cells[30]. Thereafter, mesangial cells release various pro-inflammatory and pro-fibrotic factors (including tumor necrosis factor [TNF], TGF-β, IL-6, and angiotensin II [Ang II], etc.), resulting in podocyte dysfunction and tubulointerstitial injury. Mesangial-cell-secreted TNF induces TNF synthesis in podocytes, which further promotes TNF and TNF receptor 1 (TNFR1) and TNFR2 expression. The binding of TNF to TNFR1 induces IL-6 production and apoptosis, while binding to TNFR2 activates the pro-inflammatory cell response. TNF further exacerbates interstitial damage in the renal tubulointerstitium. Aldosterone produced by mesangial cells synergizes with Ang II and induces the apoptosis of renal tubular epithelial cells, while the interaction between Ang II and Ang II type 1 receptor (AT1R) leads to further inflammatory responses[25]. The pathogenesis of IgAN is shown in Fig. 2.

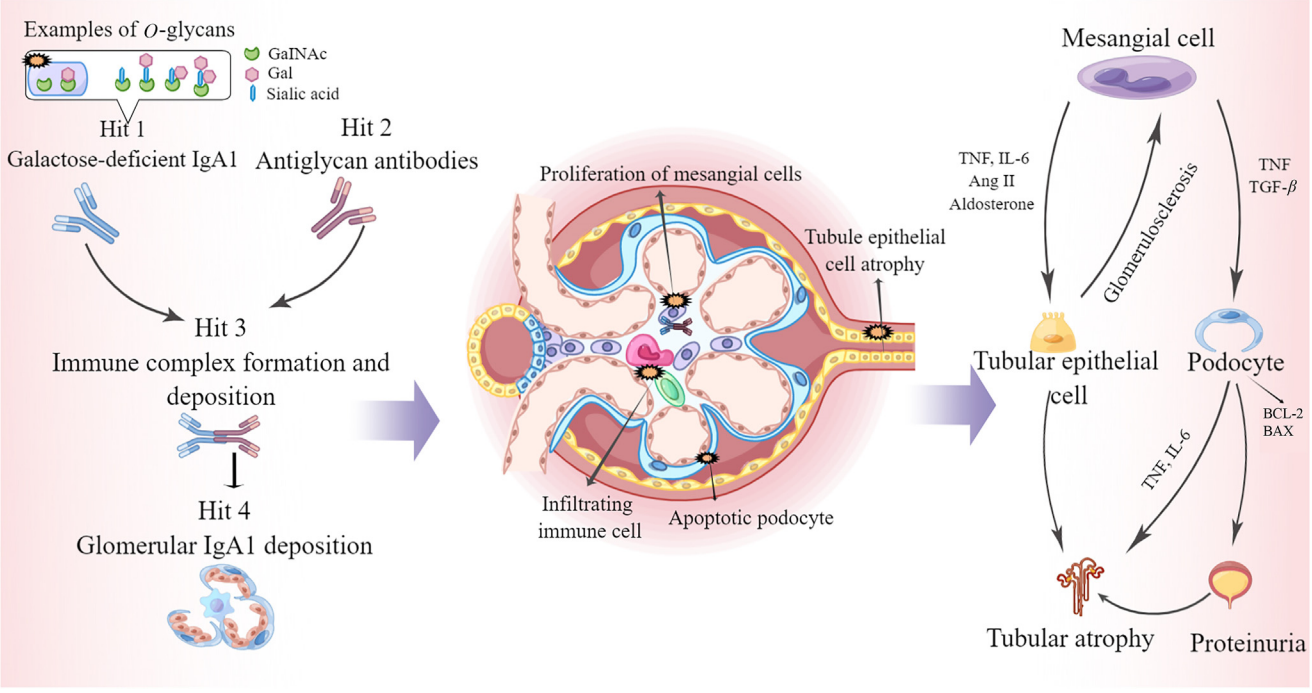

Figure 2 The pathogenesis of IgAN. Abnormal glycosylation causes Gd-IGA1 (Hit 1). Subsequently, it results in autoantibodies against Gd-IGA1 (Hit 2). These autoantibodies attach to Gd-IGA1 and create pathogenic immune complexes (Hit 3), which then penetrate the glomerular endothelial cell and deposit within the mesangium of the glomerulus, resulting in mesangial cell growth and release of various pro-inflammatory and pro-fibrotic factors (TNF, TGF-β, IL-6, aldosterone and Ang II, etc.). On the one hand, TNF secreted by mesangial cells induces podocytes to trigger inflammation (IL-6), apoptosis (BCL-2, BAX) and albuminuria production; on the other hand, mesangial cells induce apoptosis and inflammation of renal tubular epithelial cells through TNF, IL-6 and Ang II. These pathways eventually lead to kidney dysfunction (Hit 4).

2.1.4. Therapy

As there is an insufficient understanding of the pathophysiology, there is currently no treatment for IgAN. However, the use of angiotensin-converting enzyme inhibitors, ARBs, and blood pressure control strategies is advised by the new Kidney Disease Improving Global Outcomes Clinical Practice Guidelines[32]. Current treatment therapies primarily focus on adjuvant therapies that help with lowering blood pressure and proteinuria and minimizing lifestyle risk factors through measures like a low-sodium diet and high protein intake, as well as performing tonsillotomies to prevent upper respiratory tract infections, ingesting fish oil, and using immunosuppressive methods[33].

2.2. DN

2.2.1. Epidemiology

DN is one of the most common and serious chronic diabetes mellitus complications[34], the defining features of which are renal function deterioration and persistent albuminuria[35]. According to estimates, chronic kidney disease affects one in three diabetics, and the majority of patients are not identified promptly because DN has a prolonged incubation period[9,36]. Its prevalence rate also varies greatly between nations as a result of variations in health care and dietary policies. According to a study in 2017, Western Europe had the lowest DN incidence, while Oceania had the highest. In the majority of regions, females are more likely than males to present with DN[37]. In addition, DN is the main cause of ESRD, and compared with adults without diabetes, the incidence of ESRD is up to 10 times higher in those with diabetes[38].

2.2.2. Pathophysiology/diagnosis

The clinical manifestations of DN include decreased renal function, albuminuria, hypertension, and retinopathy, and some of the pathologic symptoms include mesangial expansion, thickening of the glomerular basement membrane, and tubular atrophy. Glomerulosclerosis and other abnormalities also tend to surface when the condition worsens[39]. The determination of micro-albuminuria (MA) has been a routine method for tracking DN development, but it cannot be detected in the early stages or non-albuminuric DN cases. Renal lesions can occur before MA occurrence. Currently, biomarkers (*e.g.*, bilirubin, copeptin, neutrophil gelatinase-associated lipocalin, non-albumin protein-to-creatinine ratio, and cystatin C) that predict early changes in renal structure and function, combined with urinary albumin excretion (UAE), provide multiple guarantees for the early diagnosis and prognosis of DN. However, it should be noted that the final diagnosis of DN still relies on renal biopsy[40]. Histologic classification categories and clinical detection indicators of DN are listed in Fig. 1B.

2.2.3. Pathogenesis

DN is not traditionally considered an immune disease; however, modern research efforts have confirmed that the immune system is involved during the whole progression of DN. The continuous high-glucose environment in DN patients increases the expression of immune-related localization factors. Cells involved in innate and adaptive immune responses gradually accumulate in the kidney, resulting in a release of pro-inflammatory factors (*e.g.*, IL-1, IL-6, TNF-α, monocyte chemotactic protein-1 [MCP-1], intercellular adhesion molecule-1 [ICAM-1]), which ultimately deteriorates kidney function[41].

Immune-mediated inflammation in DN involves both innate and adaptive immune responses[5], with the former being the dominant force. Innate immune cells do not express specific antigen recognition receptors similar to T cell surface receptors. Innate immune recognition receptor patterns consist of danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). Pattern recognition receptors (PRRs) on cell surfaces recognize DAMPs and PAMPs, which facilitate an innate immune response[42]. The abnormal physiological environment in DN patients leads to the release of DAMPs (*e.g.*, high-mobility group protein B1 [HMGB1], heat shock protein 70, advanced glycation end products [AGEs], and S100/calgranulins), and such danger signals are recognized by multiple PRRs, including TLRs, receptor for AGE (RAGE), nucleotide-binding oligomerization domain-like receptor (NLR), kallikrein-kinin system, and complement cascades, triggering an inflammatory response in renal cells[5,43,44]. The damaged kidney is continuously activated to recruit immune cells (macrophages, T cells, B cells, mast cells, etc.), amplifying the inflammatory response, which in the end leads to a series of pathological changes in the kidney.

TLRs are expressed by various immune cells (T cells, B cells, natural killer cells, macrophages, dendritic cells, etc.) and non-immune cells (kidney tubular epithelial cells, endothelial cells, podocytes, mesangial cells, etc.). As innate immune system receptors, TLRs play important roles in initiating and regulating innate immunity[45]. Dendritic cells, macrophages, and necrotic cells release HMGB1 in response to hyperglycemia, AGEs, dyslipidemia, and anoxia. The binding of HMGB1 to TLRs promotes inflammatory responses and triggers downstream reactive oxygen species (ROS) production in a process involving the recruitment of mediators such as myeloid differentiation factor 88 (MyD88), toll-interleukin-receptor domain-containing adaptor protein, and other adapter proteins. This process activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and releases IL-6, IL-1β, and TNF-α, leading to a state of augmentative inflammation in the kidney[46].

NLRs play important roles in innate immunity by linking the perception of microbial and metabolic stress to the activation of pro-inflammatory cascades. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a representative NLR molecule composed of the sensor NLRP3, the junction apoptosis-associated speck-like protein (ASC), and the effector pro-caspase-1[47]. The NLRP3 inflammasome can be activated by many components of PAMP (*e.g.*, K^+/Ca^{2+} influx and pore-forming toxin), triggering an inflammatory cascade that leads to the activation of caspase-1 and the production of IL-1β and IL-18. These factors then activate an inflammatory response in the kidney[46].

AGE, a major ligand of RAGE, activates NF-κB or intracellular signaling *via* p38 mitogen-activated protein kinase (p38 MAPK), c-Jun N-terminal kinase (JNK), and Janus kinase 1 (JAK1), and JAK2. Thereafter, p38 MAPK or JNK activates transcription factor-activating protein-1 and transcription factor 2. The stimulation of JAK1 or JAK2 leads to the activation of the signal transducer and activator of transcription 1 (STAT1) and STAT3. These events contribute to the development of inflammation and damage in DN[5].

The kallikrein-kinin system has been implicated in the pathogenesis of inflammatory processes in kidney disease, and it is primarily mediated by bradykinin and kallidin. These kinins bind with their respective receptors, such as B1 bradykinin receptor (B1R) and B2R, which is followed by the activation of various downstream intracellular signaling pathways. B1R's interaction with bradykinin and kallidin metabolites triggers an NF-κB-dependent

pro-inflammatory response; while B2R induces a pro-inflammatory response by activating the MAPK signaling pathway[48].

The complement system is another important part of the innate immune system; it promotes inflammation and enhances the ability of antibodies and phagocytes to remove pathogenic microorganisms and damaged cells. About 50%−60% of DN patients have been observed to have complement 3 (C3) deposition in their glomeruli[49]. The hyperglycemic environment of DN induces protein glycosylation, and glycosylated proteins are recognized by mannan-binding lectin (MBL), activating complement signaling of the lectin pathway. This ultimately induces the formation of the membrane-attack complex (MAC). At the same time, the glycosylation of the complement regulatory protein CD59 leads to increased MAC deposition, resulting in potential automatic activation of the complement cascade[50]. The pathogenesis of DN is shown in Fig. 3.

2.2.4. *Therapy*

The main treatment strategies for DN patients are comprehensive regimens that maintain renal function, reduce cardiovascular disease risk, and delay disease progression. Furthermore, good living and dietary patterns (weight loss, increased physical activity, reduced dietary sodium intake, and a cessation of smoking) and glucose and blood pressure control measures are essential to improving DN prognosis[39]. Treatment with sodium-glucose cotransporter-2 inhibitors has also achieved a good therapeutic effect in the clinic[51]. Studies have shown that combinations of these treatments can reduce DN risk[52,53].

2.3. *LN*

2.3.1. *Epidemiology*

LN is the most common manifestation of kidney damage in the autoimmune disease SLE, and most SLE patients develop LN within the five years following diagnosis[54]. Statistics show that LN appears in approximately 50% of SLE patients[55], whose mortality is significantly higher than that of patients without LN[56]. In addition, younger SLE patients appear to be more likely to have renal involvement, as a larger proportion of patients with juvenile-onset SLE are diagnosed with LN than those with adult-onset SLE[57]. The incidence of LN also varies greatly by race; the black population has a higher incidence of LN in the US, which may be related to genetic inheritance[58]. High-risk genotypes (*Fcγ RIIA-R131* allele and *APOL1* gene) and LN autoantibodies (anti-Smith, anti-ribonucleoprotein, and anti-Ro antibodies) are more likely to be observed in black individuals[8].

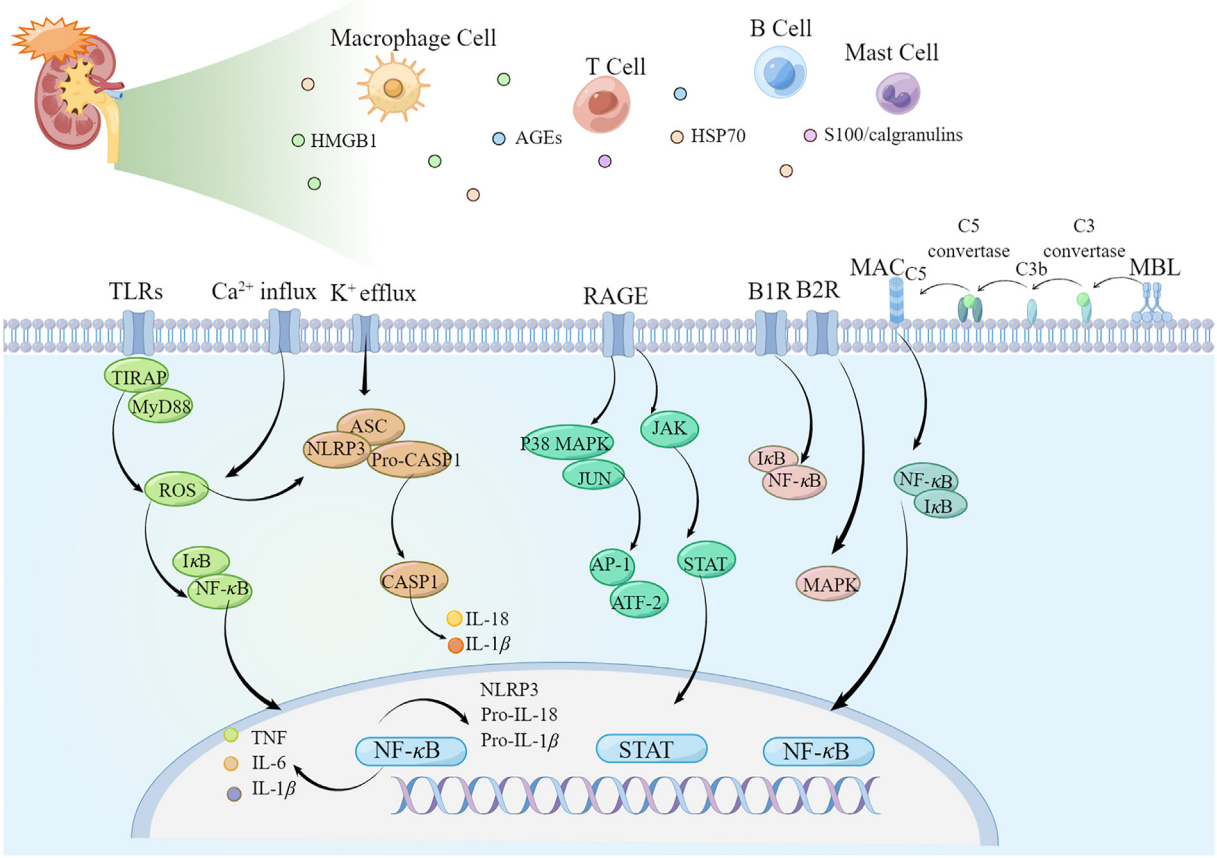

Figure 3 The pathogenesis of DN. Abnormal physiological environment of DN leads to the release of DMAPs (HMGB1, HSP70, AGEs and S100/calcineurin, etc.) and recognition by multiple PRRS (TLRs, RAGE, NLR, kallikrein-kinin system, complement cascades, etc.). Activated TLRs recruit MyD88 to produce ROS and activate the NF-κB pathway, release the danger signal (IL-6, IL-1β, TNF); K^+/Ca^{2+} influx activates NLRP3, leading to the production of IL-1β and IL-18; AGEs activate RAGE, leading to activation of NF-κB or intracellular signaling *via* p38 MAPK, JNK or JAK; pro-inflammatory pathway NF-κB and MAPK are activated by stimulation of B1/2R; hyperglycemia leads to glycosylation of proteins recognized by MBL and initiate an enzyme cascade that ultimately forms the MAC.

2.3.2. Pathophysiology/diagnosis

In the clinic, SLE patients present with fever, joint pain, and an impaired skin barrier[59]. Along with LN progression, a range of symptoms, including urinary abnormalities and glomerular, tubulointerstitial, and renal vascular damage, may occur[56]. Confirming a diagnosis of LN is difficult in the early stage of the condition because of the lack of obvious clinical manifestations. Common tests include an assessment of serum creatinine (SCr) levels and urine dipstick and urine sediment examinations, with a focus on hematuria and proteinuria[55]. Currently, kidney biopsy is the fundamental diagnostic method for LN and can be used to distinguish pathological types, define the degree of renal damage, and identify other non-LN diseases[60].

2.3.3. Pathogenesis

Although great progress has been made in the study of LN pathogenesis, the mechanisms are still not comprehensively understood. The development of LN involves multiple pathogenic pathways, such as immune complex deposition, autoantibody production, aberrant apoptosis, complement activation, etc.

Dysregulation of the immune system is a major pathogenic component of LN. Risk factors such as genetic polymorphisms, endogenous chromatin, and microbial DNA disrupt immune tolerance to nuclear autoantigens. Endogenous immunogenic molecules, including oxidized mitochondrial DNA, endogenous nucleic acids in exosomes, and apoptosis-derived microvesicles, activate nucleic acid sensors in endosomes (TLR7, TLR8, TLR9) and the cytosol (RIG1/MDA5-MAVS, cGAS−STING)[54]. Thereafter, it may trigger several further intracellular pathways, such as NF-κB and interferon regulatory factor (IRF) 5 and IRF7, leading to the increased production of multiple pro-inflammatory cytokines (such as TNF-α and IL-6) and type I interferon (IFN-I), which is the signature immune signal of SLE[61].

B cells and T cells play pivotal roles in the pathogenesis of LN and SLE. Immature dendritic cells are stimulated to mature by endogenous chromatin, which triggers the activation of B lymphocytes and T lymphocytes in response to excess B-cell-activating factor (BAFF). At the same time, T cells assist the differentiation of B cells into autoantibody-producing plasma cells that form an immune complex with antigens, leading to injury to glomerular podocytes, endothelium, tubule interstitium, and blood vessels[62]. Moreover, several other T cell types, especially Th and Tfh cells, produce cytokines that stimulate an inflammatory response and promote kidney injury[63]. Additionally, the histones and HMGB1 produced by immune cells bind to TLRs in endothelial cells, triggering an inflammatory response.

LN is usually accompanied by an increased proportion of neutrophils and decreased levels of complement in clinical patients. Neutrophils, the most abundant circulating leukocyte, have a pivotal role in innate and adaptive immunity[64]. These cells perform autoimmune actions through a unique cell death called neutrophil extracellular traps (NET)osis. NETs contain chromatin DNA coated with granular proteins. Patients with dysfunctional NETosis degradation show the continuous activation of autoantigens and autoimmunity responses[62]. The classical complement pathway is also associated with LN progression. It has been demonstrated that glomerular C4d/C3 deposits and decreased serum complement levels are signs of kidney damage and are related to poor outcomes in LN patients[65], and anti-complement antibody treatment has demonstrated promising results. The pathogenesis of DN is shown in Fig. 4.

2.3.4. Therapy

The clinical treatment of LN still faces huge challenges, but as our understanding of the pathophysiology deepens step by step, some emerging therapeutic strategies are coming to the fore. At present, traditional drugs for LN treatment, such as glucocorticoids, cyclophosphamide, and azathioprine, are still being used, but large-dose use of these drugs is often accompanied by side effects[60]. Recently, an immunity intervention strategy using agents that target specific cells was developed. For example, treatments with the CD20 antibodies rituximab and obinutuzumab targeting B lymphocytes have shown potent efficacy and low toxicity in LN treatment[66,67]. T-cell-mediated immune response inhibitors, including cyclosporine A, tacrolimus, and voclosporin, have also shown positive effects on LN progression[68]. Due to the large differences among individuals, the same treatment strategy might induce different therapeutic effects in different patients. In general, clinicians should follow the principle of individualized treatment and choose corresponding treatment methods according to the different pathological types. Histologic classification categories and clinical detection indicators of LN are listed in Fig. 1C.

2.4. Common and specific pathways

IgAN, LN, and DN are types of immune-mediated kidney injury that have similar pathological manifestations but involve different pathogenic mechanisms. Exploring their unique and common pathogenic targets is of great significance for the improvement of precision therapy and the development of broad-spectrum therapeutic drugs.

IgAN is mainly caused by the excessive production of abnormal glycoylated IgA1 and the formation of immune complexes. Gut-associated lymphoid tissue is a potential source of low *O*-galactosyl IgA1[69]. Bacterial IgA protease can specifically attack the hinge region of IgA1, inducing its degradation[70]. The clonal ligand (a proliferation-inducing ligand [APRIL]) significantly reduces the production of nephrogenic IgA[71]. In addition, BAFF plays an important role in the activation of antibody-producing B cells[71].

Similar to IgAN, the signature diagnostic features of LN are anti-DNA antibodies, anti-nuclear antibodies, and immune complex formation. APRIL/BAFF, which is associated with B cell activation, is also a potential therapeutic target for LN treatment[61]. In addition, immune complexes affect IFN-I production, an immune signature of SLE, by targeting endosomal DNA/RNA sensors (*e.g.*, TLR7/9) or cytoplasmic sensors (*e.g.*, RIG1/MDA-5, cGAS−STING) and the IRF5 or IRF7[54].

Differing from IgAN and LN, DN is not mediated by immune complexes but by immune-mediated kidney injury that is triggered by a high-glucose environment. Control of blood glucose and its metabolites seems to be an important strategy for DN patients. The polyol pathway is one of several glucose metabolism pathways in the body in which aldose reductase and sorbitol dehydrogenase promote DN development[72]. In addition, the generation of AGEs is an important pathogenic factor for DN. Therefore, AGE inhibitors and AGE−RAGE signaling pathway blockers may be potential strategies for DN treatment[73].

Although the pathogeneses of these three diseases are different, they all involve immune-mediated kidney damage and macrophage and T cell infiltration. The differentiation of $CD4^+$ T cells to Th17 cells participates in IRN progression and accelerates kidney damage. Secondly, the three IRN subtypes all involve the

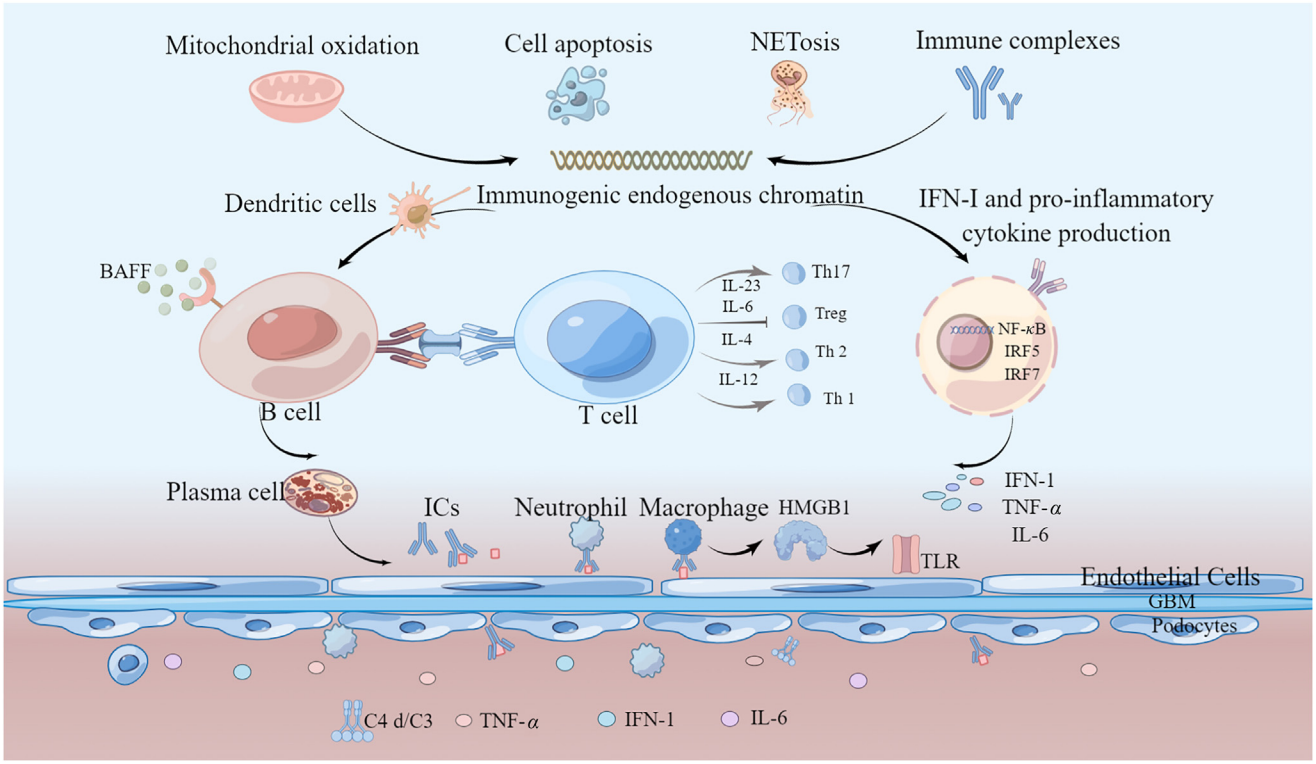

Figure 4 The pathogenesis of LN. Immunogenic endogenous chromatin activates DNA and RNA sensors in the endosomes and the cytosol of innate immune cells and B cells, producing increased levels of IFN-I and various pro-inflammatory cytokines. At the same time, dendritic cells are stimulated to mature and drive the activation of B cells and T cells. The activated B cells differentiate into plasma cells, produce autoantibodies and form immune complexes. T cells differentiate into various subgroups, leading to kidney injury. In addition, HMGB1, biglycan and histones released by immune cells bind to TLRs on endothelial cells, driving an inflammatory response.

activation of the complement system. The deposition of C3 and a decrease in serum C1q are observed in the kidneys of all three types of patients. Additionally, these immune-mediated renal diseases trigger downstream inflammatory pathways (*e.g.*, NF-κB, NLRP3, IL-1, IL-6, IL-1β, IL-18, MCP-1), oxidative stress pathways (*e.g.*, ROS, superoxide dismutase [SOD], malondialdehyde [MDA], glutathione [GSH]), and renal-fibrosis-related pathways (*e.g.*, TNF-α, TGF-β, ICAM-1, fibronectin-1 [FN1]), leading to irreversible renal damage.

3. Application of TCM in IRN treatment

Generally, modern medicine has adopted a standard treatment mode for IRN, but it is difficult to completely prevent its occurrence, development, and deterioration. Moreover, these therapies are also frequently reported to have side effects. Practitioners of TCM have a wealth of accumulated experience in IRN treatment and have unique views on its etiology and pathogenesis as well as suitable treatment modes. TCM has a set of treatment modes with traditional Chinese medical characteristics. Here, we summarize the treatment of IRN with TCM prescriptions, herbs, and bioactive compounds and their potential mechanisms.

3.1. TCM for IgAN treatment

TCM is widely used as an independent or adjuvant strategy for IgAN therapy. Compared to traditional therapy, TCM methods have shown potent efficacy and fewer adverse effects. Here, we summarized the use of several TCM prescriptions (HQGZWWD, Zhenwu decoction [ZWD], Shen San recipe, Huaiqihuang granules, and Qingre Lishi Yishen decoction) and herbal extracts (ethanolic extract of Periostracum Cicadae) for IgAN treatment[17,74–78]. HQGZWWD is a TCM prescription for the treatment of peripheral vascular diseases, and clinical practice has confirmed it has a role in alleviating albuminuria and protecting renal function in IgAN patients. Paeoniflorin, calycoside 7 glycoside, and astragaloside IV are the most abundant chemical components in HQGZWWD[17]. ZWD, first described for use in febrile diseases, is a classic prescription used for various kidney diseases. Modern studies have shown that ZWD treatment improves renal pathological damage and increases the number of exosomes in kidney tissue[77]. Shen San recipe is clinically used to improve hematuria symptoms, mainly by improving immunity and boosting the coagulation system[76]. The oral administration of Huaiqihuang granules can improve urinary protein (UP) levels in LgAN patients, an effect that is closely linked to its main component Trametes Robiniophila Murr[74]. Qingre Lishi Yishen decoction treatment was found to relieve UP levels and significantly reduce the deposition of IgA immune complexes in LgAN mice[75]. It is important to note that these prescriptions consist of a total of 34 TCMs, among which Radix Astragali is the most frequent, and Paeoniae Radix Alba, Poria, *Zingiber officinale* Roscoe, and Lycii fructus appear twice in the above preparations. The use frequencies are shown in Fig. 5A. In TCM clinical practice, Astragali Radix is often used for immune regulation and as an anti-fatigue and anti-aging agent, and saponins, flavonoids,

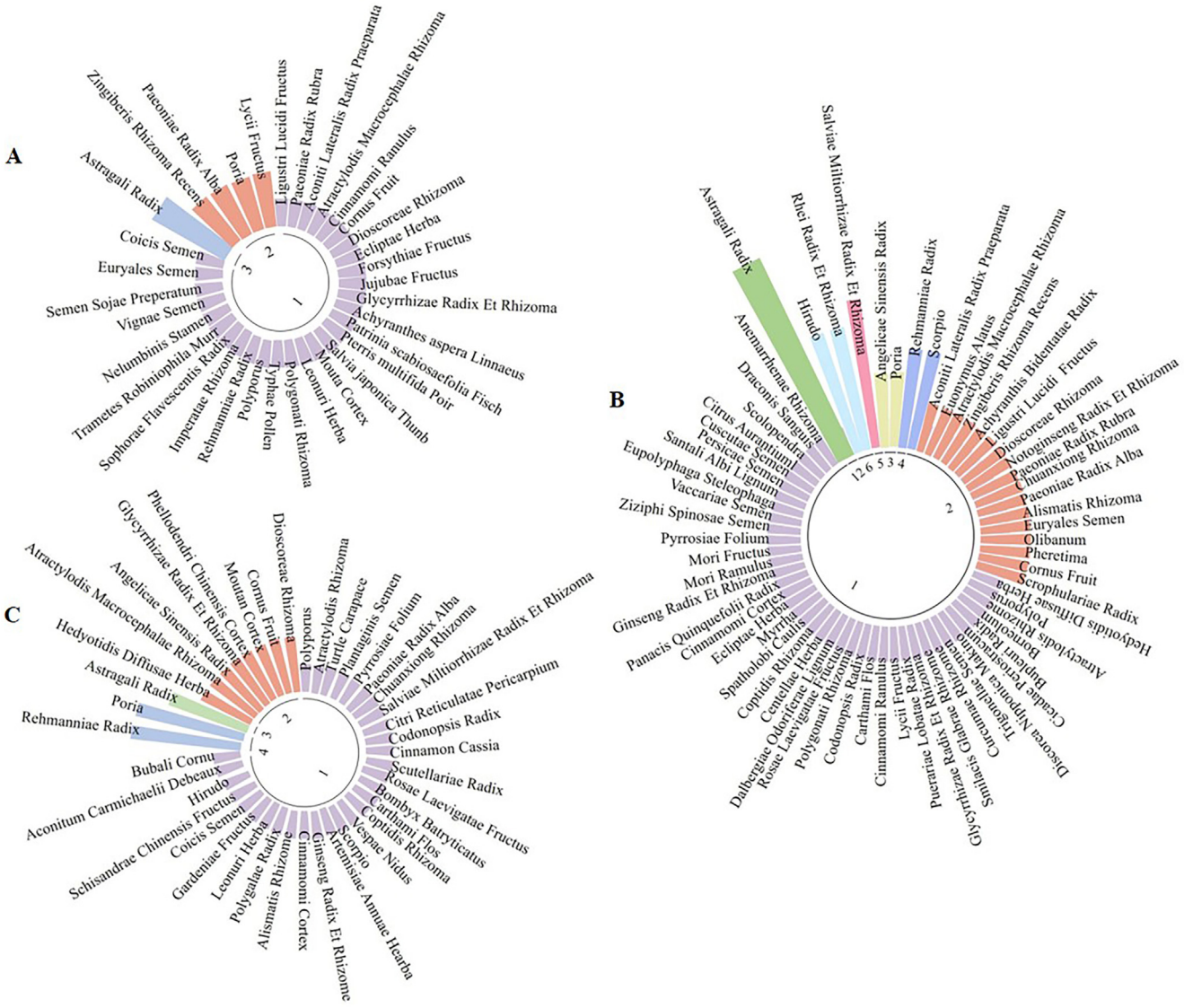

Figure 5 The use frequencies of TCM prescriptions for IRN treatment. (A) IgAN, (B) DN, (C) LN.

and polysaccharides are its main bioactive components. Studies have confirmed that Astragali Radix can promote the development of immune organs and improve the expression of antibodies in acquired immunity[79]. We speculated that most prescriptions for IgAN treatment contain Astragali Radix because of its immune-enhancing effect. This is consistent with the fact that IgAN is caused by an immune deficiency.

Combinations of Chinese and Western medicine are widely used in clinical practice. The ideal combination plays both a synergistic and detoxification role, and this treatment model has achieved good results in IRN. HKC is often used in the treatment of chronic kidney disease (No. ChiCTR1900025273), and leflunomide is a clinical drug commonly used in IgAN treatment. A combination of the above two drugs inhibits the expression of the TGF-β1/small mothers against decapentaplegic 3 (SMAD3) signaling pathway, and the therapeutic effect is superior to that of single drug therapy[80,81].

The effects of active chemical entities for IgAN treatment have been intensively investigated. The various types of compounds studied include icariin (flavonoid glycosides), osthole and acteoside (phenylpropanoid glycosides), hirudin (peptides), astragaloside IV (triterpenoid saponins), dihydroartemisinin (terpenoid), rhein (anthraquinones), etc.[82–89]. Some of these compounds alleviate the renal pathologic progression of IgAN at low dosages. For example, icariin, a major constituent of Epimedii Folium, has been shown to ameliorate increased proteinuria, SCr, and urea nitrogen without severe side effects[85]. Osthole ameliorates the renal lesions of glomerular proliferation, sclerosis, and periglomerular in an IgAN model[83]. Hirudin, a secreted polypeptide extracted from Hirudo, is viewed as the most potent natural inhibitor of thrombin and has been applied to treat IgAN with hematuria[82]. The chemical structures of these active chemical entities, which are potential drugs for IgAN treatment, are shown in Fig. 6.

In conclusion, the above components showed positive effects on improving IgAN progression, and more details on these are described in Table 1.

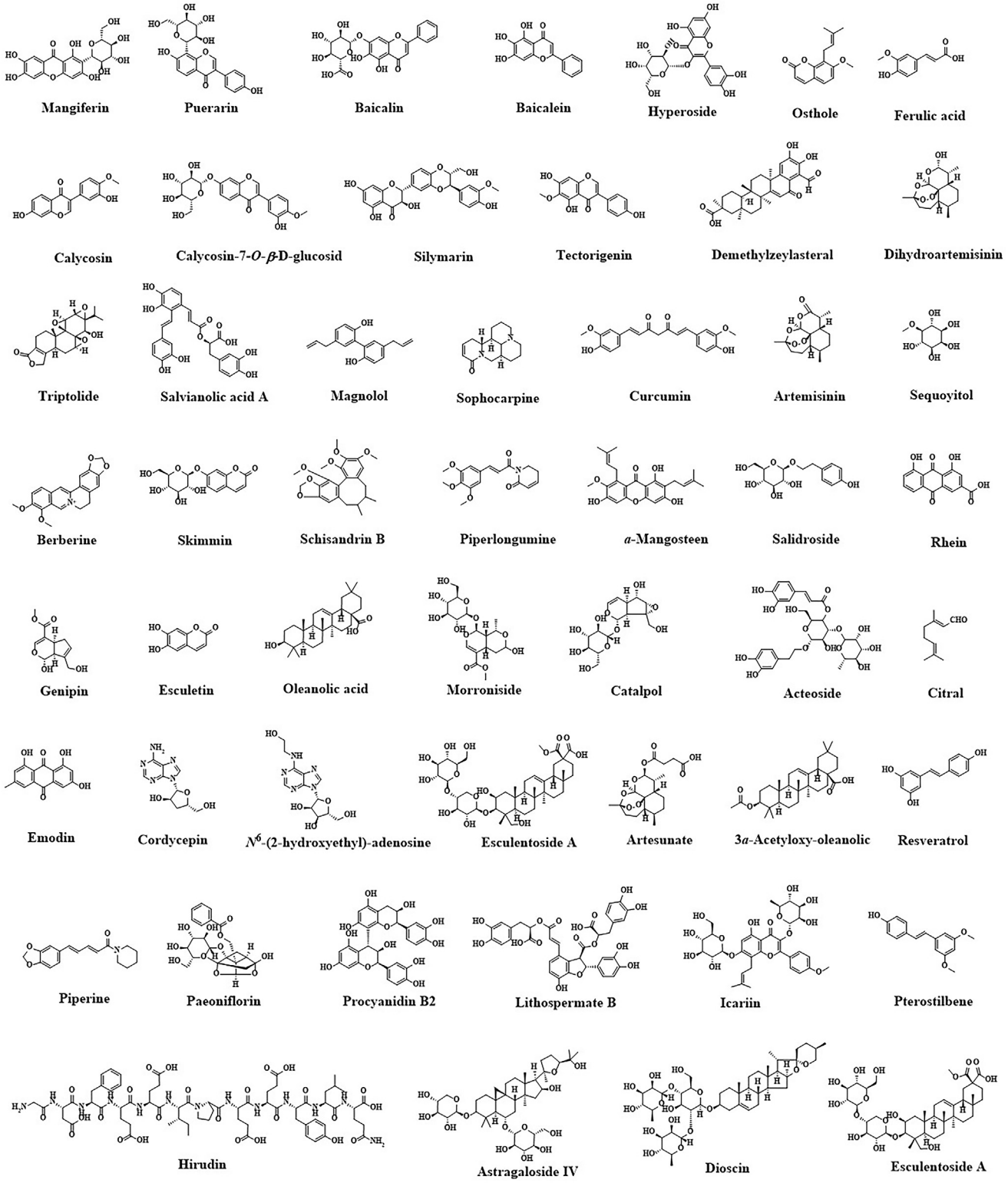

Figure 6 The chemical structures of bioactive compounds involved in IRN treatment.

3.2. *TCM for DN treatment*

The effects of TCMs on improving DN are generally recognized, and the effects of a total of 17 prescriptions (65 types of TCMs) have been summarized[15,16,90–105]. Here, we mainly focus on some of the prescriptions frequently used in the clinic. Baoshen recipe, which is widely used in treating DN, contains astragaloside IV as the major active component. Astragaloside IV achieves renal protection mainly by inhibiting oxidative stress and the apoptosis of podocyocytes[90]. Traditionally, Naoxintong capsules are used in cardio- and cerebrovascular disease treatment, but modern studies have confirmed that Naoxintong capsules inhibit renal fibrosis in DN[97]. The renal

Table 1 TCMs for IgAN treatment.

Drug	Composition	Model	Dosage	Result	Ref.
Prescriptions					
Huangqi Guizhi Wuwu decoction	Astragali Radix, *Cinnamomi Ranulus*, Paeoniae Radix Alba, Zingiberis Rhizoma Recens, Jujubae Fructus	BGG-induced IgAN rat	2.85−11.4 g/kg	SCr↓, nephrin↑, podocin↑, ACTN4↑, AT1R↓, F-actin↑, TNF-α↓, TNFR1↓	17
Huaiqihuang granule	Trametes *Robiniophila Murr*, Lycii Fructus, Polygonati Rhizoma	IgAN patient	20 g/tid	UP↓, hematuria↓	74
Qingre Lishi Yishen decoction	*Pterris Multifida Poir*, Coicis Semen, Radix Sophorae Flavescentis, *Salvia Japonica* Thunb, *Achyranthes aspera* Linnaeus, *Patrinia Scabiosaefolia* Fisch, Forsythiae Fructus, Paeoniae Radix Rubra, Astragali Radix, Dioscoreae Rhizoma, Typhae Pollen, Nelumbinis Stamen, Sojae Semen Praeparatum, Vignae Semen, Euryales Semen	BSA, CCL4 and LPS-induced IgAN rat	22 g/kg	UP↓, IgA↓, α-SMA↓, FN↓, TNF-α↓	75
Shen San recipe	Astragali Radix, Lycii Fructus, Ligustri Lucidi Fructus, Cornus Fruit, Rehmanniae Radix, Moutan Cortex, Leonuri Herba, Ecliptae Herba, Glycyrrhizae Radix et Rhizoma, Poria, Polyporus, Imperatae Rhizoma	BGG-induced IgAN rat	24 g/kg	TGF-β1↓, IgA↓, TGF↓	76
Zhenwu decoction	Aconiti Lateralis Radix Praeparata, Poria, Atractylodis Macrocephalae Rhizoma, Paeoniae Radix Alba, Zingiberis Rhizoma Recens	BSA, CCL4 and LPS-induced IgAN rat; LPS-induced HK-2 cell	7.5−16.8 g/kg	UP↓, TP↑, ALB↑, BUN↓, SCr↓, CD9↑, CD81↑, CD63↑, IL-1β↓, p-NF-κB p65↓, NLRP3↓, caspase-1↓, ASC↓, IL-1β/18↓, IgA↓, IgG↓, C3↓	77
Hydroxychloroquine + Artemisinin	/	BSA, CCL4 and LPS-induced IgAN rat	16.65 −66.66 mg/kg	Hematuria↓, TC↓, ALB↑, IgA↓, C3↓, IL-4↓, IFN-γ↑, Foxp3↑, IL-17↓	80
Huangkui capsule + leflunomide	/	BSA, CCL4 and LPS-induced IgAN rat; Th22 cells from IgAN patient	2 g/kg + 5 mg/kg	Hematuria↓, UP↓, IgA↓, TGF-β1↓, SMAD2/3/4↓, SMAD7↑, CCL20/22/27↓	81
Herbs and extracts					
Periostracum Cicadae	Ethanolic extract	BSA, CCL4 and LPS-induced IgAN rat	0.5−2 g/kg	UP↓, BUN↓, SCr↓, ALT↓, AST↓, TP↓, ALB↓, globulin↓, TAG↓, IgA↓, Fas↑, IL-6/1β↓, TNF-α↓, MCP-1↓, TLR4↓, TGF-β1↓, caspase-3↑, TC↓	78
Bioactive compounds					
Hirudin	Hirudo	BGG-induced IgAN rat	10 mg/kg	SCr↓, BUN↓, UP↓, caspase-3/9↓, TGF-β1↓, COL-IV↓, FN1↓, IL-1β/6/18↓, IκBα↓, NF-κB↓, TNF-α↓, VCAM-1↓	82
Osthole	Cnidii Fructus	IgA anti-phosphorylcholine antibodies and PnC-induced IgAN mouse; LPS and ATP-induced murine macrophage cell and mesangial cell	30 mg/kg; 0−100 μmol/L	ALB↓, BUN↓, SCr↓, COL-IV↓, TGF-β↓, Nrf2 (nuclear)↑, HO-1↑, GSH-PX↑, NF-κB p65 (nuclear)↓, NLRP3↓, caspase-1/3/9↓, p-IL-1β↓, ROS↓, MCP-1↓	83

Rhein	Rhei Radix et Rhizoma	BSA, CCL4 and LPS-induced IgAN rat	100 mg/kg	IgA↓, TLR4↓, TGF-β1↓	84
Icariin	Epimedii Folium	BGG-induced IgAN rat	10 mg/kg	UP↓, SCr↓, BUN↓, IgA↓, NLRP3↓, TGF-β1↓, COL-IV↓, FN1↓, ASC↓, caspase-1↓, IL-18/1β↓, IKKβ↓, IκBα↑, p-IκBα↓, p-IKKβ↓, NF-κB p65/p50 (nuclear)↓	85
Schisandrin B	Schisandrae Chinensis Fructus	BSA, CCL4 and LPS-induced IgAN rat; LPS-induced HK-2 cell	50 mg/kg; 10 μmol/L	UP↓, SCr↓, BUN↓, hematuria↓, TNF-α↓, IgA↓, IL-1β↓, MCP-1↓, NF-κB↓, NF-κB p65 (nuclear)↓	86
Dihydroartemisinin	Artemisiae Annuae Herba	Aggregated IgA1-induced IgAN mesangial cell	0–15 mmol/L	p-mTOR↓, pS6K1↓, LC3B↓	87
Acteoside	Rehmanniae Radix	$CD4^+$ T lymphocytes from IgAN patient	20–100 mmol/L	CCL20/22/27↓, CCR4/6/10↓, IL-1/6↓, TNF-α↓, TGF-β1↓	88
Astragaloside IV	Astragali Radix	Dakiki Cells	0–80 mmol/L	Mir-98-5p↓, C1GALT1↑	89

protective function of Fuxin granules is associated with its ability to reduce serum lipid, urea nitrogen, and creatinine profiles and the excretion of MA[93]. Chaihuang Yishen granules are formulated based on TCM theory for chronic kidney disease treatment and include protocatechuic acid, chlorogenic acid, calycosin 7-*O*-β-D-glucoside, formononetin, dioscin, etc. Chaihuang Yishen granules inhibit DN by blocking the TGF-β/SMAD3 signaling pathway[91]. In China, HKC is currently approved for the routine treatment of DN. It alleviates renal tubular epithelial-to-mesenchymal transition (EMT) by inhibiting NLRP3 inflammasome activation and TLR4/NF-κB signaling[16]. The combination of HKC with metformin ameliorates DN *via* the Klotho/TGF-β1/p38MAPK signaling pathway[106]. Jixuepaidu decoction, obtained from the decoction of the three medicinal plants Centellae Herba, Astragali Radix, and Draconis Sanguis has been shown to have a protective effect in DN. The mechanism of Jixuepaidu decoction is associated with the inhibition of the TGF-β1/serum and glucocorticoid-inducible kinase 1 (SGK1) signaling pathway[96]. Interestingly, the top six TCM most frequently used ingredients in these prescriptions are Astragali Radix, Hirudo, Rhei Radix et Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Scorpio, and Rehmanniae Radix, among which Astragali Radix is the most frequently used (similar to the IgAN treatments), as it appears in 12 prescriptions. Hirudo and Rhei Radix et Rhizoma are included in five prescriptions, while Salviae Miltiorrhizae Radix et Rhizoma, Scorpio, and Rehmanniae Radix are found in four prescriptions. Their use frequencies are shown in Fig. 5B.

Focusing on extracts, the ethanol or water extracts of the following plants have been shown to slow DN progression: Eucommiae Cortex, Chuanxiong Rhizoma, Polygoni Avicularis Herba, Moutan Cortex, Cassiae Semen, Lycii Fructus, Taxus Chinensis, Rehmanniae Radix, and Trichosanthis Fructus[14,107–116]. Modern technologies can be applied to separate the active components from a single TCM to provide the advantage of a clearer pharmacodynamic material basis. Thus, these extracts enhance the multi-target properties of the compounds and remove any ineffective and toxic components, so the preparation exhibits a more logical efficacy.

The above bioactive components offer a fresh approach to the creation of therapeutic medicines and are a promising source of DN treatments. We summarized 26 active chemical entities in total, including alkaloids (berberine), iridoid glycosides (genipin, morroniside, catalpol), flavonoids (puerarin, hyperoside, calycosin, calycosin-7-*O*-D-glucoside, silymarin, icariin, and tectorigenin), and phenylpropanoids (ferulic acid, salvianolic)[13,72,117–143]. These compounds are crucial in both controlling lipid and glucose metabolism and slowing the progression of DN lesions. For example, berberine, an alkaloid active component isolated from Coptidis Rhizoma, protects against diabetic kidney disease by promoting peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)-regulated mitochondrial energy homeostasis[143]. Genipin has been used for hundreds of years to alleviate the symptoms of diabetes, and recent studies have shown that it inhibits uncoupling protein 2 (UCP2) expression and ameliorates podocyte injury in DN mice[137]. Puerarin, the active compound of Puerariae Lobatae Radix, attenuates diabetic kidney injury through the suppression of NADPH oxidase 4 (NOX4) expression in podocytes[140]. Salvianolic acid A, which is a water-soluble phenolic acid extracted from the dried root and rhizome of Salviae Miltiorrhizae Radix et Rhizoma, protects glomerular endothelial function and alleviates renal structural deterioration *in vivo*[126]. The chemical structures are shown in Fig. 6.

In addition to the above-detailed descriptions, Table 2 shows the various prescriptions, single TCM herbs, and active

Table 2 TCMs for DN treatment.

Drug	Composition	Model	Dosage	Result	Ref.
Prescription					
Baoshen recipe	Astragali Radix, Salviae Miltiorrhizae Radix et Rhizoma, Ligustri Lucidi Fructus, Hirudo, Scorpio	DN patients; SZT-induced DN rat; HG-induced murine podocytes cell	750 mg/kg; drug containing serum	ALB↓, SCr↓, UP↓, BUN↓, nephrin↑, p-p38↓, NOX4↓, MDA↓, NOS↓, ROS↓, T-SOD↑, BAX↓, BCL-2↑, caspase-3↓	90
Chaihuang Yishen granule	Astragali Radix, *Discorea Nipponica* Makino, Bupleuri Radix, Angelicae Sinensis Radix, Panacis Quinquefolii Radix, Hirudo	Unilateral nephrectomy combined with SZT-induced DN rat	0.56 g/kg	UP↓, COL-I/IV↓, FN↓, TGF-β1↓, TβR II↓, p-TβR I↓, p-SMAD3↓, SMAD7↑	91
Er Huang recipe	Astragali Radix, Rhei Radix et Rhizoma, Trigonellae Semen, Achyranthis Bidentatae Radix, Vaccariae Semen, Smilacis Glabrae Rhizome, Curcumae Rhizome	SZT-induced DN rat; HG-induced NRK-49F cell	1−4 g/kg; 0.01 −1 mg/mL	BG↓, SCr↓, BUN↓, ALB↓, UAE↓, IL-6↓, TNF-α↓, TGF-β1↓, COL-I/III↓, MMP2/9↓, CXCL6↓, CXCR1↓, PCNA↓, p-STAT3↓	92
Fuxin granules	Scrophulariae Radix, Rhei Radix et Rhizoma, *Euonymus alatus*, Astragali Radix, Alismatis Rhizoma, Anemarrhenae Rhizoma, Cuscutae Semen	C57BL/*Ksj*^{db} mice	14.43−28.66 g/kg	BG↓, TC↓, TAG↓, LDL↓, HbAlc↓, BUN↓, SCr↓, UCr↓, MA↓, TGF-β1↓, COL-I↓, SMAD2/3↓, eNOS↑, VEGFA↓, VEGFR2↓	93
Fufang Xueshuantong capsule	Notoginseng Radix et Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Scrophulariae Radix, Astragali Radix	SZT-induced DN rat	0.45−1.8 g/kg	UP↓, CCr↓, SOD↓, MDA↓	94
Gushen Jiedu capsule	Euryales Semen, Rosae Laevigatae Fructus, Coptidis Rhizoma, Rhei Radix et Rhizoma, Astragali Radix, Angelicae Sinensis Radix	SZT-induced DN rat	0.12−0.48 g/kg/day	UP↓, SCr↓, BUN↓, TG↓, TC↓, TP↓, podocin↑, nephrin↑, BAX↓, BCL-2↑, AKT↓	95
Huangkui capsule	*Abelmoschi Corolla*	Unilateral nephrectomy combined with SZT-induced rat	1−2 g/kg	BG↓, UA↓, SCr↓, COL-I↓, vimentin↓, α-SMA↓, NLRP3↓, caspase-1↓, IL-1β↓, TLR4↓, NF-κB p65↓, p-IKK↓	16
Jixuepaidu decoction	Centellae Herba, Astragali Radix, *Draconis Sanguis*	SZT-induced DN mice; HG-induced murine podocytes cell	3.15−12.6 g/kg; drug containing serum	BG↓, UP↓, p-cadherin↑, nephrin↑, desmin↓, vimentin↓, TGF-β1↓, SGK1↓, LOC498759↓	96
Naoxintong capsule	Astragali Radix, Paeoniae Radix Rubra, Salviae Miltiorrhizae Radix et Rhizoma, Persicae Semen, Angelicae Sinensis Radix, Achyranthis Bidentatae Radix, Chuanxiong Rhizoma, Cinnamomi Ranulus, Carthami Flos, Mori Ramulus, Olibanum, Myrrha, Scorpio, Pheretima, Hirudo, Spatholobi Caulis	BKS.C g−m +/+ *Lepr*^{db} mice	620 mg/kg	BG↓, TC↓, LDL↓, VLDL↓, TAG↓, ALT↓, AST↓, BUN↓, U-ALB↓, TNF-α↓, WT-1↑, VEGFA↓, COL1A2↓, COL4A1/3↓, MMP2/9↓, TGF-β1↓, TβR II↓, SMAD2/3↓, CTGF↓, AGEs↓, AGER↓, VCAM-1↓, ICAM-1↓, IL-1β/6↓, TNF-α↓, ERK1/2↓, GCK↑, FASN↓, ACC↓, IRS1/2↑, AKT1/2↑, p-AKT↑, AMPKα↑, HSL↑, FABP4↓, GLUT4↑, p-GSK3β↑, GSK3β↓	97
Oryeongsan	Alismatis Rhizoma, Polyporus, Atractylodis Macrocephalae Rhizoma, Poria, Cinnamomi Cortex	C57BLKS/+*Lepr*^{db} mice	100 mg/kg	BG↓, U-ALB↓, BUN↓, CCr↓, TC↓, TAG↓, HDL↑, LDL↓, HOMA-IR↓, TGF-β1↓, SMAD-2/4/7↓, COL-IV↓, CTGF↓, TIMP-2↓, MT1-MMP↑, ICAM-1↓, MCP-1↓	98
Qidi Tangshen granule	Rehmanniae Radix, Astragali Radix, Euryales Semen, Cornus Fruit, Hirudo, Rhei Radix et Rhizoma, Hedyotidis Diffusae Herba	C57BL/*Ksj*^{db} mice	3.37−10.29 g/kg	KIM-1↓, MCP-1↓, UAE↓, Lactobacillus↓, Bacteroides↓, Alloprevotella↑, Roseburia↓, β-MCA↓, TCA↓, Tβ-MCA↓, deoxycholic acid↓	99

Tangshen recipe	Astragali Radix, *Euonymus alatus*, Rehmanniae Radix, Citrus Aurantiuml, Cornus Fruit, Rhei Radix et Rhizome, Notoginseng Radix et Rhizoma	Unilateral nephrectomy combined with SZT-induced DN rat	1.36 g/kg	SCr↓, ALB↓, Bifidobacteriaceae genus↑, Actinobacteria↑, Serum AHR↓, Serum LPS↓, TLR4↓, p-JNK↓, IL-1β↓, TNF-α↓, MCP-1↓	100
Tongxinluo	Ginseng Radix et Rhizoma, Hirudo, Scorpio, Paeoniae Radix Rubra, Cicadae Periostracum, Eupolyphaga Steleophaga, Scolopendra, Santali Albi Lignum, Olibanum, Ziziphi Spinosae Semen, Borneolum, Dalbergiae Odoriferae Lignum	KK-Ay mice model; HG -induced HKCs cell	750 mg/kg; 50−500 μg/mL	UAlB/UCr↓, miR-21↓, E-cadherin↑, α-SMA↓, TGF-β1↓, SMAD7↑, SMAD3↓	101
Wenshen Jianpi recipe	Aconiti Lateralis Radix Praeparata, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Poria, Paeoniae Radix Alba, Glycyrrhizae Radix et Rhizoma, Zingiberis Rhizoma Recens	SZT-induced DN rat	7.5−30 g/kg	TP↑, ALB↑, nephrin↑, podocin↑	15
Yiqi Yangyin Huayu Tongluo recipe	Rehmanniae Radix, Astragali Radix, Salviae Miltiorrhizae Radix et Rhizoma, Chuanxiong Rhizoma, Polygonati Rhizoma, Pheretima, Hirudo, Scorpio	SZT-induced DN rat	1 g/kg	UP↓, ROS↓, JNK↓, COL-I↓, caspase-3↓	102
Zhenqing recipe	Ligustri Lucidi Fructus, Ecliptae Herba, Dioscoreae Rhizome	SZT-induced DN rat	4−8 g/kg	BG↓, TAG↓, TC↓, FN↓, TGF-β1↓, SREBP-1c↓, ACC↓, Fas↓, COL-IV↓	103
Zhenwu decoction	Aconiti Lateralis Radix Praeparata, Poria, Paeoniae Radix Alba, Zingiberis Rhizoma Recens, Atractylodis Rhizoma	SZT-induced DN rat	80−320 mg/kg	UP↓, SCr↓, BUN↓, Ang II↓, nephrin↑, podocin↑	104
FCM (fucoidan + a TCM formula)	Fucoidan, Astragali Radix, Rehmanniae Radix, Puerariae Lobatae Radix, Salviae Miltiorrhizae Radix et Rhizoma, Dioscoreae Rhizome, Lycii Fructus, Mori Fructus, Panacis Quinquefolii Radix	SZT-induced DN rat	100−600 mg/kg	BG↓, HOMA-IR↓, TC↓, TAG↓, HDL↓, LDL↓, MDA↓, SOD↓, GSH-PX↓, *Insr*↑, *Gck*↑, *Glut-2*↑, UCr↓, UP↓	105
Huangkui capsule + metformin	Abelmoschi Corolla	SZT-induced DN rat; HG-induced HK-2 cell	1.0 g/kg + 0.1 g/kg; 25−400 μg/mL + 2.5−40 mmol/L	BG↓, SCr↓, BUN↓, UP↓, LDL↓, TAG↓, TC↓, HDL↑, Klotho↑, TGF-β1↓, p-p38↓, FN↓, α-SMA↓, E-cadherin↑	106
Herbs and extracts					
Eucommiae Cortex	95% ethanol extract	SZT-induced DN rat	1 g/kg	BUN↓, CCr↓, UP↓, TGF-β↓, CTGF↓, p-SMAD2/3↓	107
Chuanxiong Rhizoma	Ethanol extract	SZT-induced DN mice	25−50 mg/kg	UP↓, UAE↓, UACR↓, TNF-α↓, TGF-β1↓, 8-OHdG↓	108
Polygoni Avicularis Herba	Ethanolic extract from rhizome	C57BL/6J *Lepr*^{db} mice; HG-induced primary human renal mesangial cell	10−50 mg/kg; 0−10 μg/mL	BG↓, HbA1c↓, insulin↓, HOMA-IR↓, UCr↓, CCr↓, U-ALB↓, CRP↓, KIM-1↓, nephrin↑, TGF-β1↓, COL-IV↓, ICAM-1↓, NLRP3↓, ASC↓, caspase-1↓, MCP-1↓	109
Moutan Cortex	Ethanol extract	SZT-induced DN rat; AGEs-induced HBZY-1 cell	1.25−5 g/kg; 50−200 μg/mL	BG↓, UP↓, SCr↓, IL-6↓, MCP-1↓, TGF-β1↓, ICAM-1↓, RAGE↓	110
Cassiae Semen	Cassiae Semen was extracted with 80% ethanol and treated with D101 macroporous resin	SZT-induced DN rat	27−81 mg/kg	BG↓, FINS↑, HOMA-IR↓, HbA1c↓, TC↓, TAG↓, LDL↓, HDL↑, TNF-α↓, IL-1β/6↓, T-SOD↑, MDA↓, CAT↑, GSH-Px↑, UP↓, SCr↓, BUN↓, RAGE↓	111

(*continued on next page*)

Table 2 (*continued*)

Drug	Composition	Model	Dosage	Result	Ref.
Lycii Fructus	Methanol extract of leaves	SZT-induced DN rat	100−400 mg/kg	SCr↓, BUN↓, ALB↑, UP↓, CCr↑, GSH↑, SOD↑, CAT↑, MDA↓, TNF-α↓, IL-6/1β↓, TGF-β1↓	14
Taxus chinensis	Aqueous extract	SZT-induced DN rat	0.32−1.28 g/kg	BG↓, SCr↓, UA↓, BUN↓, TGF-β1↓, α-SMA↓, p-SMAD2/3↓	112
Rehmanniae Radix	Distilled water extract	SZT-induced DN rat	100 mg/kg	BG↓, UN↓, TBA↓	113
Cyclocarya paliurus	Triterpenic acids-enriched fraction	SZT-induced DN rat; HG-induced HK-2 cells	40−160 mg/kg; 1−50 μg/mL	BG↓, BUN↓, SCr↓, MA↓, caspase-3↓, p-AMPK↑, LC3II↑, P-mTOK↓, P62↓	114
Trichosanthis Fructus	*Trichosanthes kirilowii* lectin	SZT-induced DN rat; HG-induced HK-2 cell	60 mg/kg; 62.5 −250 nmol/L	Caspase-9↓, IKKβ↓, IκBα↓, NF-κB p65 (cytoplasm)↑, NF-κB p65 (nuclear)↓	115
Moutan Cortex	MC-Pa	Human umbilical vein endothelial cells; type 2 diabetic rat	160 mg/kg; 64.5 μg/mL	BG↓, SCr↓, BUN↓, UP↓, AGEs↓, ROS↓, RAGE↓, FN↓, Col-IV↓, ICAM-1↓, VCAM-1↓, TGF-β1↓	116
Bioactive compounds					
Salidroside	Rhodiolae Crenulatae Radix et Rhizoma	SZT-induced DN mice	50−100 mg/kg	BG↓, TC↓, TAG↓, U-ALB↓, BUN↓, SCr↓, podocin↑, nephrin↑, COL-I↓, FN↓, α-SMA↓, sirtuin 1↑, PGC-1α↑, Prohibitin 1↑	117
Paeoniflorin	*Paeonia lactiflora* Pall root	*db/db* mice; BSA or AGEs-induced RAW264.7 cell	15−60 mg/kg; 10^{-8}−10^{-3} mol/L	UAE↓, CCr↓, TLR2/4↓, CD68↓, NF-κB p65↓, MyD88↓, p-IRAK1↓, TRIF↓, p-IRF3↓, iNOS↓, IL-1β↓, MCP-1↓, TNF-α↓	118
Skimmin	*Hydrangea paniculata*	SZT-induced DN rat	7.5−30 mg/kg	SCr↓, BG↓, CCr↑, TGF-β1↓, TβR I↓	119
Morroniside	Verbenae Herba	AGEs-induced rat GMCs	0.1−10 μmol/L	RAGE↓, p38MAPK↓, NF-κB↓, TGF-β↓, laminin↓, FN↓, COL-IV↓	120
Catalpol	Rehmanniae Radix root	KK-Ay mice; AGEs induced-GECs	50−100 mg/kg; 1−10 μmol/L	UP↓, SCr↓, BUN↓, VEGF↓, ICAM-1↓, MCP-1↓, E-cadherin↑, occludin↑, CD68↓, IL-1β/6↓, TNF-α↓, RhoA↓, ROCK↓, RAGE↓, VEGF↓	121
Astragaloside IV	Astragali Radix	SZT-induced DN rat; HG-induced MPC5 cell	5 mg/kg; 100 μg/L	U-ALB↓, TRAF5↓, TUG1↑, cleaved-caspase-3↓	122
Dioscin	*Dioscorea nipponica* Makino or *Dioscorea zingiberensis* Wright	SZT-induced DN mouse	15−60 mg/kg	BG↓, SCr↓, ALB↓, BUN↓, IL-6/1β↓, TLR4↓, p- NF-κB p65↓, TNF-α↓	123
Curcumin	Curcumae Longae Rhizoma	SZT-induced DN rat; DN rat serum-induced MPC5 cell	300 mg/kg/day; 40 mmol/L	BG↓, SCr↓, U-ALB↓, E-cadherin↑, vimentin↓, LC3↑, TWIST1↓, p62↓, p-mTOR↓, p-AKT↓, P13K↓	124
Pterostilbene	Vaccinium Uliginosum L. and *Santali Albi* Lignum	SZT-induced DN rat	5−25 mg/kg/day	BG↓, UP↓, SOD↑, GSH-PX↑, MDA↓, TGF-β↓, SMAD1↓, FN↓, TNF-α↓, IL-6/1β↓, MCP-1↓, p-NF-κB p65↓, p-Iκ-Bα↑, p-IKKβ↑	125
Salvianolic acid A	Salviae Miltiorrhizae Radix et Rhizoma	SZT-induced type 2 DN rat; AGEs-induced HRGECs	1 mg/kg/day; 0.3−3 μmol/L	BG↓, TAG↓, TC↓, LDL↓, U-ALB↓, BUN↓, SCr↓, UACR↓, AGEs↓, RAGE↓, RhoA↓, ROCK↓, E-cadherin↑, claudin-5↑, ROS↓, NOX4↓, MDA↓, 8-OHdG↓, NO↓, SOD↑, TNF-α↓, IL-6/1β↓, ICAM-1↓, VCAM-1↓, sirtuin1↑, FOXO3a↑, BNIP3↑, ATG5/7/12↑	126

Tectorigenin	Belamcandae Rhizoma	BKS.C g−m +/+ *Lepr*^{db} mice; HG-induced HRGECs	75 mg/kg; 5 −10 μmol/L	HOMA-IR↓, ALB↓, SCr↓, insulin↓, WT1↑, nephrin↑, TGF-β1↓, CCr↑, COL-IV↓, SMAD4↓, TAG↓, NEFA↓, LDL↓, PPARα↑, ACOX1↑, CPT1α↑, LCAD↑, MCAD↑, p-ACC↑, SREBP1c↑, p-eNOS↑, p-IRS1↑, MgI2↑, GLUT4↑, p-IRS1↑, p-AKT↑, p-FOXO1↑, GCK↑, CL2/BAX↑, TNF-α↓, CXCL1↓, IL-6↓, Arg1↑, IL-10↑, AdipoR1/2↑, p-LKB1↑, p-AMPKα↑, VCAM-1↓, ICAM-1↓, NF-κB p65↓	127
Silymarin	Silybi Fructus seeds coat	SZT-induced DN rat; HG-induced MPC-5 cell	100−900 μg/kg; 0−128 μg/mL	BG↓, BUN↓, UP↓, SCr↓, podocin↑, nephrin↑, ICAM-1↓, TGF-β1↓, Col-I↓, FN↓, MDA↓, SOD↑, CAT↑, GSH↑, IL-6/8/10↓, TNF-α↓, p-JAK2↓, p-STAT3↓, SOCS1↑, SMAD6/7↑, SMAD2/3↓, TGF-β1↓	13
Triptolide	*Tripterygium wilfordii* Hook F	*db/db* mice	25−50 μg/kg	U-ALB↓, TC↓, TAG↓, LDL↓, HDL↓, MCP-1↓, 4-HNE↓	128
Emodin	Rhei Radix et Rhizoma	KK-Ay mice; HG-induced mouse podocyte cell	40−80 mg/kg; 20−40 μmol/L	U-ALB↓, BUN↓, SCr↓, GRP78↓, nephrin↑, p-PERK↓, p-eIF2α↓, ATF4↓, CHOP↓, BCL-2↑, BAX↓	129
Sequoyitol	*Amentotaxus yunnanensis*	SZT-induced DN rat; HG-induced rat mesangial cell	12.5−50 mg/kg; 1−10 μmol/L	BG↓, insulin↑, BUN↓, SCr↓, COL-IV↓, T-AOC↑, ROS↓, MDA↓, p22-*phox*↓, p47-*phox*↓, NF-κB↓, TGF-β1↓	130
Hirudin	Hirudo	SZT-induced DN rat	1 mg/kg	BUN↓, SCr↓, UP↓, TGF-β1↓, VEGF↓	131
Cordycepin	Cordyceps and *Cordyceps militaris*	SZT-induced DN rat; HG-induced HRGECs	10−500 mg/kg; 10−100 μg/mL	UP↓, BG↓, TC↓, TAG↓, CCr↓, IL-1β/6/18↓, α-SMA↓, TAG↓, TIMP-1↓, BCL-2↑, BAX↓, caspase3↓, Beclin1↑, p62↓	132
N^6-(2-Hydroxyethyl)-adenosine	*Cordyceps cicadae*	Alloxan-induced DN rat	20−40 mg/kg	BG↓, SCr↓, BUN↓, U-ALB↓, UP↓, CCr↑, TNF-α↓, IL-1β↓, IL-6↓, NF-kB↓, TGF-β1↓, MDA↓, SOD↑, CAT↑, GSH↑	133
Berberine	Coptidis rhizoma	SZT-induced DN rat	50−200 mg/kg	BG↓, TAG↓, TC↓, LDL↓, HDL↑, TGF-β1↓, COL- IV↓, GRK2/3/6	134
Ferulic acid	Angelicae Sinensis Radix	OLETF rats	0.2% Ferulic acid -containing chow	UP↓, TGF-β1↓	135
Hyperoside	Abelmoschi Corolla	AGE-BSA-induced podocytes	50−200 μg/mL	Caspase-3/8↓	136
Genipin	Gardeniae Fructus	SZT-induced DN mice; HG-induced podocyte cell	50 mg/kg	UP↓, podocin↑, WT1↑, UCP2↓	137
Icariin	Epimedii Folium	SZT-induced DN rat	80 mg/kg	BUN↓, SCr↓, MDA↓, hydroxyproline↓, SOD↓, TGF-β1↓, COL-IV↓	138
Lithospermate B	Salviae Miltiorrhizae Radix et rhizoma	SZT-induced DN rat; HG-induced mesangial cell	10 μg/kg; 40 μg/mL	UP↓, MDA↓, TGF-β1↓, FN↓, COL-I↓, ROS↓, PKC↓	139
Puerarin	Puerariae Lobatae Radix	SZT-induced DN rat	100 mg/kg	UP↓, nephrin↑, podocin↑, 8-OHdG↓, MMP-9↓	140
Rhein	Rhei Radix et Rhizoma	C57BL/KsJ^{db} mice	150 mg/kg	TC↓, TAG↓, LDL↓, UAE↓, TGF-β1↓, FN↓, apolipoprotein E↓	141

(*continued on next page*)

Table 2 (*continued*)

Drug	Composition	Model	Dosage	Result	Ref.
Calycosin	Astragali Radix	AGEs-induced glomerular endothelial cell, HG-induced mesangial cell	1−100 μmol/L	Apoptosis↑	142
Calycosin-7-*O*-*β*-D-glucoside	Astragali Radix	AGEs-induced glomerular endothelial cell, HG-induced mesangial cell	1−100 μmol/L	Apoptosis↑	142

constituents used for DN treatment. These new pharmacological developments can significantly lower blood sugar, UP, inflammatory factors, and oxidative stress, offering new resources for innovative medicine development for clinical application.

3.3. *TCM for LN treatment*

TCM has a wealth of clinical experience in treating LN and has compiled several prescriptions with potent curative effects. Traditionally, the main aim when treating the condition is to nourish the liver and remove heat. In this review, we described six prescriptions (Huanglian Jiedu decoction, Bawei Dihuang pills, Renshen Yangrong decoction [RSYRD], Qingshen recipe, Qingyang Toujie mixture, Shenqi granules) and two herbal extracts (total glucosides of Paeonia Lactiflora Pall, Tripterygium extracts) that are used in LN treatment[144−150]. Huanglian Jiedu decoction has been traditionally used for heat dissipation and detoxification in China, and it can reduce serum double-stranded DNA (dsDNA) levels and immune complex deposition in LN[144]. Bawei Dihuang pills effectively inhibit the production of autoantibodies in LN mice[145]. RSYRD, which consists of 12 species of medical herbs, is mainly used to improve the symptoms of anemia and low physical strength in patients. *In vivo* experiments have confirmed that RSYRD can significantly improve the symptoms of increased UP[146]. Clinical trials (No. 2007LCSY006) demonstrated that Shenqi granule can improve renal function in LN patients, and it has similar efficacy but fewer adverse events than standard therapy with prednisone and cyclophosphamide[147]. Qingshen recipe, a Chinese medicine prescription with the properties of clearing heat, benefiting kidneys, and resolving blood stasis, improves treatment effects by reducing the levels of IgG and UP[148]. Qingyang Toujie mixture addresses the Th1/Th2 cytokine imbalance, decreases levels of pro-inflammatory cytokines, and reduces immune complex deposition[148].

We analyzed the compositions of these prescriptions and found that they are made up of 41 different kinds of TCMs. Rehmanniae Radix, Poria, and Astragali Radix are frequently used and are included in at least three prescriptions. The use frequencies are shown in Fig. 5C.

With a focus on pure compounds and single TCM herbs, we summarized 21 compounds, including phenols (procyanidin B2, resveratrol, curcumin), alkaloids (piperlongumine, piperine, sophocarpine), flavonoids (mangiferin, baicalin, baicalein, icariin), and phenylpropanoids (honokiol, chinoethin)[151−171] and selected representative compounds based on their chemical structure types. Proanthocyanidin B2, a representative phenolic compound used in LN treatment, exists naturally in cocoa, apples, and grapes; it significantly slows LN progression by inhibiting the activation of the NLRP3 inflammasome[159]. Sophorine is a quinoline alkaloid widely employed in TCM, and research in LN mice has shown that the treatment reduces UP excretion and serum dsDNA[160]. Icariin, a bioactive component of flavonoids isolated from Epimedii Folium reduces kidney damage by inhibiting the activation of the NLRP3 inflammasome[154]. Magnolol is a bioactive compound obtained from Magnoliae Officinalis Cortex that reduces serum dsDNA and kidney IgG levels in LN mice[158]. The chemical structures and their classification are shown in Figs. 6 and 7.

The prescriptions, extracts, and bioactive compounds used in LN treatment are displayed in Table 3. In general, these prescriptions and pure compounds with biological effects offer a way to address the underlying problems with LN control.

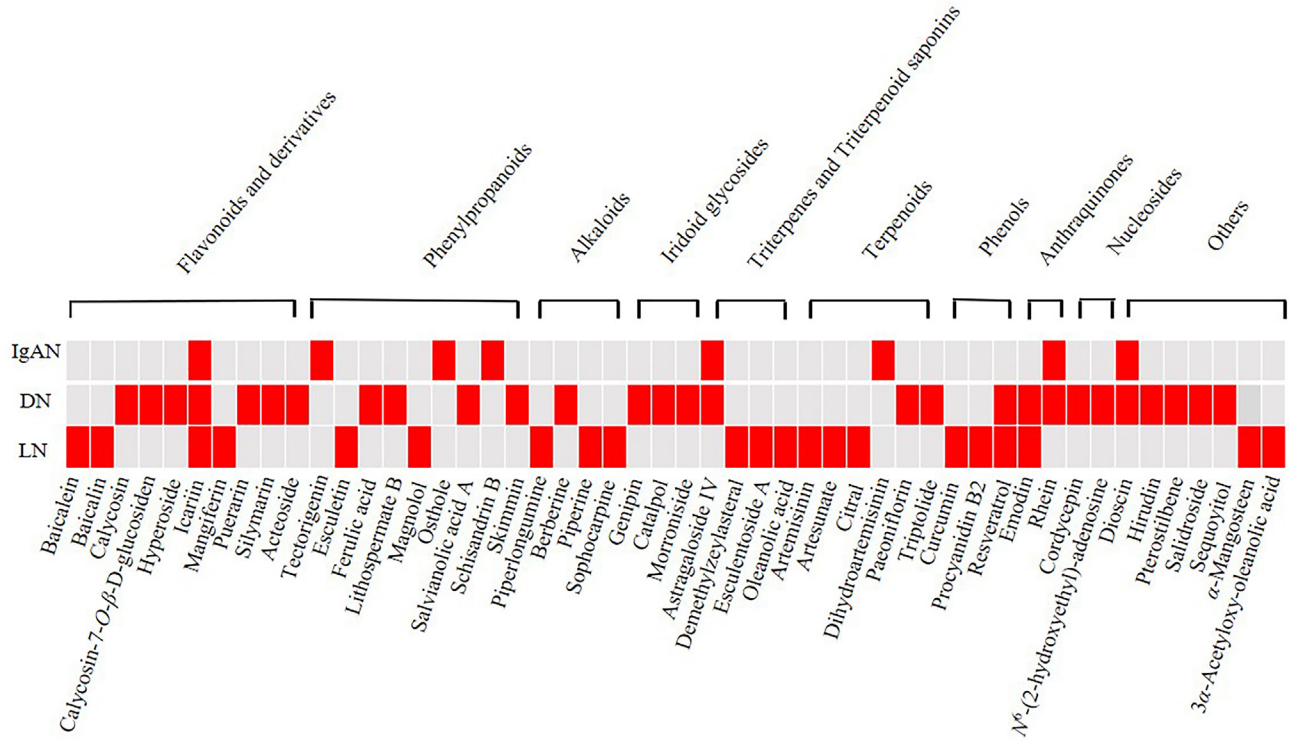

Figure 7 The bioactive compounds used in IgAN, DN, LN treatment, and their classification.

4. Mechanisms of TCMs in IRN treatment

4.1. *Regulation of immunity*

In IRN, T and B lymphocytes are usually in a highly active state. Also commonly observed are abnormal autoantibody production levels, immune complex deposition, macrophage infiltration, and other phenomena. Hence, the regulation of immune activity is now an important strategy to prevent and treat IRN.

In IgAN, a combination of artemisinin and hydroxychloroquine inhibits Th2 and Th17 cell differentiation but promotes Th1 and Treg cell differentiation, and it specifically produces immunosuppressive effects by regulating the differentiation of $CD4^+$ T cell subsets[80]. Hirudin protects against IgAN by maintaining the homeostasis of the immune system through reversing the down-regulation of $CD4^+CD25^+FoxP3^+$ Treg cells and Th1/Th2 levels[82]. In addition, rhein, icariin, and schisandrin B can significantly improve the deposition of IgA immune complexes in the kidneys[84–86].

In DN, paeoniflorin blocks macrophage recruitment and decreases MyD88, NF-κB p65, p-IRF3, TNF-α, IL-1β, MCP-1, phospho-interleukin 1 receptor-associated kinase (p-IRAK1) and inhaled nitric oxide synthase (iNOS) expression[118]. Tangshen recipe alleviates the expression of TLR4, inhibits the activation of the NF-κB signaling pathway, and decreases IL-1β, TNF-α, and MCP-1 levels[100].

In LN, mangiferin expands the $CD4^+FoxP3^+$ Treg proportion, inhibits T cell proliferation, and protects renal function by regulating the mammalian target of rapamycin (mTOR)/p70 ribosomal protein S6 kinase (p70S6K) pathway[153]. Baicalin inhibits mTOR activation, Th cells differentiation, and IL-21 production, and stimulates $Foxp3^+$ Treg expansion[151]. Piperlongumine suppresses the frequency of Th17 cells and promotes $CD4^+FoxP3^+$ Treg accumulation by participating in JAK/STAT3 signaling pathway activity[162]. Additionally, icariin, sophocarpine, piperlongumine, α-mangosteen, and 3β-acetyloxy-oleanolic acid reduce the deposition of IgG and IgM in immune complexes[154,160,162,169,171]. The mechanisms are shown in Fig. 8.

4.2. *Inhibition of inflammation*

Inflammation is a defensive response of the body to external stimuli that leads to inappropriate or excessive inflammatory reactions when immune responses are abnormal. Recent studies have confirmed that the pathogenesis of IRN is accompanied by inflammation, and therefore inhibiting inflammation may be an effective therapeutic strategy to delay disease progression[172].

Some active monomers and prescriptions show potent anti-inflammatory effects on IgA prevention. Hirudin, a natural thrombin inhibitor, regulates phosphorylated inhibitor of phosphorylated inhibitor of kappa B alpha (p-IκBα), NF-κB p65, TNF-α, vascular cell adhesion molecule 1 (VCAM-1) proteins, and decreases the levels of the inflammatory factors IL-1β, IL-6, and IL-18, rescuing the occurrence of proteinuria in IgAN rats[82]. Icarin attenuates the inflammatory response in the IgAN rat by blocking NF-κB nuclear translocation and NLRP3 activation, and it decreases the expression of ASC, caspase-1, IL-18, and IL-1[85]. Schisandrin B protecteds IgAN rats from inflammation damage by inhibiting NF-κB and reducing the levels of several inflammatory factors, including TNF-α, IL-1β, and MCP-1[86]. Acteoside regulates the functional disorder of Th22 cells; preventes C−C motif chemokine ligand (CCL) 20, CCL22, and CCL27 expression; and alleviates inflammatory injury in mesangial cells[88].

In DN-associated inflammation, catalpol decreases macrophage infiltration and IL-1β, IL-6, and TNF-α release in DN mice.

Table 3 TCMs for LN treatment.

Drug	Composition	Model	Dosage	Result	Ref.
Prescriptions					
Huanglian Jiedu decoction	Coptidis Rhizoma, Scutellariae Radix, Phellodendri Chinensis Cortex, Gardeniae Fructus	MRL/lpr mice	5.4 g/kg	BUN↓, SCr↓, UP↓, IL-6/10↓, IFN-γ↓, anti-dsDNA↓, C3↑, p-STAT3↓	144
Bawei Dihuang pill	Rehmanniae Radix, Cornus Fruit, Dioscoreae Rhizoma, Alismatis Rhizome, Poria, Moutan Cortex, Cinnamomi Cortex, Aconitum Carmichaelii Debeaux	MRL/lpr mice	1 g/kg	UP↓, IFN-γ↓, IL-4↑, IL-12↓	145
Renshen Yangrong decoction	Angelicae Sinensis Radix, Rehmanniae Radix, Ginseng Radix et Rhizome, Atractylodis Macrocephalae Rhizoma, Poria, Cinnamon Cassia, Citri Reticulatae Pericarpium, Paeoniae Radix Alba, Polygalae Radix, Astragali Radix, Schisandrae Chinensis Fructus, Glycyrrhizae Radix et Rhizoma	MRL/lpr mice	200 mg/kg	IL-6↓, IFN-7↑, UP↓	146
Shenqi granule	Astragali Radix, Angelicae Sinensis Radix, Atractylodis Rhizoma, Atractylodis Macrocephalae Rhizoma, Dioscoreae Rhizoma, Polyporus, Poria, Bombyx Batryticatus, Hedyotidis Diffusae Herba, Coicis Semen, Codonopsis Radix, Salviae Miltiorrhizae Radix et Rhizoma, Hirudo	LN patients	9.6 g/tid	UP↓, SCr↓	147
Qingshen recipe	Phellodendri Chinensis Cortex, Hedyotidis Diffusae Herba, Vespae Nidus, Rehmanniae Radix, Cornus Fruit, Rosae Laevigatae Fructus, Astragali Radix, Chuanxiong Rhizoma, Scorpio, Carthami Flos, Leonuri Herba, Poria, Plantaginis Semen, Pyrrosiae Folium, Glycyrrhizae Radix et Rhizoma	LN patients	/	UP↓, HMGB1↓, IgG↓, IL-17↓, C3/4↑	148
Qingyang Toujie mixture	Artemisiae Annuae Herba, Trionycis Carapax, Bubali Cornu, Rehmanniae Radix, Moutan Cortex	SLE patients	/	IL-4/10/12↓, IFN-γ↓	148
Herbs and extracts					
Paeonia Lactiflora Pall	Total glucosides	Pristane-induced LN mice; IL-4 or LPS plus IFN-γ-induced Raw264.7 cell	0.1−0.2 g/kg; 20−40 μg/mL	UP↓, SCr↓, anti-ds-DNA↓, PD-L1/2↑, p-STAT6↑, CD206↑	149
Tripterygium wilfordii Hook F	Tripterygium extracts	MRL/lpr mice	0.125 mg/kg	UP↓, BUN↓, SCr↓, C3↓, IgG↓, p-JAK1↓, p-STAT1↓	150
Bioactive compounds					
Baicalin	Scutellariae Radix	MRL/lpr mice; Naive $CD4^+$ T cell	200 mg/kg; 0−40 μmol/L	UP↓, SCr↓, anti-dsDNA↓, α-SMA↓, IgG↓, C3↓, BCL-6↓, STAT3↓, IL-21↓, Foxp3↑, TGF-β↑, IL-10↑, p-4EBP1↓, p-S6 kinase↓, mTOR↓	151
Baicalein	Scutellariae Radix	Pristane-induced LN mice; LPS-induced myeloid-derived suppressor cell	0.025−0.1 g/kg; 0.01 −0.04 μmol/L	U-ALB↓, anti-dsDNA↓, IgG↓, IL-1β/6/18/17A↓, IFN-α↓, GSH-PX↑, ROS↓, Nrf2↑, HO-1↑, NLRP3↓, caspase-1-p20↓, NF-κB p65↓, NF-κB↓, arginase-1↓, p47-*phox*↓, GP91-*phox*↓, iNOS↓, Nrf2↑, HO-1↑	152
Mangiferin	Anemarrhenae Rhizoma	MRL/lpr mice; $CD3^+CD25^-$ T cell	20−40 mg/kg; 40 μmol/L	UP↓, SCr↓, anti-ds-DNA↓, α-SMA↓, IgG↓, C3↓, IFN-γ↓, IL-6↓, TNF-α↓, p-mTOR↓	153
Icariin	Epimedii Folium	MRL/lpr mice	10 mg/kg	UP↓, BUN↓, SCr↓, IgG↓, anti-dsDNA↓, NF-κB↓, TNF-α↓, NF-κB p65↓, p-IκB↓, F4/80↓, NLRP3↓, caspase-1-p20↓, IL-1β↓	154

Emodin	Rhei Radix et Rhizoma	BXSB mice; mouse mesangial cell	5−20 mg/kg; 40 μmol/L	UP↓, anti-dsDNA↓, TNF-α↓, ICAM-1↓, FN1↓	155
Resveratrol	Polygoni Cuspidati Rhizoma et Radix	MRL/lpr mice	20 mg/kg	anti-dsDNA↓, Fcgamma receptor IIB↑, IgG/M↓, sirtuin1↑, acetylated-NF-κB p65 (K310)↓, p-NF-κB p65 (S468)↓, p-NF-κB p65 (S536)↑	156
Curcumin	Curcumae Longae Rhizoma	MRL/lpr mice	200 mg/kg	UP↓, anti-dsDNA↓, NLRP3↓, caspase-1-p20↓	157
Magnolol	Magnoliae Officinalis Cortex	MRL/lpr mice	5 mg/kg	BUN↓, p-IκB↓, NF-κB↓, NLPR3↓, IL-1β↓, C3↓, IgG↓, CCL2↓, F4/80↓, TNF-α↓, anti-dsDNA↓	158
Procyanidin B2	Cocoa, apples or grapes	MRL/lpr mice	100 mg/kg	UP↓, BUN↓, SCr↓, IgG↓, NLRP3↓, ASC↓, p-caspase-1↓, IL-1β/18↓, caspase-1-p20↓, anti-ds-DNA↓	159
Sophocarpine	Sophorae Flavescentis Radix	MRL/lpr mice; HEK293 cell	100 mg/kg; 0−800 μg/mL	UP↓, BUN↓, IgG↓, C3↓, anti-ds-DNA↓, NLRP3↓, ASC↓, caspase-1↓, IL-1β/6↓, p-IKKα/β↓, p-IκBα↓, NF-κB p65↓, TNF-α↓	160
Piperine	Piperis Fructus	Pristane-induced LN mice; LPS and ATP induced HK-2 cell	12.5−50 mg/kg; 12.5 −50 μmol/L	IL-1β/18↓, p-IL-1β↓, HMGB1↓, p-caspase-1↓, NLRP3↓, p-AMPK↓	161
Piperlongumine	Piperis Fructus	MRL/lpr mice; splenocytes of MRL-Fas(lpr) mice	2.4 mg/kg; 5 μmol/L	BUN↓, SCr↓, IgG↓, C3↓, anti-dsDNA↓, IL-6/17/23↓, TNF-α↓, p-JAK↓, p-STAT3↓	162
Oleanolic acid	Loquat	Pristane-induced LN mice; RORγt-Jurkat cell	50 mg/kg; 1.25 −20 μmol/L	anti-dsDNA↓, IL-17A↓, IFN-γ↓, IgG/M↓	163
Demethylzeylasteral	*Tripterygium wilfordii* Hook F	MRL/lpr mice	30−120 mg/kg	UP↓, anti-dsDNA↓, IL23↓ TNF-α↓, COX-2↓, ICAM-1↓, p- NF-κB p65 (nuclear)↓, p-IKK (cytoplasm)↓	164
Esculentoside A	Phytolaccae Radix	BXSB mice	20 mg/kg	UP↓, SCr↓, BUN↓, IL-6↓, TNF-α↓, PCNA↓, caspase-3↑, FasL↑, Fas↑	165
Esculetin	*Hydrangea paniculata*	MRL/lpr mice; antibody sensitized sheep erythrocytes	20−40 mg/kg; 0−50 μmol/L	BUN↓, SCr↓, U-ALB↓, anti-dsDNA↓, IgG↓, TNF-α↓, INF-γ↓, IL-4/6/17/12p35/12p40/1α/1β↓, MCP-1↓, ICAM-1↓, VCAM-1↓, TGF-β1↓, GSH↑, MDA↓, SOD↑, FN↓, C3↓, CD46/55/59↑, Nrf2↑, HO-1↑, NQO-1↑, Keap1↓, ROS↓, p-SMAD3↓, NF-κB p65 (nuclear)↓	166
Citral	*Litsea cubeba*	LPS-induced LN mouse, LPS/ATP-induced peritoneal macrophages, murine macrophage cell	200 mg/kg	BUN↓, SCr↓, IgG↓, C3↓, NLRP3↓, IL-1β↓, caspase-1↓, ROS↓, COX-2↓, prostaglandin E2↓, p47-*phox*↓, Nrf2 (nuclear)↑, NF-κB p65 (nuclear)↓	167
Artesunate	Artemisiae Annuae Herba	MRL/lpr mouse	125 mg/kg	UP↓, SCr↓, anti-ds-DNA↓, MCP-1↓	168
α-Mangosteen	Mangosteens	Pristane-induced LN mouse, RORγt-Jurkat cells	50 mg/kg; 0.08−10 μm/L	anti-ds-DNA↓, IFN-γ↓, IL-17A/17F↓, IgG/M↓	169
Artemisinin	Artemisiae Annuae Herba	TNF inhibitor protein-induced LN mouse	150 mg/kg	UP↓, NF-κB p65↓, TGF-β1↓, TNF-α↓, IL-6↓	170
3β-Acetyloxy-oleanolic acid	*Symplocos theophrastifolia*	Pristane-induced LN mouse, RORγt-Jurkat cells	50 mg/kg; 0.08 −10 μmol/L	IL-17A/17F/17/22↓, Foxp3↑, anti-ds-DNA↓, RORγt↓, IgG/M↓	171

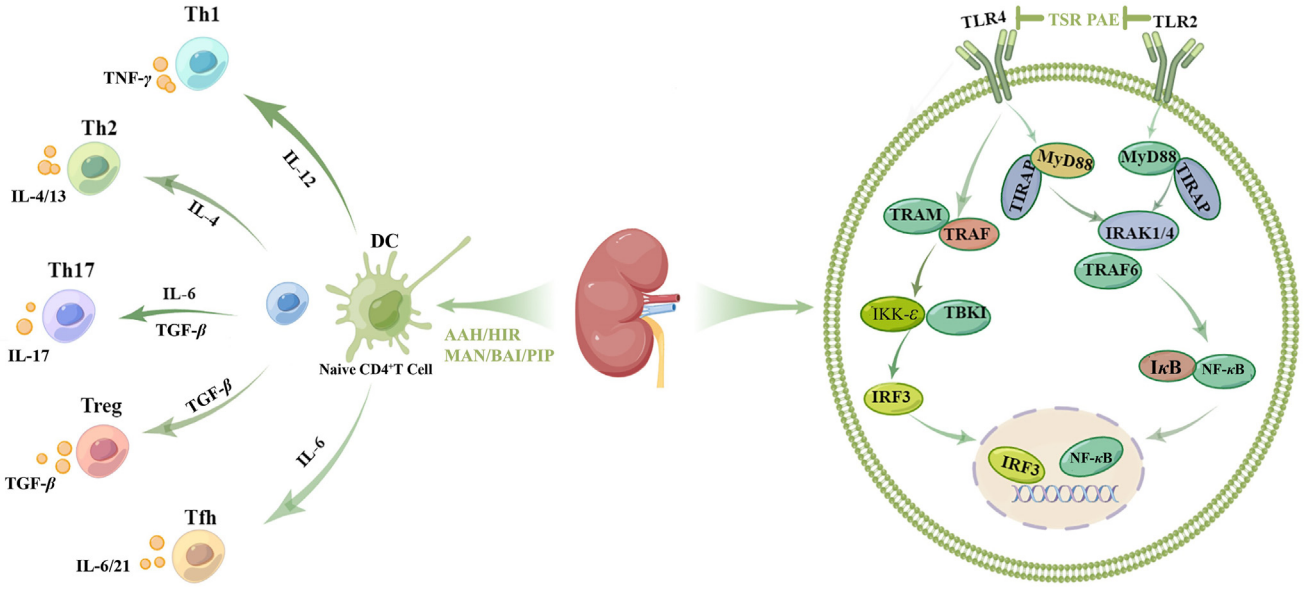

Figure 8 The immunity-related signaling pathways involved in IRN. AAH, HIR, MAN, BAI and PIP protects the kidney from damage by participating in the mediation of T cell differentiation; TSF alleviates the expression of TLR4, inhibits the activation of NF-κB signaling pathway; PAE decreases the expression of MyD88 and NF-κB p65, and inhibits the recruitment of immune cells; RHE, ICA, Sch B, SOP, PIP, α-MAN, and 3β-AOA improves the deposition of immune complexes in kidney (Not shown). Abbreviations: AAH, artemisinin and hydroxychloroquine combination; HIR, hirudin; RHE, rhein; ICA, icariin; SchB, schisandrin B; PAE, paeoniflorin; TSR, Tangshen recipe; MAN, mangiferin; BAI, baicalin; PIP, piperlongumine; α-MAN, α-mangosteen; 3β-AOA, 3β-acetyloxy-oleanolic acid.

Inflammatory responses and RAGE/Ras homolog gene family member A (RhoA)/Rho-associated coiled-coil kinase (ROCK) activity are also significantly decreased, suggesting that catalpol has potential as an agent for DN treatment[121]. Dioscin inhibits the release of inflammatory factors in streptozotocin (SZT)-induced DN mice but did not affect SZT-induced TLR4$^{-/-}$ mice, indicating that dioscin antagonizes the TLR4/NF-κB pathway[123]. Silymarin alleviates the high-glucose-induced inflammatory response of podocytes and the levels of IL-6, IL-8, TNF-α, IL-10, TGF-β, and ICAM-1 in DN rats by regulating the JAK2/STAT3/suppressor of cytokine signaling 1 (SOCS1) signaling pathway[13].

Icariin inhibits inflammatory responses in LN mice by regulating the NF-κB signaling pathway and the NLRP3 inflammasome[154]. Similar effects are also observed following treatment with honokiol, which affects macrophage infiltration and down-regulates IL-1β levels[158]. Procyanidin B2[159], piperine[161], demethylzeylasteral[164], and sophorine[160] also alleviate inflammation in LN by regulating NLRP3 or the NF-κB signaling pathway. The mechanisms are shown in Fig. 9.

4.3. *Amelioration of renal fibrosis*

Renal fibrosis is a fundamental pathological change that leads to ESRD. Modern studies have confirmed that the excessive deposition of extracellular matrix in glomeruli promotes glomerular sclerosis[173]. Thus, fibrosis prevention is an important breakthrough in IRN treatment.

In IgAN, hirudin and icariin significantly down-regulate the renal fibrosis indexes TGF-β1, collagen-IV (COL-IV), FN1 and alleviate disease progression by inhibiting fibrosis[82,85]. Whereas rhein attenuates glomerular pathological changes and tubulointerstitial fibrosis by inhibiting TLR4-mediated fibrosis signals and the expression of the fibrosis molecule TGF-β1[84].

In DN, salidroside improves extracellular matrix deposition and glomerular fibrosis by inhibiting COL-I and FN expression[117]. HKC prevents DN development by reducing EMT progression in the renal tubular, and decreasing vimentin, alpha-smooth muscle actin (α-SMA), and COL-I expression[16]. Evidences indicate that Jixue Paidu decoction reverses renal injury and EMT through the TGF-β1/SGK1-LOC498759 signaling pathway[96]. In addition, Er Huang recipe alleviates the increase in C−X−C motif chemokine ligand 6 (CXCL6), C−X−C chemokine receptor type 1 (CXCR1), matrix metallopeptidase 2 (MMP2), MMP9, COL-I/III, and proliferating cell nuclear antigen (PCNA) that occur in DN rats by inhibiting the CXCL6/JAK/STAT3 signaling pathway, suggesting it might be an effective drug for the treatment of fibrotic nephropathy[92].

In LN, emodin inhibits the differentiation of mouse mesangial cells into cells with a fibroblast-like phenotype and decreases TNF-α, ICAM-1, and FN1 expression in renal tissues[155]. Esculetin blocks the TGF-β/SMAD3 pro-fibrotic pathway and decreases FN protein expression[166]. The mechanisms are shown in Fig. 10.

4.4. *Inhibition of oxidative stress*

Oxidative stress is a negative force caused by free radicals in the body and is considered an important factor in aging and IRN disease[174]. Recent studies have demonstrated that ROS plays a major pathogenic role in many types of nephritis[175].

In IgAN, osthole was found to reduce ROS production in adenosine triphosphate (ATP)-induced macrophages and lipopolysaccharide (LPS)-treated mesangial cells, and it significantly improved renal function, reduced UP excretion, and alleviated the degree of renal deterioration in mice[83].

In DN, salvianolic acid A reduces oxidative stress in AGE-induced glomerular endothelial cells and DN rats by decreasing

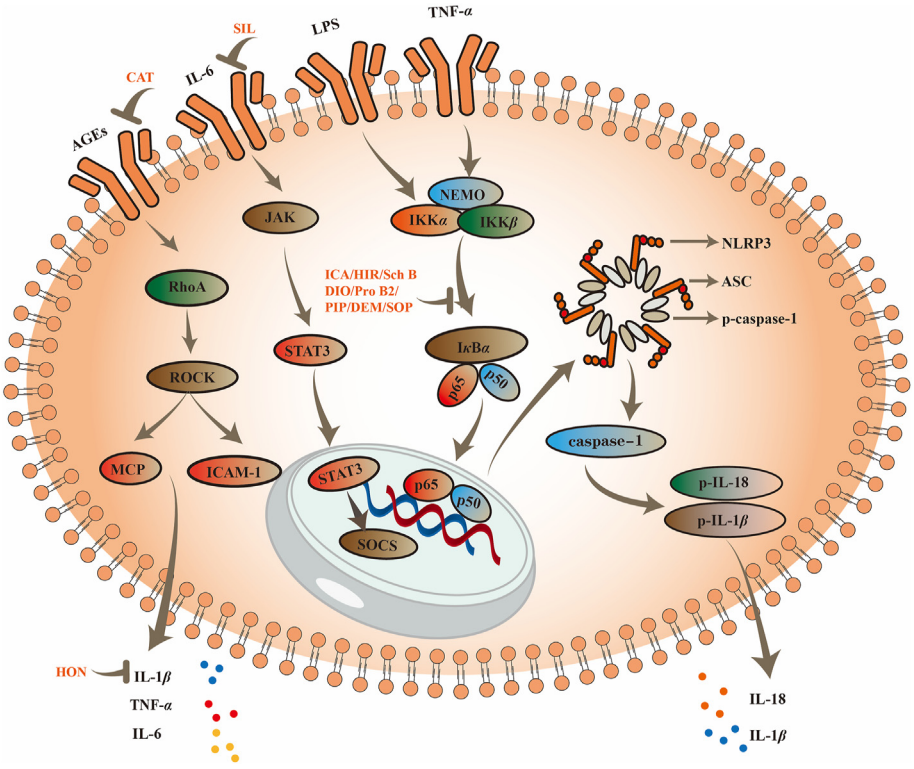

Figure 9 The inflammatory-related signaling pathways involved in IRN. ICA, HIR, Sch B, DIO, Pro B2, PIP, DEM and SOP inhibit NF-κB and NLRP3 signaling pathway; CAT inhibits RAGE/RhoA/ROCK activation; SIL regulates the JAK2/STAT3/SOCS1 signaling pathway; HON down-regulates the levels of inflammatory factor IL-1β; ultimately alleviating renal inflammation. Abbreviations: HIR, hirudin; ICA, icarin; Sch B, schisandrin B; DIO, dioscin; Pro B2, procyanidin B2; PIP, piperine; DEM, demethylzeylasteral; SOP, sophorine; CAT, catalpol; SIL, silymarin; HON, honok.

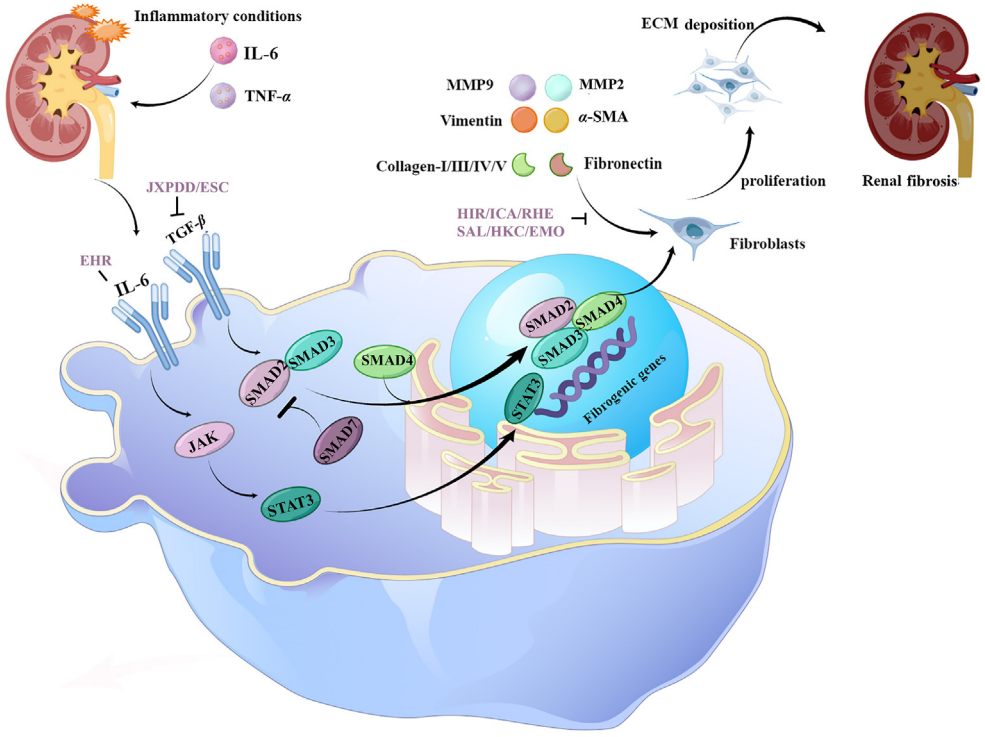

Figure 10 The renal fibrosis-related signaling pathways involved in IRN. HIR, ICA, RHE, SAL, HKC, EMO down-regulates the expression of renal fibrosis indexes TGF-β1, collagen-I/III/IV/V, vimentin, MMP2/9, α-SMA and fibronectin; JXPDD reverses renal injury through TGF-β1/SGK1-LOC498759 signaling pathway; Esculetin blocks TGF-β/SMAD3 pro-fibrotic pathway and decreases fibronectin protein expression; EHR prevents renal fibrosis by regulating CXCL6/JAK/STAT3 signaling pathway. Abbreviations: HIR, hirudin; ICA, icariin; RHE, rhein; SAL, salidroside; HKC, Huangkui capsule; JXPDD, Jixue Paidu decoction; EMO, emodin; ESC, esculetin; EHR, Er Huang recipe.

MDA, 8-hidroxy-2-deoxyguanosine (8-OHdG), and NO and increasing SOD levels. These effects of salvianolic acid A are mainly achieved through its regulation on AGE/RAGE/NOX4 signaling pathway[126]. FCM (a combination of fucoidan and a TCM formula), pterostilbene, N^6-(2-yethyl)-adenosine, and Cassiae Semen extract show similar effects. Most of these compounds play anti-oxidative stress roles by reducing MDA levels and increasing the activities of the antioxidant enzymes SOD, catalase (CAT), and heme oxygenase-1 (HO-1)[105,111,125,133].

In LN, esculetin blocks oxidative stress by activating nuclear factor erythroid 2-related factor 2 (Nrf2), which leads to a reduction in MDA and ROS and an increase in SOD and CAT[166]. Similarly, the antioxidant effect of citral is also dependent on Nrf2 activation and has been observed to reduce the levels of ROS, 47 kDa subunit of the NADPH-oxidase system (p47-*phox*), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) in LN mice[167]. The mechanisms are shown in Fig. 11.

4.5. *Inhibition of autophagy*

Autophagy has attracted an increasing amount of attention in recent years, as it is involved in phagocytosing pathogens, regulating inflammatory responses, and maintaining the homeostasis of the body's internal environment[176]. Recently, it has been proven to play a role in IRN progression[176].

In lgAN, dihydroartemisinin inhibits the expression of a representative autophagy protein LC3B by regulating the mTOR/ribosomal protein S6 kinase beta 1 (S6K1) pathway[87]. In DN, the triterpenic acid in *Cyclocarya paliurus* activates adenosine monophosphate-activated protein kinase (AMPK) and microtubule-associated protein light chain 3 (LC3), inhibits mTOR phosphorylation, and reduces sequestosome1 protein (p62) levels, suggesting that it improves renal injury by regulating the AMPK/mTOR pathway[114]. Curcumin alleviates DN by regulating the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway and induces autophagy in MPC5 cells[124]. In addition, cordycepin protects against DN by increasing beclin1 and LC3, inhibiting p62 expression, and inducing autophagy in the SZT-induced DN rat model[132].

4.6. *Others*

Intestinal microbes play an important role in maintaining intestinal homeostasis and barrier function. An imbalance in intestinal microbes leads to the leakage of pro-inflammatory bacterial products, which endangers host health[177]. Studies have reported that Qidi Tangshen granules protect against DN damage by regulating the gut microbiota−bile acids axis[18]. The Tangshen formula was shown to maintain the homeostasis of gut microbiota, inhibit the expression of MCP-1 and TNF-α, and alleviate renal injury in DN mice[178]. Apoptosis, which refers to genetically controlled spontaneous cell death, is closely related to biological processes involved in IRN[179]. Previously, hirudin was reported to reduce the number of apoptotic bodies and inhibit the expression

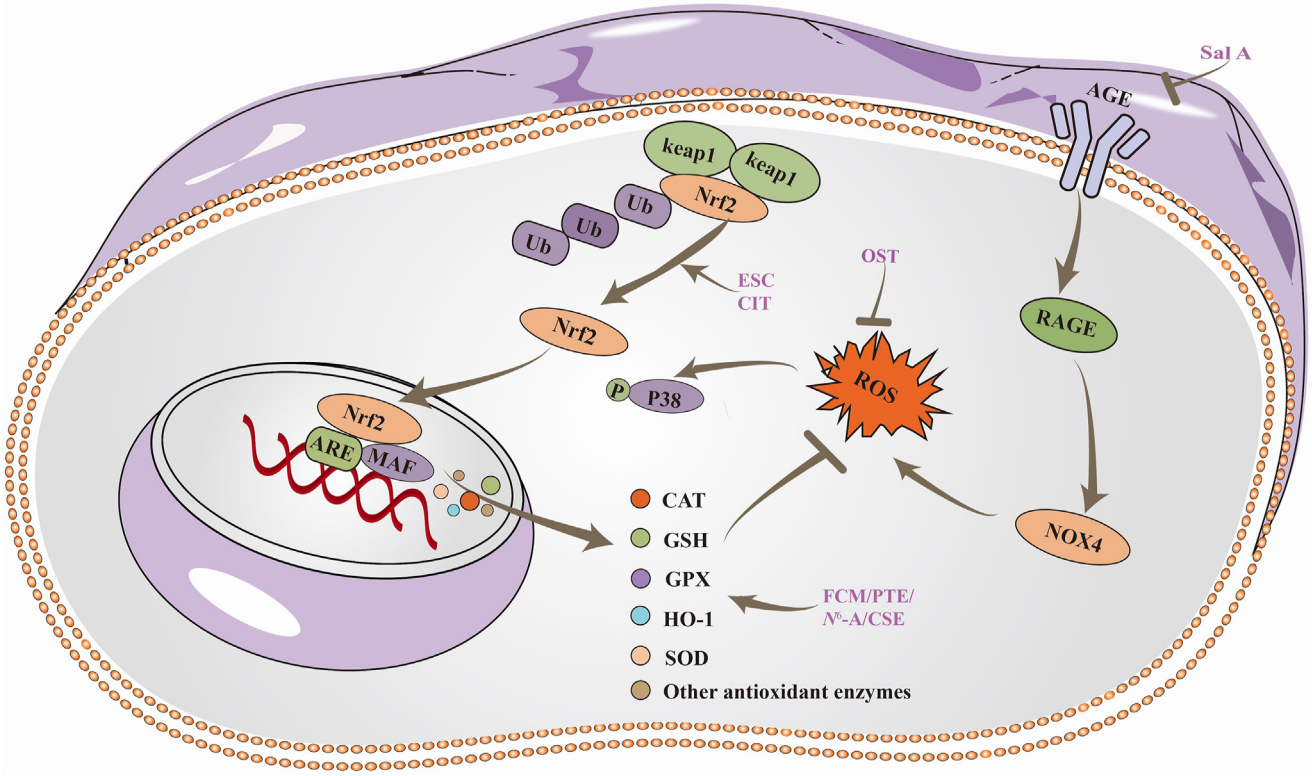

Figure 11 The oxidative stress-related signaling pathways involved in IRN. OST reduces ROS production; Sal A regulates AGE/RAGE/NOX4 signaling pathway and inhibits ROS level; FCM, PTE, N^6-A, and CSE increases the activities of antioxidant enzymes SOD, CAT, and HO-1; ESC and CIT activates Nrf2 and leading to ROS reduction. These pathways finally prevent renal oxidative stress. Abbreviations: OST, osthole; Sal A, salvianolic acid A; FCM, the combination of fucoidan and a TCM formula (composed of *Astragalus membranaceus*, *Rehmannia glutinosa*, *Pueraria lobate*, *Salviae miltiorrhizae*, *Dioscoreae rhizome*, *Lycii fructus*, *Morus alba* and *Panacis quinquefolia*, 23:20:10:20:10:8:5:4); PTE, pterostilbene; N^6-A, N^6-(2-yethyl)-adenosine; CSE, Cassiae Semen extracts; ESC, esculetin; CIT, citral.

of the apoptotic protein caspase-3 and caspase-9 in IgAN rats[82]. Gushen Jiedu capsules were demonstrated to protect against renal function by inhibiting apoptosis in glomeruli and renal tubule cells. Mechanistically, hirudin inhibits BCL-2-associated X protein (BAX) and p-AKT and up-regulated B-cell lymphoma-2 (BCL-2) expression in DN rats[95]. In another study, HQGZD protects against damage to podia cytoskeleton proteins and restores the normal morphology of the kidneys in IgAN rats[17].

5. Conclusion and perspective

Persistent IRN may develop into ESRD, which is considered incurable and can only be relieved with dialysis and kidney transplantation. However, because of the lack of obvious clinical symptoms, IRN is difficult to detect in the early stages of the condition. Traditionally, renal function tests (urea, creatinine, etc.) only reflect changes to the glomerular filtration rate, and increases in these indicators are mostly observed in the irreversible stage of renal disease. Currently, immunotherapy modalities for IRN mainly include non-selective immunosuppressants and cell-specific inhibitors. These treatment strategies effectively improve patients' clinical symptoms, reduce their risk of UP and SCr doubling, and slow the progression of IRN to ESRD. Unfortunately, some adverse effects are common, including infection, decreased glucose tolerance, and obesity. Despite the substantial amount of progress made in the treatment of IRN, these drugs are not effective in improving long-term renal outcomes or reversing kidney damage in the early stages. Therefore, researching effective interventions is still important for IRN treatment breakthroughs.

Although TCM have unique therapeutic effects in IRN, some of their effects cannot be verified or clarified from the perspective of modern pharmacology. The multi-component and multi-target therapeutic characteristics of TCM need further scientific explanation. Therefore, using purified bioactive compounds or mixes of known bioactive ingredients may result in more reliable clinical tests. At present, there is a lack of standards for using and testing TCM. The dosage and duration of treatment should be adjusted according to the disease type, and clinical-problem-oriented evaluation mechanisms should be established to improve their efficiency.

In addition, it is difficult to control the quality of the treatments as the identity of the active ingredients is not always clear. Currently, quality control is mainly focused on the medicinal materials themselves, and more research on the control of pharmacologically relevant ingredients should be given attention. The chemical structures of the active ingredients in TCMs have been optimized for millennia throughout evolution, and most of them have stable chemical properties. Many drugs used in clinical practice are directly or indirectly derived from TCMs, such as artemisinin, paclitaxel, huperzine A, etc. Modern studies have shown that the main active substances of TCMs used for IRN treatment include cycloenols, coumarins, and alkaloids, which have characteristics that could make them ideal compounds for the treatment of IRN. However, most studies on the efficacy of these compounds are in vitro or animal experiments, and only a few clinical studies have been conducted. In addition, there have been almost no studies evaluating the safety of these compounds. Thus, it is still an important challenge to explore the mechanisms, ascertain the targets, and clarify the safety of the compounds.

The effects of TCMs on IRN have not been fully elucidated. At present, the mechanisms of TCMs used in the treatment of IRN are mainly believed to be involved in inhibiting apoptosis, anti-oxidative stress, anti-inflammation, inhibiting renal fibrosis, and participating in immune regulation. Most of these studies have focused on detecting changes in proteins or signaling pathways and rarely focused on the detection of specific targets. In recent years, drug target identification technologies, such as drug affinity responsive target stability, cellular thermal shift assay, and biotin-labeled probes, have had a significant impact in guiding the discovery of small-molecule targets, and these may be applied to scientifically explain the efficacy of TCM treatments at the molecular level. Moreover, the application of new technologies and methods, including transcriptomics, proteomics, metabolomics, and single-cell sequencing, could also lead to breakthroughs. In addition, it is worth noting that the incidence of IRN is closely related to heredity. However, research on TCM in this field is almost non-existent, which is an unavoidable problem when studying the effects of TCM on IRN.

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Author contributions

Pu Jiang: Writing—original draft, Conceptualization. Changliang Yao: Conceptualization. De-an Guo: Writing—Review & Editing, Supervision, Funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

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