



Traditional Chinese medicine in lupus nephritis: mechanistic insights and integrative therapeutic strategies

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ARTICLE INFO

Article history

Received 27 April 2025

Accepted 01 August 2025

Available online 25 September 2025

Keywords

Lupus nephritis

Traditional Chinese medicine

Autoimmune disease

Chinese herbs

Renal protection

ABSTRACT

Objective To review and synthesize preclinical and clinical evidence regarding traditional Chinese medicine (TCM) formulations and bioactive herbal compounds in lupus nephritis (LN), and to identify direction and research priorities for integrating TCM with professional care.

Methods A narrative literature review was conducted by searching Scopus, PubMed, Web of Science, and Google Scholar for articles published between January 1, 2011 and March 31, 2024. Search terms combined controlled vocabulary [e.g., medical subject headings (MeSH)] and free-text words including lupus nephritis, traditional Chinese medicine, Chinese herbal medicine, formulation, and names of specific herbs [Leigongteng (*Tripterygii Wilfordii* Radix et Rhizoma), Baishao (*Paeoniae Radix Alba*), and Yinghao (*Artemisiae Annuae* Herba)]. Both randomized controlled trials and observational studies were included, along with mechanistic preclinical studies and pharmacologic investigations. Inclusion criteria were studies that reported renal outcomes (proteinuria and estimated glomerular filtration rate), immune-modulatory mechanisms, or safety and herb-drug interaction data. Studies without primary data, case reports, or those lacking relevance to LN were excluded. References of key articles were manually screened to identify additional eligible studies.

Results TCM formulas [e.g., Liuwei Dihuang Pills (六味地黄丸), Zhibai Dihuang Pills (知柏地黄丸), and Huanglian Jiedu Decoction (黄连解毒汤)] and herbal medicines [e.g., extracts from Leigongteng (*Tripterygii Wilfordii* Radix et Rhizoma), Baishao (*Paeoniae Radix Alba*), and Yinghao (*Artemisiae Annuae* Herba)] were commonly used in the above studies. TCM formulations and their constituent compounds showed multi-modal mechanisms relevant to LN pathogenesis, encompassing immunomodulation (reduction of autoreactive B/T cell activity, regulatory T cell enhancement), inhibition of pro-inflammatory signaling pathways nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), mitogen-activated protein kinase (MAPK), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR) and pyrin domain-containing protein 3 (NLRP3 inflammasome), anti-fibrotic and antioxidant effects, and direct renal-protective properties. In many studies, these indicators can reduce proteinuria and improve renal function. Clinical data, while promising, are heterogeneous in design, sample size, endpoints, and TCM formulation standardization. Safety

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Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: [10.1016/j.dcmcd.2025.09.005](https://doi.org/10.1016/j.dcmcd.2025.09.005)

Citation: EDWIN E, ELUMALAI K, JAYAPRAKASH N. Traditional Chinese medicine in lupus nephritis: mechanistic insights and integrative therapeutic strategies. Digital Chinese Medicine, 2025, 8(3): 323-334.

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concerns (notably with Tripterygium preparations) and potential herb-drug interactions with immunosuppressants remained important considerations.

Conclusion TCM offers biologically plausible and multi-targeted adjuvant strategies for LN that may enhance therapeutic efficacy and reduce toxicity when combined with modern therapies. To translate these promises into clinical practice, future work should prioritize the standardization of TCM preparations, randomized controlled trials with clinically meaningful renal endpoints, elucidation of molecular mechanisms, and systematic evaluation of pharmacokinetic and safety interactions. Such integrative research will be essential to define the TCM's role in evidence-based, patient-centered LN management.

1 Introduction

Autoimmune kidney diseases, particularly lupus nephritis (LN), remain as a critical challenge owing to their intricate pathophysiology and unfavorable long-term prognosis. As a severe manifestation of systemic lupus erythematosus (SLE), LN is defined by immune complex deposition within renal tissues. It develops in approximately 30% – 60% of patients with SLE during the disease course, with higher prevalence reported in Asian, African, and Hispanic populations compared with Caucasians. Globally, LN represents a major contributor to SLE-related morbidity and mortality, accounting for up to 10% – 30% of cases progressing to end-stage renal disease (ESRD) within a decade despite therapeutic intervention [1]. Incidence rates vary geographically, ranging from 0.4 to 3.4 per 100 000 person-years, which reflects differences in genetic susceptibility, environmental exposures, and healthcare accessibility. While LN predominantly affects women of childbearing age, its severity is more pronounced in men and younger patients. Mortality rates remain significantly higher in LN patients compared with the general population, underscoring the urgent need for improved therapeutic strategies and early detection methods. This pathological process triggers a cascade of immune-mediated responses, including persistent inflammation, glomerular injury, tubular damage, and interstitial fibrosis, ultimately leading to progressive renal dysfunction and failure. Despite significant advancements in understanding LN and the development of targeted therapies, current management strategies remains suboptimal [2].

The current standard of care for LN includes glucocorticoids, immunosuppressive agents (e.g. cyclophosphamide and mycophenolate mofetil), and biological therapies targeting specific immune pathways (e.g. anti-B cells or anti-cytokine agents). While these treatments can suppress disease activity and delay progression, they are often accompanied by challenges including incomplete remission, frequent relapses, cumulative organ damage, and significant adverse effects, such as infections, metabolic disturbances, and cardiovascular risks [3]. Moreover, therapeutic resistance and variability in patient responses further complicate disease management. These

limitations underscore the urgent need for novel or complementary therapeutic approaches that simultaneously address underlying disease mechanisms and improve patient quality of life [4].

Traditional Chinese medicine (TCM), an ancient medical system rooted in holistic principles, offers a promising adjunctive strategy for managing autoimmune diseases, including LN. TCM integrates Chinese herbal formulations and some traditional herbs, each characterized by a diverse range of therapeutic properties [5]. The cornerstone of TCM lies in restoring systemic balance and targeting the root causes of disease, rather than merely alleviating symptoms. For LN, TCM therapies have demonstrated potential for modulating immune responses, reducing renal inflammation, mitigating oxidative stress, and promoting tissue repair. Additionally, TCM's organ-protective properties are particularly relevant in addressing the multi-organ impact of SLE [6].

An growing body of scientific evidence supports the efficacy of TCM in improving clinical outcomes for patients with LN. Studies have suggested that TCM can significantly reduce proteinuria, ameliorate histological damage in kidney tissues, and enhance the overall therapeutic efficacy of standard treatments by minimizing their side effects. Herbal medicines, such as Huangqi (*Asragali Radix*), Shengdihuang (*Rehmanniae Radix*), and Huangqin (*Scutellariae Radix*) have been extensively studied for their immunomodulatory and nephroprotective properties. These formulations contain bioactive compounds capable of attenuating inflammatory pathways, suppressing autoantibody production, and restoring renal function [7].

This review aims to systematically examine the TCM role in the LN management, with a focus on its bioactive components, underlying mechanisms pathways, and therapeutic applications, both as monotherapy and in combination with conventional treatments.

2 Data and methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological

rigor and transparency. Comprehensive literature searches were performed across Scopus, PubMed, Web of Science, and Google Scholar to identify studies published between January 1, 2011 and March 31, 2024. The search strategy incorporated medical subject headings (MeSH) terms and free-text keywords, including “traditional Chinese medicine” “TCM” “lupus nephritis” “autoimmune kidney disease” “immunomodulation” “anti-inflammatory” “herbal medicine” and “complementary therapy” with Boolean operators (AND/OR) applied to refine the search results. Records were initially screened based on titles, abstracts, and keywords, followed by a full-text review of potentially eligible articles. Inclusion criteria comprised: (i) clinical trials, *in vivo* or *in vitro* studies evaluating TCM interventions for LN; (ii) studies focused on herbal formulations, active compounds, or integrative therapies combining TCM with western medicine; (iii) relevant outcomes included improved renal function, proteinuria reduction, immunomodulatory effects, and anti-inflammatory mechanisms. Only peer-reviewed English language publications were included. Exclusion criteria were: (i) studies involving non-TCM herbal formulations; (ii) studies of autoimmune kidney diseases unrelated to LN; (iii) non-peer-reviewed sources, such as commentaries and conference abstracts; (iv) studies with poor methodological quality or insufficient data. The PRISMA flowchart illustrates the selection process (Figure 1).

3 LN pathophysiology

LN, a severe SLE complication, is characterized by complex immune and inflammatory mechanisms that lead to kidney damage. A hallmark feature of LN is the deposition of immune complexes (ICs) within glomeruli, which triggers complement system activation. This process initiates a cascade of inflammatory responses that damage renal structures [8]. Several molecular signalling pathways critically contribute to LN pathogenesis, including Janus kinase/signal transducer and activator of transcription (JAK/STAT), tumor necrosis factor (TNF)- α , nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT). The JAK/STAT pathway mediates responses to various cytokines [e.g., interferons (IFN) and interleukins (IL)], promoting inflammatory gene expression, and immune cell activation in renal tissues. Abnormal activation of this pathway drives glomerular injury and tubulointerstitial inflammation. The TNF- α pathway driven by the pro-inflammatory cytokine TNF- α , plays a key role in recruiting immune cells, promoting renal cell apoptosis, and inducing fibrosis. Elevated TNF- α levels correlated with disease activity in LN patients [9]. The NF- κ B pathway is a primary mediator of inflammatory

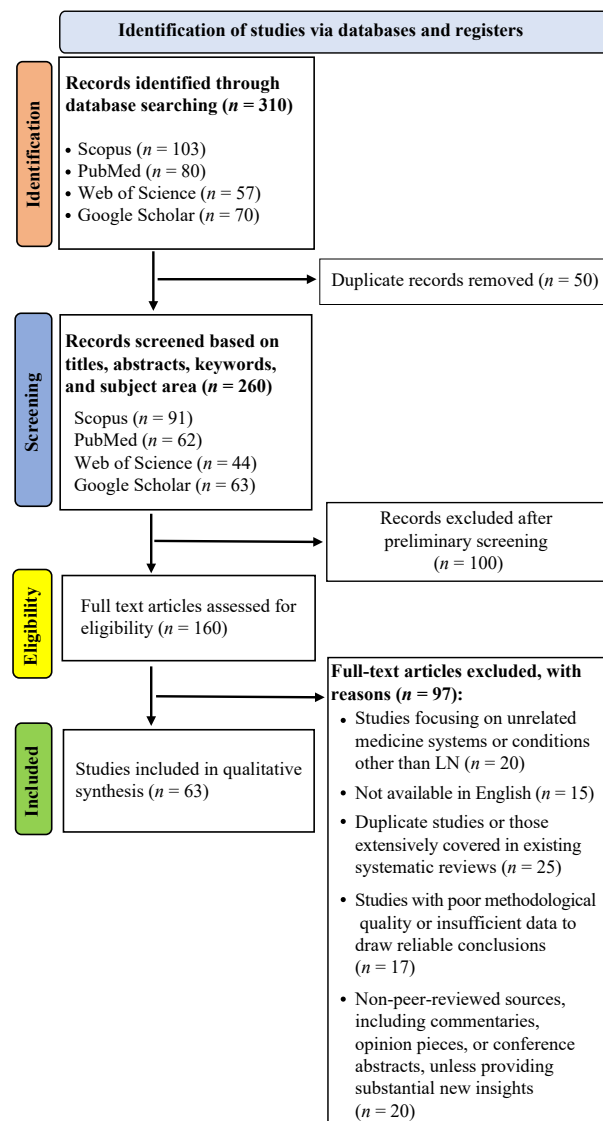


Figure 1 Study selection process

responses, its activation in renal cells and infiltrating immune cells leads to sustained production of cytokines, chemokines, and adhesion molecules, exacerbating renal inflammation. The PI3K/AKT pathway can regulate cell survival, metabolism, and proliferation, maintaining immune cell activation and promoting mesangial cell proliferation and fibrosis in LN. Collectively, these pathways form a network of dysregulated signalling cascades that drive renal inflammation, immune complex deposition, and progressive kidney damage in LN. The classical complement pathway further contributes by generating inflammatory mediators, such as complement component 3a (C3a) and 5a (C5a), which recruit immune cells to the kidney and exacerbate tissue injury. Additionally, cytokines, such as IL-6, IL-1 β , and TNF- α , can amplify local inflammatory responses, perpetuating renal damage [10].

Dysregulation of immune cell function further contributes to LN pathogenesis. CD4+ T helper cells, particularly the T helper type 1 cells (Th1) and T helper type 17

cells (Th17) subsets, produce pro-inflammatory cytokines (e.g., IFN- γ and IL-17), which intensify the inflammatory response. Regulatory T cells (Tregs), which typically suppress excessive inflammation, are often deficient in patients with LN [11]. Hyperactive B cells produce pathogenic autoantibodies that exacerbate immune IC deposition and stimulate inflammatory cascades. Neutrophils also play a key role through the formation of neutrophil extracellular traps (NETs), which activate dendritic cells and perpetuate immune activation [12].

Renal structural damage in LN occurs via several pathways. Mesangial cell proliferation, driven by inflammatory signals, leads to extracellular matrix accumulation and glomerular sclerosis. Podocyte injury disrupted the glomerular filtration barrier, resulting in proteinuria, a hallmark of renal dysfunction. Chronic inflammation also extends to the tubulointerstitial space, promoting fibrosis and further renal function loss [13].

Epigenetic and genetic factors influence LN susceptibility and progression. DNA hypomethylation in immune cells results in the overexpression of pro-inflammatory genes. Concurrently, dysregulation of microRNAs further contributes to immune activation. Genetic predispositions, such as variants in complement components or cytokine receptors, are also implicated in LN pathogenesis, underscoring the multifactorial nature of the disease [14].

The transition from inflammation to fibrosis is pivotal to LN progression. Transforming growth factor (TGF)- β , a key mediator of fibrosis, promotes extracellular matrix deposition and renal fibrosis. Myofibroblast activation, driven by immune signals, contributes to excessive collagen secretion, leading to irreversible kidney damage. Fibrosis ultimately results in end-stage renal disease (ESRD), a major cause of morbidity and mortality in patients with LN [15]. Figure 2 shows molecular and cellular mechanisms involved in LN pathogenesis.

Despite advancements in therapeutic options, lymph node management remains a significant challenge. Current treatments, including glucocorticoids and immunosuppressants, target inflammation but often fail to address the multifaceted nature of the disease [16]. These therapies are associated with severe side effects, frequent relapses, and incomplete resolution of renal damage. Biological agents, such as B-cell inhibitors, offer greater specificity, but are costly and exhibit variable efficacy. Moreover, fibrosis remains a therapeutic challenge, with limited options to prevent irreversible renal damage [17].

Understanding these complex pathophysiological mechanisms provides a foundation for exploring the TCM's role in LN management. TCM's immunomodulatory, anti-inflammatory and anti-fibrotic effects address multiple aspects of LN, presenting a holistic approach for improving patients' outcomes [18]. Figure 3 shows the schematic representation of pathophysiology of LN and its modulation by TCM components.

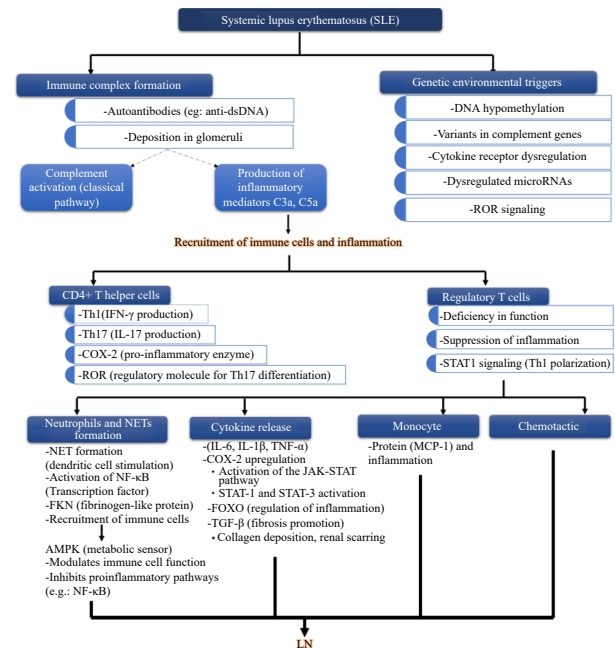


Figure 2 Molecular and cellular mechanisms involved in LN pathogenesis

dsDNA, double-stranded DNA. COX-2, cyclooxygenase-2. ROR, retinoic acid receptor-related orphan receptor. FKN, fractalkine (CX3CL1). AMPK, AMP-activated protein kinase. FOXO, forkhead box O (transcription factor). MCP-1, monocyte chemoattractant protein-1.

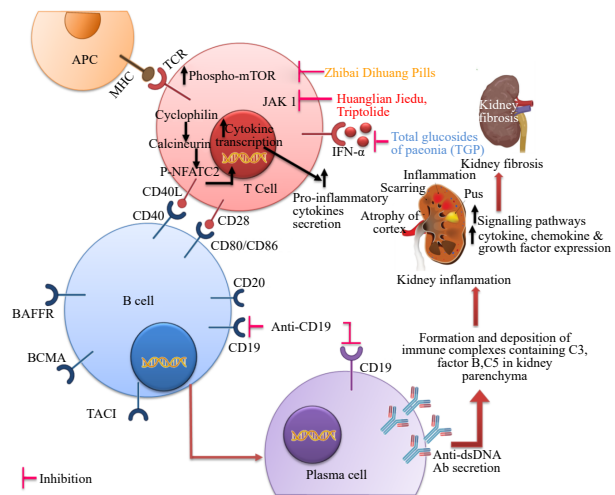


Figure 3 Pathophysiology of LN and its modulation by TCM components

Ab, antibody. APC, antigen-presenting cell. BAFFR, B cell activating factor receptor. BCMA, B cell maturation antigen. TACI, transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor. CD, cluster of differentiation. mTOR, mammalian or mechanistic target of rapamycin. NFATC2, nuclear factor of activated T cells 2. TCR, T cell receptor. MHC, major histocompatibility complex.

4 The role of TCM in LN management

TCM has emerged as a promising complementary and alternative approach to the LN management. TCM therapies of herbal formulations, monomers, and natural

extracts targeted the complex mechanisms of LN with minimal adverse effects compared to conventional treatments. TCM's efficacy lies in its ability to modulate immune responses, reduce inflammation, and protect renal structures, aligning well with the pathophysiology of LN [19]. Below is a detailed overview of how TCM contributes to LN management.

4.1 Herbal formulations

4.1.1 Liuwei Dihuang Pills (六味地黄丸) Liuwei Dihuang Pills are a classic TCM formulation comprising six herbs: Shudihuang (*Rehmanniae Radix Praeparata*), Shanyao (*Rhizoma Dioscoreae*), Shanzhuyu (*Fructus Corni*), Mudanpi (*Cortex Moutan*), Fuling (*Poria*), and Zexie (*Alismatis Rhizoma*). Consistent with TCM theory, Liuwei Dihuang Pills nourish Yin and tonify the kidneys. Modern studies have demonstrated their efficacy in LN, with evidence showing enhanced renal function, reduced proteinuria, and improved immune balance. Mechanistically, Liuwei Dihuang Pills suppress pro-inflammatory mediators, including IL-6 and MCP-1, thereby reducing renal inflammation and tissue damage [20, 21].

A retrospective cohort study using the Taiwan National Health Insurance Research Database (1997 – 2011) further supported the integrative potential of TCM in LN management. Patients receiving conventional medicine combined with herbal medicine exhibited a significantly lower risk of developing LN compared with those receiving conventional medicine alone [adjusted hazard ratio (HR): 0.68, 95% CI: 0.54 – 0.87, $P < 0.01$]. Core herbal medicine patterns included Liuwei Dihuang-related prescriptions [eg. Dihuang (*Rehmanniae Radix*) and Mudanpi (*Moutan Cortex*)], further reinforcing its relevance in integrative therapy [22].

4.1.2 Zhibai Dihuang Pills (知柏地黄丸) Zhibai Dihuang Pills, an enhanced formulation of Liuwei Dihuang Pills, include Zhimu (*Anemarrhenae Rhizoma*) and Huangbai (*Phellodendri Chinensis Cortex*). These herbal components exhibit antioxidant, anti-inflammatory, and immunomodulatory properties. Their acting mechanisms include inhibition of the AKT/mTOR/FOXO signalling pathway, reduction of oxidative stress and protection of renal epithelial cells from inflammation-induced damage. Studies have highlighted their ability to improve renal function and mitigate immune complex deposition [23, 24].

A comprehensive review of Liuwei Dihuang Pills and related prescriptions highlights their pharmacological versatility and favorable safety profile in managing diverse diseases. The findings suggest that the neuroendocrine immunomodulation network may underlie the pharmacological activities of these formulations, supporting their potential in integrative therapies for chronic diseases [25, 26].

4.1.3 Huanglian Jiedu Decoction (黄连解毒汤) Huanglian Jiedu Decoction, a renowned traditional Chinese medicinal formulation comprising Huanglian (*Coptidis Rhizoma*), Huangbai (*Phellodendri Chinensis Cortex*), Huangqin (*Scutellariae Radix*), and Zhizi (*Gardeniae Fructus*), is characterized by its detoxifying and heat-clearing properties. It has been demonstrated significant potential in treating inflammation-related diseases, including LN [27].

The renoprotective effects of Huanglian Jiedu Decoction have been demonstrated in MRL/lpr mice, a model of LN. Treatment with Huanglian Jiedu Decoction significantly reduced proteinuria, serum anti-dsDNA levels, and renal immune complex deposition, while improving renal pathology. Additionally, systemic inflammation was attenuated through decreased levels of pro-inflammatory cytokines (IL-6, IL-10, and IFN- γ) and suppression of STAT3 phosphorylation, indicating inhibition of the JAK/STAT signalling pathway. These findings suggest that Huanglian Jiedu Decoction may help alleviate LN progression and represent a potential therapeutic target [28].

The anti-inflammatory activity of Huanglian Jiedu Decoction has been investigated in both LPS-induced RAW264.7 cells and carrageenan-induced paw edema in mice to further elucidate its mechanisms of action. Upon fractionation into two extracts (Huanglian Jiedu Decoction-1 and Huanglian Jiedu Decoction-2), the major bioactive components—iridoids, flavonoids, and alkaloids—were found to act synergistically to exert anti-inflammatory effects. Huanglian Jiedu Decoction significantly reduced inflammatory markers, including malondialdehyde (MDA), nitric oxide (NO), prostaglandin E2 (PGE2), TNF- α , and IL-6, while enhancing superoxide dismutase (SOD) activity and IL-10 levels. These results underscore the importance of using Huanglian Jiedu Decoction as a holistic formulation and highlight the necessity of quality control based on its key components. Collectively, the findings confirm Huanglian Jiedu Decoction's efficacy in managing inflammation and renal complications of LN by targeting pro-inflammatory pathways and modulating immune responses. This evidence not only supports its traditional use but also provides a scientific framework for its application in modern medicine [29].

4.1.4 Qingshen Decoction (清肾汤) Qingshen Decoction, a TCM formula, is recognized for its potential therapeutic benefits in treating autoimmune diseases, particularly LN. Composed of key herbal components such as Huangqi (*Astragali Radix*), Renshen (*Ginseng Radix et Rhizoma*), Danshen (*Salviae Miltiorrhizae Radix et Rhizoma*), Dahuang (*Rhei Radix et Rhizoma*), Gouqi (*Lycii Fructus*), and Rougui (*Cinnamomi Cortex*), it has been studied for its ability to modulate immune responses and mitigate inflammation [30]. A network pharmacology study demonstrated that bioactive components, including astragalus polysaccharide, ginsenoside Rg1, salidroside,

and quercetin, could regulate critical immune targets (IL-1 β and TNF- α) and pathways (PI3K/AKT and NF- κ B). These interactions suggest that Qingshen Decoction may reduce inflammatory responses and promote immune balance [31]. Clinically, a study conducted with 107 patients with LN showed that those receiving Qingshen Decoction in combination with cyclophosphamide and prednisolone had significantly improved outcomes compared with the control group. This included better serum

levels of immune markers (IFN- γ and IL-4) and improved clinical scores [systemic lupus erythematosus disease activity index (SLEDAI) and TCM symptom severity score (TCMSSS)]. The results indicated that Qingshen Decoction can enhance the efficacy of conventional treatments, modulate immune activity, and serve as a potential biomarker for assessing treatment response in LN [32]. Table 1 summarized herbal formulations for LN treatment.

Table 1 Summary of herbal formulations for LN treatment

Herbal formulation	Key herb/ingredient	Mechanism of action	Clinical finding	Indication	Dosage form	Adverse effect	Reference
Liuwei Dihuang Pill	Shudihuang (Rehmanniae Radix Praeparata), Shanyao (Dioscoreae Rhizoma), Shanzhuyu (Corni Fructus), Mudanpi (Moutan Cortex), Fuling (Poria), Zexie (Alismatis Rhizoma)	Suppresses IL-6, MCP-1; reduces inflammation and tissue damage	Enhances renal function, reduces proteinuria, and improves immune balance	Chronic kidney disease (CKD), aging-related conditions	Pills	Mild gastrointestinal discomfort	[22]
Zhibai Dihuang Pill	Liuwei Dihuang Pill + Zhimu (Anemarrhenae Rhizoma), Huangbai (Phellodendri Chinensis Cortex)	Inhibits AKT/mTOR/FOXO signaling; reduces oxidative stress	Improves renal function, reduces immune complex deposition; supports in diabetic complications	Diabetic nephropathy, CKD	Pills	None reported in clinical studies	[26]
Huanglian Jiedu Decoction	Huanglian (Coptidis Rhizoma), Huangbai (Phellodendri Chinensis Cortex), Huangqin (Scutellariae Radix), Zhizi (Gardeniae Fructus)	Inhibits JAK/STAT pathway, reduces inflammatory cytokines	Reduces proteinuria and anti-dsDNA, improves renal pathology	LN, SLE	Decoction	Nausea, bitter taste, rare allergic reactions	[28]
Qingshen Decoction	Huangqi (Astragali Radix), Renshen (Ginseng Radix et Rhizoma), Danshen (Salviae Miltiorrhizae Radix et Rhizoma), Dahuang (Rhei Radix et Rhizoma), Gouqi (Lycii Fructus), Rougui (Cinnamomi Cortex)	Modulates IL-1 β , TNF- α , PI3K/AKT, NF- κ B pathways	Enhances outcomes with cyclophosphamide and prednisolone; improves immune markers	Immunomodulation in SLE and CKD	Decoction, capsules	Diarrhea, potential drug-herb interactions	[31]

4.2 Pharmacological mechanisms and therapeutic roles of TCM in LN management

4.2.1 Immunomodulatory effects of TCM In LN, TCM plays a key role in immune system modulation. Herbs such as Leigongteng (*Tripterygii Wilfordii* Radix et Rhizoma) reduce production of pro-inflammatory cytokines (e.g., IL-6 and IL-17) by modulating critical pathways including NF- κ B and JAK/STAT. Total glucosides of paeonia (TGP), extracted from Baishao (*Paeoniae Radix Alba*), further influences LN pathophysiology by suppressing IFN- α production and lowering anti-dsDNA antibody levels. Another formulation, Qingshen Decoction has shown efficacy in balancing cytokine production and improving

SLEDAI scores through regulation of IL-4 and IFN- γ . Huangqi (*Astragali Radix*) supports immunological homeostasis in autoimmune conditions like LN by modulating T-cell and B-cell immunity. Further underscoring TCM’s immunomodulatory potential in LN management are artemisinin derivatives, such as SM934 from Qinghao (*Artemisiae Annuae Herba*), which have shown significant effects in reducing Th17 cell responses and enhancing regulatory T-cell activity [33].

4.2.2 Anti-inflammatory properties of TCM TCM is also effective at targeting inflammatory pathways associated with LN. Huanglian Jiedu Decoction significantly reduces the pro-inflammatory cytokines levels including TNF- α and IL-6, while suppressing the JAK/STAT pathway,

a critical mediator of inflammatory responses in LN. Similar to the Huanglian Jiedu Decoction, Zhibai Dihuang Pills can decrease inflammation and lower oxidative stress by modifying the AKT/mTOR/FOXO signaling pathway. Pipaye (*Eriobotryae Folium*) extract, rich in ursodiol and oleanolic acid, further reduces renal inflammation and damage by inhibiting IL-17 release and Th17 cell development. To mitigate renal inflammation, glycyrrhiza uralensis, or licorice, has been demonstrated to inhibit NF- κ B activation, which in turn downregulates multiple pro-inflammatory cytokines. Huangqin (*Scutellariae Radix*), rich in flavonoids, also fights inflammation and oxidative stress, preventing damage to the kidneys. Collectively, these herbs exhibit potent anti-inflammatory properties, offering a comprehensive therapeutic approach for alleviating renal and systemic inflammation in LN [34].

4.2.3 Anti-fibrotic and tissue remodeling effects Given the critical role of fibrosis and tissue repair in the development of end-stage renal disease (ESRD), reducing fibrosis and promoting tissue repair are essential components of LN management. A number of TCM herbs have demonstrated potential in reducing renal fibrosis. While derivatives of Qinghao (*Artemisiae Annuae Herba*), such as artemisinin, minimize chronic scarring by inhibiting fibrosis-associated pathways, Leigongteng (*Tripterygii Wilfordii Radix et Rhizoma*) has been shown to suppress fibroblast activation, a crucial stage in the fibrotic process. Huangqi (*Astragali Radix*) modulates TGF- β signaling, a major mediator of fibrosis in LN, thereby reducing the extracellular matrix accumulation. These anti-fibrotic effects underscored the TCM's integral role in the comprehensive management of LN, as they are vital for maintaining renal function and stopping disease progression to ESRD [35].

4.2.4 Renal protective and antioxidant property TCM formulations also exert significant renal protective benefits by lowering oxidative stress and improving kidney function. Liuwei Dihuang Pills have demonstrated efficacy in lowering MCP-1 levels, thereby lowering renal inflammation and improving glomerular filtration. Zhibai Dihuang Pills have been associated with improved renal function and decreased immune complex deposition, both of which are critical in preventing further renal damage. Dihuang (*Rehmanniae Radix*), a key herb in TCM, is well-known for its nephroprotective benefits, especially due to its antioxidant qualities, which protect kidney cells from damage and lessen oxidative stress. Tusizi (*Cuscutae Semen*) and Heshouwu (*Polygoni Multiflori Radix*) also improve kidney function and minimize oxidative stress, thereby contributing to renal protection [36].

4.2.5 Other herbs Several traditional Chinese herbs have demonstrated the potential for managing LN through various mechanisms. Huangqi (*Astragali Radix*),

widely used for its immunomodulatory and nephroprotective properties, has been shown to improve kidney function, reduce proteinuria and enhance immune responses [37]. Dihuang (*Rehmanniae Radix*) exhibits efficacy in decreasing autoantibody production and mitigating inflammation through its antioxidant and anti-inflammatory effects, thus contributing to better renal health. Gancao (*Glycyrrhizae Radix et Rhizoma*) suppressed NF- κ B activation, lowering pro-inflammatory cytokine levels and contributing to renal protection [38, 39]. Heshouwu (*Polygoni Multiflori Radix*) not only helped mitigate oxidative stress but also improved renal function and protected against tissue damage. Tusizi (*Cuscutae Semen*) possessed anti-inflammatory properties, reduced oxidative damage, and supported immune modulation, contributing to the preservation of renal function [40, 41]. Danggui (*Angelicae Sinensis Radix*) promoted blood circulation, improved nutrient and oxygen supply to organs, and reduced inflammation, thus supporting renal health. Huangqin (*Scutellariae Radix*), rich in flavonoids, combated oxidative stress and inflammation to protect renal tissues [42, 43]. Additionally, Chuanxiong (*Chuanxiong Rhizoma*) can enhance blood circulation, promote toxin elimination, and reduce inflammation, contributing to renal cell protection. These herbs are often used in combination to harness their synergistic effects, offering promising support for LN management. However, further research is needed to elucidate their full mechanisms and optimize clinical application [44]. Table 2 summarizes active compounds from traditional herbs and their effects on LN. Figure 4 shows various molecular pathways targeted by TCM components.

Collectively, these herbal interventions target multiple pathways involved in LN pathogenesis, demonstrating the multi-faceted therapeutic potential of TCM. Figure 5 provides a schematic summary of the pathogenic mechanisms of LN and the corresponding therapeutic targets modulated by TCM, highlighting the integrative and multi-targeted nature of these interventions.

5 TCM-western medicine combined therapies

Combined TCM and western medicine therapies has shown promising efficacy in treating LN. For instance, systematic reviews and meta-analysis studies have found that combining Leigongteng (*Tripterygii Wilfordii Radix et Rhizoma*) with prednisone significantly reduced proteinuria and improved renal function in patients with LN, compared to prednisone alone [50]. Another randomized controlled trial demonstrated that Huangqi (*Astragali Radix*) combined with cyclophosphamide was more effective in reducing proteinuria and improving renal function than cyclophosphamide alone in patients with LN [51]. Furthermore, a systematic review and meta-analysis revealed that Qingre Jiedu Huoxue Decoction combined with prednisone significantly reduced proteinuria

Table 2 Active compounds from traditional herbs and their effects on LN

Compound	Source herb	Property	Mechanism of action	Finding	Indication	Dosage form	Adverse effect	Reference
Triptolide	Leigongteng (Tripterygii Wilfordii Radix et Rhizoma)	Immuno suppressive, anti-inflammatory	Modulates NF-κB, JAK/STAT; reduces IL-6, TNF-α	Reduces proteinuria, improves survival, decreases anti-dsDNA	LN, rheumatoid arthritis	Capsules, extracts	Potential hepatotoxicity, gastrointestinal issues, reproductive toxicity	[45]
Artemisinin	Qinghao (Artemisiae Annuae Herba)	Anti-inflammatory, immune modulatory	Inhibits Th17 cells; promotes regulatory T-cells	Ameliorates proteinuria, renal lesions; inhibits STAT pathways	Autoimmune diseases, malaria	Tablets, decoctions	Rare gastrointestinal discomfort, dizziness	[46]
TGP	Baishao (Paeoniae Radix Alba)	Anti-inflammatory, immune modulatory	Reduces TNF-α, IFN-α; decreases kidney inflammation	Decreases urinary protein, anti-dsDNA, Antinuclear antibodies (ANA); improves renal pathology	LN, inflammatory disorders	Capsules, powders	Mild gastrointestinal upset	[47]
Paeoniflorin	Baishao (Paeoniae Radix Alba)	Anti-inflammatory, immune modulatory	Reduces oxidative stress, downregulates IL-6, TNF-α	Enhances renal function, reduces inflammation	Renal diseases, inflammation-related conditions	Capsules, injectable forms	Rare allergic reactions, mild gastrointestinal (GI) discomfort	[48]
Saponins	Renshen (Ginseng Radix et Rhizoma), Huangqi (Astragali Radix)	Immuno modulatory, anti-inflammatory	Inhibits NF-κB pathway; regulates T cell activation	Enhances immune balance, improves proteinuria and kidney function	Chronic kidney disease, immune modulation	Capsules, herbal teas	Few adverse effects reported in moderate doses	[49]

and improved renal function in patients with LN compared with prednisone alone. These findings suggest that TCM-western medicine combination therapy may be a promising therapeutic approach for treating LN, potentially offering clinical outcomes and reduced side effects compared with western medicine alone [40].

6 Comparative analysis of TCM and modern therapies

Modern management of LN primarily relies on glucocorticoids, immunosuppressants, and targeted biological agents. These therapies provide rapid control of inflammation and help prevent organ damage. However, long-term use is frequently accompanied by adverse effects (e.g., increased infection risk, metabolic disturbances, and organ toxicity), drug resistance, and a high relapse rate [41].

TCM offers a complementary strategy characterized by multi-targeted actions, including immune modulation, anti-inflammatory effects, antifibrotic activity, and renal protection. Compared with modern drugs, TCM interventions are generally associated with fewer severe side effects and can address both acute and chronic disease processes [42].

Where modern therapies excel in rapid suppression of disease activity, TCM provides broader systemic regulation aimed at restoring physiological balance. For instance, certain herbal formulations and bioactive compounds, including Liuwei Dihuang Pills, Huanglian Jiedu Decoction, triptolide, and artemisinin derivatives, have demonstrated efficacy in improving renal outcomes and modulating pathogenic immune pathways (e.g., NF-κB and JAK/STAT) with lower toxicity profiles in appropriately monitored use [43].

Integrative approaches, combining TCM with modern agents, can potentially enhance therapeutic efficacy and reduce the required doses of immunosuppressants, thereby lowering the risk of adverse effects. For example, adjunctive TCM use has been reported to improve proteinuria reduction, enhance immune regulation, and support renal tissue recovery [44].

Despite these advantages, broader adoption of TCM faces challenges, including variability in herbal preparation quality, a lack of large-scale randomized controlled trials, and limited standardization in clinical protocols. Addressing these gaps through rigorous research, quality control, and regulatory oversight will be essential for optimizing combined TCM-modern therapy regimens. In summary, modern therapies remain indispensable for acute LN control, while TCM serves as a valuable adjunct

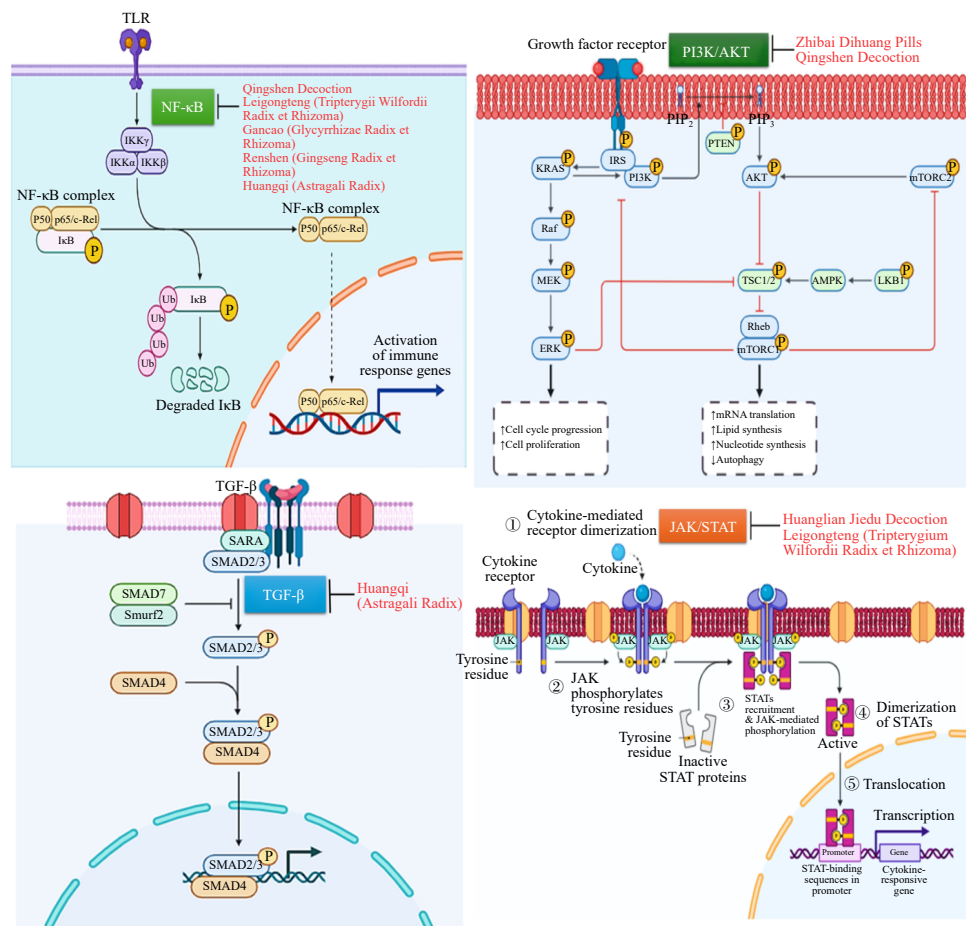


Figure 4 Various molecular pathways targeted by TCM components

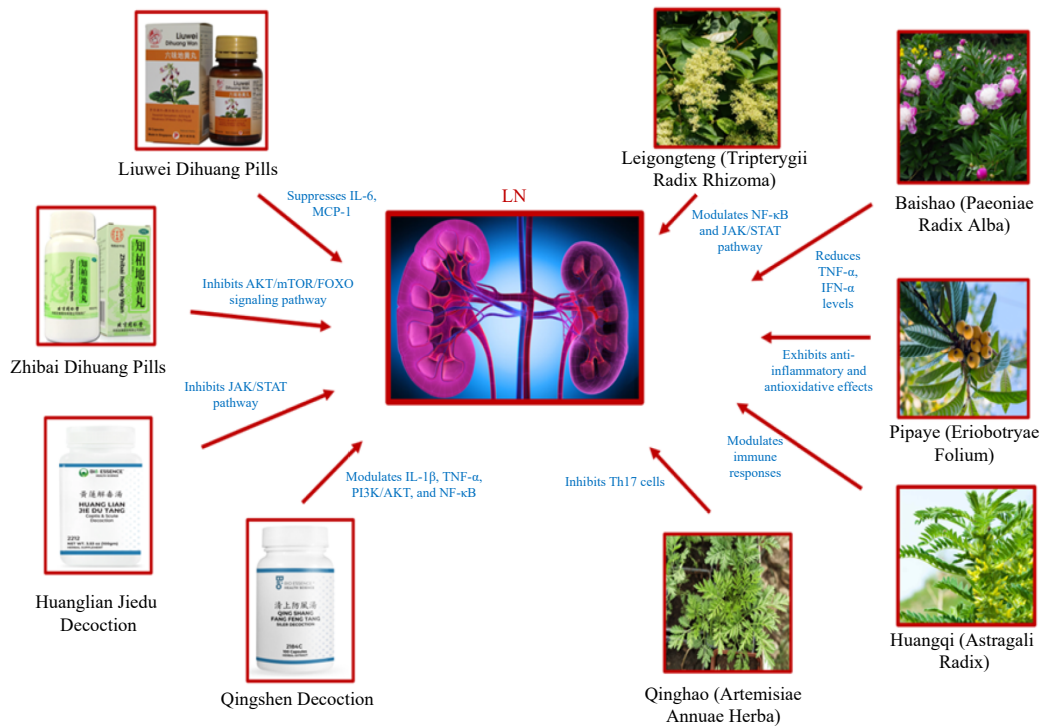


Figure 5 Integrated schematic of LN pathogenesis and therapeutic targets of TCM

for long-term disease management and progression prevention. An evidence-based integration of both approaches holds promise for more comprehensive, patient-centered LN care [45].

7 Challenges and prospects

TCM has demonstrated promise as a complementary approach for treating LN, but several limitations and challenges must be addressed to enhance its efficacy and integration with modern therapies. Key challenges include variability in herbal formulations, limited scientific validation, safety concerns and potential toxicity, herb-drug interactions, and variability in patient response [46].

Variability in herbal formulations can lead to variable clinical outcomes, complicating the establishment of standardized dosages and treatment protocols. Addressing this requires rigorous quality control and standardization procedures. Limited scientific validation hinders the TCM's integration into conventional medical practice, thus future research should prioritize well-designed, multicenter, randomized controlled trials (RCTs) to provide robust evidence of TCM's benefits and establish its role as an evidence-based treatment option for LN [47].

Safety concerns and potential toxicity are also significant in TCM treatment. Certain herbal ingredients can pose risks when used incorrectly or at high doses, limiting their clinical application. Comprehensive toxicity studies and structured monitoring protocols are necessary to identify safe dosage ranges and minimize these risks [48].

Herb-drug interactions are another important consideration in TCM treatment, as patients receiving conventional medications may take TCM as a complementary therapy without full awareness of how herbal components interact with their medications. Research into potential herb-drug interactions and patient education regarding these risks are crucial to ensure safe TCM use [49].

Advances in biomedical technology are paving new avenues for integrating TCM into LN management. Artificial intelligence-driven network pharmacology and big data analytics can accelerate the identification of bioactive compounds, predict herb-drug interactions, and optimize multi-component formulations. High-throughput omics platforms (genomics, transcriptomics, and metabolomics) coupled with systems biology modeling, enable precise mapping of TCM effects on LN pathophysiology [50]. Nanotechnology-based delivery systems, such as herbal nanoparticle carriers, may enhance the bioavailability, targeted tissue delivery, and safety profiles of TCM-derived compounds. In parallel, organ-on-chip and three-dimensional (3D) bioprinting models can provide physiologically relevant platforms for preclinical testing, reducing reliance on animal models and enabling personalized therapeutic strategies. The convergence of

these technologies hold promise to transform TCM research from empirical tradition to precision, mechanism-based medicine in LN care [51].

8 Conclusion

TCM offers a multi-targeted, holistic approach to LN management, complementing modern therapeutic strategies immune response modulation, anti-inflammatory effects, renal tissue protection, and fibrosis mitigation. Key formulations (e.g., Liuwei Dihuang Pills, Zhibai Dihuang Pills, and Huanglian Jiedu Decoction), along with bioactive compounds (e.g., triptolide and artemisinin derivatives), have shown potential to reduce proteinuria, improve renal function, and enhance treatment outcomes with fewer side effects compared with conventional immunosuppressants. Integrating TCM with standard care may provide synergistic benefits, addressing both acute disease control and long-term kidney preservation. However, challenges persist including formulation variability, limited large-scale clinical evidence, and safety concerns, particularly regarding herb-drug interactions. Future priorities entail standardizing TCM preparations, conducting rigorous randomized controlled trials and fostering interdisciplinary collaboration to define TCM role in evidence-based LN management.

Acknowledgements

The authors extend appreciation to the Department of Pharmaceutics, Saveetha College of Pharmacy, Saveetha University, Chennai, Tamil Nadu 602105, India.

Competing interests

The authors declared no conflict of interest.

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中医药在狼疮性肾炎中的应用：作用机制探讨与整合治疗策略

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【摘要】目的 综述并整合有关中医药方剂及活性草本化合物在狼疮性肾炎中的前临床与临床证据，提出中医药与常规医疗整合的研究方向与研究重点。**方法** 采用系统梳理与综合评价方法，检索数据库包括PubMed、Scopus、Web of Science与Google Scholar，检索时限为2011年至2025年6月。检索词将受控词汇（如医学主题词表）与自由词汇相结合，包含“狼疮性肾炎”“中医药”“中药”“方剂”及若干特定药用植物名称（如雷公藤、白芍和青蒿）。纳入随机对照试验与观察性研究，以及机理性前临床研究及药理学研究。纳入标准为报告肾脏结局（蛋白尿、肾小球滤过率估算值）、免疫调节机制或安全性与草药-药物相互作用数据的研究。无原始数据的综述、病例报告或与狼疮性肾炎无关的研究被排除。对关键参考文献进行人工筛查以识别出符合条件的其他研究。**结果** 在纳入的研究中常见的中药方剂包括六味地黄丸、知柏地黄丸、黄连解毒汤，常见的草本化合物包括雷公藤、白芍和青蒿的提取物。中医方剂及其成分在与狼疮性肾炎发病相关的机制上表现出多模式作用，涵盖免疫调节（降低自身反应性B细胞/T细胞活性、增强调节性T细胞）、抑制促炎信号通路[如核因子（NF）-κB、促分裂原活化蛋白激酶（MAPK）以及含NOD结构域、LRR序列及pyrin结构域的蛋白3（NLRP3炎症小体）]、抗纤维化与抗氧化作用以及直接的肾脏保护作用。在多项研究中，这些指标可减少蛋白尿并改善肾功能。尽管临床数据结果良好，但在研究设计、样本量、终点选择及中药制剂标准化方面存在异质性。安全性问题（尤其与雷公藤制剂相关）以及与免疫抑制剂相关的草药-药物相互作用仍为重要考虑因素。**结论** 中医药为狼疮性肾炎的治疗提供了基于生物学的多靶点的辅助治疗策略，联合现代疗法有望增强疗效并减少毒性。为将这一潜力转化为临床实践，未来研究应该优先关注推进中药制剂的标准化、开展临床上有意义的以肾脏终点为核心的随机对照试验、深入阐明分子作用机制，并系统评估药代动力学与安全性相互作用的问题。此类整合性研究对于明确中医药在基于循证和以患者为中心的狼疮性肾炎管理中的角色至关重要。

【关键词】 狼疮性肾炎；中医药；自身免疫性疾病；中草药；肾脏保护