REVIEW ARTICLE

Role of Traditional Chinese Medicine for the Treatment of Lupus nephritis: Mechanisms and Applications

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ABSTRACT

Background • Lupus nephritis (LN), caused by Systemic lupus erythematosus, is a chronic autoimmune renal disease and a key risk factor for morbidity and fatality involving 50% damage to the kidney. LN is associated with aberrant functioning of the immune system, characterized by increased systemic inflammation, altered lymphocyte count, perivascular infiltration of inflammatory cells, and declined organ functioning.

Current Therapies and Limitations • Conventional therapies to LN include high-dose glucocorticoids, immunosuppressants, calcineurin inhibitors, immune boosters, and targeted medicines that improve kidney functioning. However, these drugs triggered severe adverse side effects, and their prolonged usage resulted in drug resistance, accentuating LN complications.

TCM in LN Treatment • Hence, safe and functional Traditional Chinese Medicines (TCM), with supporting clinical trials and observational studies, received significant recognition worldwide for the Treatment of LN. In the form of herbal extracts and preparations, TCM proved effective in treating immunodeficient disorders, including LN. Additionally, acupuncture as a TCM appeared promising in reducing LN-induced inflammation and joint pain.

Mechanisms and Benefits • The therapeutic mechanisms included reduced antibody generation, pro-inflammatory cytokine release, immune complex formation, complement activation, extracellular matrix damage and proteinuria levels that played vital roles in chronic kidney diseases. They generated immunosuppressive effects by modulating apoptosis, oxidative stress, and inflammatory signaling pathways, such as JAK/STAT, NF-κB, AP-1 and MAPK and their cross-talk in LN and associated renal injury. These therapies improved blood circulation, alleviated renal pathological changes, restored glomerular capillary functioning, and regenerated renal tissues. However, an essential requisite for these therapies for LN included reduced side effects and improved hepatoprotection and detoxification. Clinical studies suggest that TCM formulations may demonstrate therapeutic benefits in alleviating the symptoms of LN, suggesting prospects of combined applications with Western medicine to enhance treatment efficiencies. Overall, TCM is beneficial for treating LN, and may serve as a potential alternative to conventional medicines. (*Altern Ther Health Med.* 2024;30(6):154-165).

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INTRODUCTION

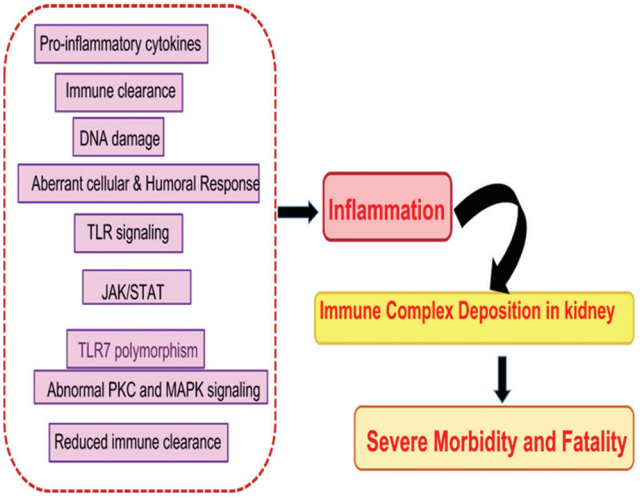
Background of Lupus Nephritis

Lupus nephritis (LN) is a type of inflammatory renal disease that develops as a secondary complication to the autoimmune disease, Systemic lupus erythematosus (SLE).[1,2] The main challenges that LN pose include inflammation and immune complex deposition in glomeruli, small blood vessels of kidneys, and renal interstitium.[3,4] This could result in severe morbidity and even fatality, with gender- and ethnicity-based varied effects.[5,6] LN involves binding circulating polyclonal autoantibodies to nucleosomes and associated autoantigens of the kidneys.[7] This subsequently leads to an unrestricted inflammatory response, marked by pro-inflammatory cytokine and chemokine secretion, renal injury, and organ damage.[8] Ineffective clearance of immune complexes and cellular wastes comprises an important pathogenic feature of LN.[9]

Pathogenesis of LN

The pathogenesis of LN comprises of primary events that require sequential cellular and humoral reactions in the

Figure 1. Aberrant inflammatory mechanism inducing LN-associated pathogenesis. The inflammatory mechanisms that promote immune complex deposition in kidney and an ultimate severe morbidity and probable mortality.



kidney.[10] LN belongs to the proliferative (III/IV) and membranous (class V) classes and culminates in end-stage renal disease if left untreated.[11] A direct participation of renal resident cells, such as podocytes, mesangial cells, and tubular epithelial cells, have been reported in the pathogenesis of LN.[12] Podocyte dysfunction in LN is associated with proteinuria and increased expression of costimulatory molecules, such as Cluster of differentiation 80 (CD80), Nod-like receptor 3 and pro-apoptotic proteins.[12-15] It also involves the activation of calcium/calmodulin-dependent protein kinase IV and T-cells.[16] An aberrant functioning of the mesangial cells that sustain normal debris-free glomerular filtration has as well been observed via key immune system-related factors and cellular processes involving the altered Toll like receptor (TLR) signaling and generation of the cytokine, interferon-gamma (IFNγ).[17] The abnormal protein kinase C and mitogen-activated protein kinase (MAPK) signaling mechanisms, together with fibrotic pathways of mesangial cells and matrix protein deposition, also contributed to renal parenchymal pathology.[12,17] LN also involves the generation of autoantibodies that form immune complexes accumulating in the kidneys, triggering the process and pathogenesis of LN and related renal damage. The inflammatory response of LN involves chromatin modification and Deoxyribonucleic acid (DNA) damage, resulting in dysregulated apoptosis.[18] This feature appears prominent in patients with SLE-associated alleles related to chromatin clearance.[19] Additionally, it results in the disordered functioning of DNA and Ribonucleic acid (RNA) sensors of endosomal TLR and lymphocytes.[20] This helps in the generation of IFNγ and cyclic guanosine monophosphate-adenosine monophosphate synthase,[20] which may include the maturation of dendritic cells, T-cell activation, and an adaptive immune response.[21] Genetic polymorphisms in TLR7, also contribute to the pathogenesis of LN, along with altered DNA methylation within these genes.[22] Here, the Signal transducer and activator of transcription 4 (STAT4) havebeen identified as a predominant lupus risk gene with polymorphism, linked with anti-nuclear antibodies.[23] Moreover, IFNγ activated the Janus kinase (JAK)/STAT signaling pathway, with enhanced participation of STAT1 and STAT4 in the glomeruli of LN patients.[24] The overall aberrant inflammatory mechanism that comprises a predominant pathway of LN pathogenesis is summarized in Figure 1.

Current Therapies for LN and their mechanism of action

Clinical observations, pharmacokinetic data, international guidelines for LN management, and observations using immunosuppressants, revealed the mechanism of action for LN therapeutics.[25]. The first-line drugs for LN include glucocorticoids, which often function through the genomic mode via transcription factors, such as Activator protein-1 (AP-1), nuclear factor kappa B (NFκB), and interferon regulatory factor.[26] Cyclophosphamide, which functions as a DNA alkylating agent, arrests the cell cycle and proliferation in LN.[27] It attenuates the functioning of B cells, restricts Immunoglobulin (Ig)G, IgM, and autoantibody generation, and also affects CD4 and CD8 T lymphocytes.[28]. A fungal fermentation product, mycophenolate mofetil, inhibits the type II isoform of inosine monophosphate dehydrogenase in activated B and T lymphocytes causing cell arrest in S phase.[29] The imidazole derivative, azathioprine that generates mercaptopurine and 6-thioinosinic acid (inhibitor of purine synthesis) blocks replication in T lymphocytes and regulates apoptosis in the kidneys.[25]. Calcineurin inhibitors interact with calcium-calmodulin-calcineurin and hinder interleukin (IL) synthesis as an essential step of T-cell proliferation, via reduced dephosphorylation and translocation of the nuclear factor of activated T-cell for controling LN pathogenesis.[30] Antimalarials reduce T cell immune response by inhibiting antigen presentation and decrease proteinuria too.[7] Antimalarials also suppress drug resistance of T lymphocytes by hindering the multidrug resistance protein 1, P-glycoprotein.[25] Further, the monoclonal antibody and IgG1λ immunoglobulin (belimumab) inhibit B-cell activating factor (BAFF) that belongs to the tumor necrosis factor (TNF) ligand family.[31]

Limitatiuons of current therapies for LN

However, these drugs induce cytotoxicity from immunosuppressive and pharmacologic effects [32]. Reduced hematopoiesis, involving leukocytes, platelets and erythrocytes, is associate with megaloblastic and non-megaloblastic macrolytic anemia.[33] There have been drug-induced hepatic dysfunction, pancreatitis, and cardiac failure results for LN.[32] The long-term effects of these drugs often include malignancy (non-Hodgkin's lymphoma, myelocytic leukemia), squamous cell carcinoma, and bladder cancer. Due to reduced granulocyte formation and a chronic and

Table 1. Mechanism of action of TCM for LN therapy

TCM	Composition	Mechanism of action
LiuweiDihuang	*Rehmanniaglutinosa, Cornus officinalis, Dioscoreaopposita, Alisma orientale, Poriacocos and Paeonia suffruticosa*	Target monocyte chemoattractant protein-1, IL-1, IL-6, TNFα and fractalkine, matrix metalloproteinases, cyclooxygenase-2
ZhibaiDihuang	ZhibaiDihuang pill	Improved complement C3 and C4 levels, regulated increase in white blood cells, balanced glycemic effect and increased androgen-like property, regulated TLR pathway, NF-κB and JAK-STAT and Akt/mammalian target of rapamycin (mTOR) pathways
Hachimi-jio-gan	*Rehmanniaglutinosa, Cornus officinalis, Dioscoreaopposita, Alisma orientale, Poriacocos, Paeonia suffruticosa, Cinnamomum cassia*	Nourished the blood, reduced IFN-γ and IL-2, Th1/Th2 balance, regulated IL-12
Huang Lian Jie Du Decoction	Flavonoids, alkaloids and iridoids	Targeted Regulatory T cells, anti-complement autoantibodies, anti-tumor, anti-hypoglycemic and antimicrobial host defense peptides and activity
Zhenwu decoction	*Aconitum carmichaeliiDebeaux, the radix of Paeonia tacti lora Pall., Poria, AtractylodesmacrocephalaKoidz., and Zingiber officinale Roscoe*	Anti-inflammatory, antioxidative, anti-tumor and lipid-lowering properties
Tripterygium wilfordii Hook F	*Triptolide, tripdiolide and wilforlide*	Strong anti-inflammatory, anti-rheumatic and immunosuppressive effects; reduced albuminuria, BUN levels, persistent proteinuria, inhibited the proliferation of antigen- and mitogen-stimulated T cells and B cells and production of IL-2 and IFNγ
Tripterygium glycosides	*Radix et RhizomaTripterygii*	Down-regulated the NFκB, AP-1 and the NFκB regulatory components; triggered anti-apoptotic pathways
Total glucosides of paeony	*Radix Paeoniae Alba* that belongs to Ranunculaceae family	Reduced proteinuria, serum creatinine and anti-dsDNA antibody; inactivated STAT6 signaling; balanced M1/M2 polarization
Integrative medicine	Used in combination with conventional medicines	Down-regulated the binding affinity between eosinophil cationic protein (ECP) and epithelial cells; attenuated caspase-3 and caspase-7 expression
Cordyceps	Composed of cordycepin, adenosine, polysaccharides and ergosterol	Immunomodulatory potential
Curcumin		Suppressed the production of autoantibodies (including anti-dsDNA IgG) and activation, signaling and expression of TLR4; Regulated the peripheral blood mononuclear cell levels of costimulatory molecules, CD40L and CTLA-4
Loquat leaf and Osmanthus extracts	bioactive compounds, including triterpenes, flavonoids and polysaccharides	Anti-inflammatory and immunomodulatory properties
Realgar nanoparticles	Realgar, arsenic mineral	Reduced IFNγ and IL-6, infiltration of inflammatory cells and the deposition of immune complexes
Acupuncture and cupping		Immunosuppressant
Dietary therapy	Food items high in antioxidants and anti-inflammatory compounds	Reduced inflammation

inherent loss of the physiological defense mechanisms, infections have been demonstrated in relation to the immunosuppressant therapies for LN. They induce pulmonary fibrosis as an interstitial lung disease as well.[34] Moreover, these drugs induced toxic effects on gonadal tissue, associated with a loss in the testicular germ cells and primordial ovarian follicles, and reproductive problems.[35]

Rationale for TCM

The search for newer therapies for LN led to the generation of Traditional Chinese Medicines (TCM) and natural extracts. The TCMs have varied pharmacological effects attenuating the progression of LN. They also showed significantly reduced adverse side effects, increasing their acceptability and efficacy in the Treatment of LN.

Objectives of the Review

The current review summarizes the potential benefits of TCMs for treating LN and exploring their mechanism of action (Table 1).

TCM AND MECHANISM OF ACTION FOR THE TREATMENT OF LN

1. LiuweiDihuang, also known as Six Flavor *Rehmanni,* is a TCM formula that has been used for centuries to nourish the liver and kidney and promote overall health and longevity. The formula of LiuweiDihuangconsists of six herbs, including *Rehmanniaglutinosa*, *Cornus officinalis*, *Dioscoreaopposita*, *Alisma orientale*, *Poriacocos* and *Paeonia suffruticosa*.

LiuweiDihuang is well-known for its distinct therapeutic effect on chronic kidney diseases (CKD), and associated symptoms of fatigue, dizziness, tinnitus, etc.[36,37]

One of the *key mechanism*s of action of LiuweiDihuang in LN comprises the restoration of immune functions and kidney nourishment.[38,39] The TCM, particularly in combination with hormone therapy, helped in decreasing the levels of receptors for advanced glycation end products, monocyte chemoattractant protein-1, IL-1, IL-6, TNFα, and fractalkine that have been implicated in the pathogenesis of LN.[40]

LiuweiDihuang showed the ability to inhibit the breakdown of the extracellular matrix through reduced production of matrix metalloproteinases, preventing kidney tissue damage and fibrosis. This also resulted in the restricted proliferation of mesangial cells, supporting the structure of the glomeruli in the kidneys.[39]

Through an inhibition of cyclooxygenase-2 (COX-2)-induced cell stress, LiuweiDihuang reduced prostaglandin generation and decreased vascular permeability in the kidneys of LN.[39] A regulated activation of these inflammatory molecules restricts the differentiation of immune cells into effector cells, leading to a normal inflammatory response in the kidneys. Further, LiuweiDihuang pills helped to limit the recruitment of immune cells to the kidneys and prevent tissue scarring and damage that lead to a decline in renal activity.[37]

Additionally, the TCM reduced injury to the endothelial cells, which prevented the formation of blood clots and the blockage of blood flow.

Moreover, the LiuweiDihuang-induced mechanisms decreased the chances of proteinuria and hematuria for improved kidney functioning in LN.[41]

2. Another type of TCM included a combination of LiuweiDihuang with *RhizomaAnemarrhenae* and *Phellodendron chine,* in the name of **ZhibaiDihuang** pills that have been used as adjuvant therapy, particularly for treatments requiring steroids to reduce SLE and associated conditions of LN.[42] A meta-analysis study showed that a modified ZhibaiDihuang pill combined with steroid therapy led to a significantly higher steroid withdrawal rate than steroid therapy alone, which improved the levels of complement C3 and C4.

- As pharmacologic effects, **ZhibaiDihuan** helped in regulating the increase in white blood cells, anti-hemorrhagic shock, and regulated blood flow through heart muscle contraction in the SLE patients.
- Additionally, a balanced glycemic effect, increased androgen-like property, and immune system homeostasis, resulted in improved sustenance and attuning of kidney functions in LN.[42] The effects involved homeostasis in T and B cell receptor signaling and the TLR pathway.
- **ZhibaiDihuang** pills modulated several inflammatory mechanisms, including the NF-κB and JAK-STAT, for LN.
- In addition, ZhibaiDihuang sustained the expression of antioxidant enzymes and proteins involved in apoptosis.[43]
- **ZhibaiDihuang** pills have been found to be effective in treating chronic kidney inflammation, diabetic nephropathy, and renal injury. The mechanism related to these effects involveda regulated 5' adenosine monophosphate-activated protein kinase K expression, inhibited Akt/mammalian target of rapamycin (mTOR), and activated Forkhead box O (Fox O) pathways in the kidneys, suggesting the protective effects of these pathways in LN.
- The pills further helped reduce the abundant serum and renal-tissue-based C3 protein and IgG levels that are part of the cellular and humoral immunity.[37,39]

3. Hachimi-jio-gan (traditional Japanese herbal medicine), also known as **Ba-Wei-Dihuang**in, is composed of eight herbs, including *Rehmanniaglutinosa*, *Cornus officinalis*, *Dioscoreaopposita*, *Alisma orientale*, *Poriacocos*, *Paeonia suffruticosa*, *Cinnamomum cassia,* and *Schisandra chinensis*. The herbs comprise licorice root, ginger and peony roots that have been used for centuries to treat allergies and autoimmune disorders. Like ZhibaiDihuang, Ba-Wei-Dihuang is often used to support kidney health and promote overall vitality.[44] It is believed to sustain the kidneys, nourish the blood, and promote the production of essential fluids in the body.

- Ba-Wei-Dihuang showed antioxidant and anti-inflammatory properties and helped alleviating symptoms associated with kidney disorders and LN, such as lower-back pain, weakness, and frequent urination.
- The impact of Ba-Wei-Dihuang treatment on Th1 cells in MRL/lpr mice of LN demonstrated a significantly reduced production of IFN-γ and IL-2, attenuating the severity of glomerulonephritis.[45]
- Ba-Wei-Dihuang herbal pill limited IFN-γ generation from anti-CD3 antibody-stimulated B220-T cells, and thereby reduced immune cell activation by suppressing the binding to CD3 protein on the surface of T cells.
- Treatment with Ba-Wei-Dihuang attenuated Th1 cytokine production and increased Th2 cytokine generation, shifting the Th1/Th2 balance towards aTh2 predominance in LN. This shift in the Th1/Th2 balance is associated with the reduction in autoimmune pathology in the mice.[45]

Hachimi-jio-gan also lessened the serum levels of IgG2a anti-dsDNA autoantibodies that are particularly pathogenic in LN and often used as a diagnostic marker for the disease. IL-12 mRNA expression demonstrated an increased expression in the kidneys of patients with LN, and Hachimi-jio-gan blocked IL-12 cytokine production through the activation of dendritic cells and macrophages. Hachimi-jio-gan activated T cells and natural killer (NK) cells in response to infection or inflammation, as observed in MRL/lpr mice [45].

4. The TCM, **Huang Lian Jie Du Decoction**, comprises flavonoids, alkaloids, and iridoids from four herbs and demonstrated renoprotective effects. Huang Lian Jie Du Decoction induced regulatory T cells, anti-complement autoantibodies, anti-tumor, anti-hypoglycemic, and antimicrobial host defense peptides, and activity.

- Huang Lian Jie Du Decoction prevented inflammatory cell infiltration (involving altered generation, functioning, and activation of chemokines, cytokines (TNFα and IL-6), p-STAT-3, TLR, and classical complement pathway) and reduced the tumor microenvironment that actively suppressed the function of invading T cells in the MRL/lpr mice of LN.[46] The study also showed that Huang Lian Jie Du Decoction modulated the levels of an important mediator of the immune response, IL-10, produced by T cells, B cells, and macrophages, and reduced inflammation. The IL-10 may have played a complex role, leading to reduced TNFα and IL-1β and causing a suppression in the T cells and macrophages, resulting in the Huang Lian Jie Du Decoction-induced decrease in thedevelopment and progression of LN.[46]
- Further, the Huang Lian Jie Du Decoction-induced suppression in p-STAT3 could be responsible for the increased survival rate in the mice[46] (equivalent to the benefit in longevity in LN patients). These effects involved the expression of genes directing cell proliferation, differentiation, and survival that are generally modulated by p-STAT3.[47]
- The Huang Lian Jie Du Decoction-mediated reduction in serum creatinine levels also improved the kidneys' glomerular architecture and cell structure, comprising mainly of mesangial cells, glomerular endothelial cells, and some renal tubular epithelial cells.[46]
- Huang Lian Jie Du reduced the Blood urea nitrogen (BUN) in the mice, signaled an upgraded liver functioning, particularly in relation to protein metabolism, decreased inflammation of the glomerular capillaries, and enhanced kidney functioning.
- A decreased proteinuria level in the Huang Lian Jie Du Decoction-treated MRL/lpr mice[46] further suggested an improved urine protein-to-creatinine ratio and reduced nephropathy.[48]

5. Zhenwu decoction is another TCM that regulates the body's water metabolism, probably by affecting the kidneys.

Zhenwu comprises five herbs, namely, *Aconitum carmichaelii Debeaux,* the radix of *Paeonia tacti lora Pall., Poria, AtractylodesmacrocephalaKoidz.,* and *Zingiber officinale Roscoe,* which trigger renoprotective impact via anti-inflammatory, antioxidative, anti-tumor and lipid-lowering properties.[49,50]

- Although relatively less explored, Zhenwu decoction helped to reduce inflammation in the kidneys, and slowed the progression of the disease. Additionally, Zhenwu decoction regulated the physiological blood pressure and sugar levels that played an important role in reducing complications associated with CKD, renal fibrosis, and related disorders.
- Notably, Zhenwu decoction showed a protective effect against gentamycin-induced apoptosis of renal tubular cells and has been proposed as a potential TCM for LN.[50]

6. Tripterygium wilfordii Hook F, also known as Thunder God Vine, is a TCM whose main medicinal parts are the dried root and rhizome. It is grown in China, Korea, and Japan and has been used to treat a variety of health conditions, including Lupus.

- *Triptolide*, *tripdiolide*and *wilforlide* are the principal active components found in Tripterygium wilfordii Hook F.[51] These compounds demonstrated potential therapeutic effects in various autoimmune and inflammatory diseases, including (NZB x NZW)F1 mice with nephritis. Tripterygium wilfordii Hook Fshowed strong anti-inflammatory, anti-rheumatic, and immunosuppressive effects and demonstrated unique efficacy in the field of rheumatic immune diseases and kidney diseases.
- It has also been shown that treatment with the active ingredients of Tripterygium wilfordii Hook F, predominantly triptolide and tripdiolide, effectively reduced inflammation, oxidative stress and fibrosis in the kidneys, decreased disease severity of LN, improved body weight, and extended the lifespan of the (NZB x NZW)F1 mice.
- These active ingredients also helped reduce albuminuria, BUN levels, persistent proteinuria (marked by IgG and C3 staining in the n renal glomeruli) and anti-dsDNA antibody-induced immune complexes in the kidney.[52] These protective features suggested a decreased risk for complications such as high blood pressure, metabolic disturbances and cardiovascular disease that are directly related to LN.[53,54]
- Tripterygium wilfordii suppressed the development of diffuse proliferative glomerulonephritis, which reduced the infiltration of mononuclear cells and rare neutrophils in the glomeruli, perivascular regions and interstitium. This TCM could restrict the activation and glomerular migration of cells lining the Bowman's capsule, preventing the formation of crescent-shaped lesions and scar tissue in the kidneys.
- Moreover, Tripterygium wilfordiiis associated with attenuated fibrinoid necrosis 52, which is generally characterized by blood vessel damage, vessel rupture and hemorrhage.[55] Tripterygium wilfordii-induced reduction in tubular atrophy also suggested a regulated reabsorption of nutrients, fluid, and electrolytes. Consistent observations were seen through *in vitro* study, where the Tripterygium wilfordii extract inhibited the proliferation of antigen- and mitogen-stimulated T cells and B cells and the production of IL-2 and IFNγ.[56] This involved an altered tyrosine phosphorylation and protein kinase activation mechanism.[56]
- Additionally, the Tripterygium wilfordii-mediated reduction in the macrophages and dendritic cell levels and limited NF-κB activity hypothesized a decreased participation of inflammation-associated genes, as well as adhesion molecules that are involved in leukocyte recruitment and infiltration into inflamed tissues.
- Other mechanisms by which Tripterygium wilfordii could exert its anti-inflammatory effects included inhibiting prostaglandin and leukotriene synthesis and suppressing reactive oxygen species and nitric oxide production. Tripterygium wilfordii reduced the secretion of total rheumatoid factors, IgM, and IgM-RFby peripheral-blood mononuclear cells in patients with rheumatoid arthritis (that has a key link with LN). These features additionally pointed to the beneficial role of the TCM in preventing development and progression of the disease.[57]
- A study in China also demonstrated that Tripterygium wilfordii Hook F, combined with prednisone and a short course of cyclophosphamide, was effective in inducing clinical remission in a patient with LN. The recovery using Tripterygium wilfordii Hook F was to the extent that the patient could be kept free of prednisolone after the next eight months and had a normal pregnancy.[58]

7. Tripterygium glycosides originate from Tripterygium wilfordii Hook F, and is extracted from Radix et RhizomaTripterygii through column chromatography. Of the 380 metabolites identified in the Radix et RhizomaTripterygii extracts, triptolide comprised the key component having immunoprotective and pain-relieving properties. Hence, Tripterygium glycosides have been used to treat autoimmune diseases and systemic autoimmune aberration.[59]

- One of the main functions of Tripterygium glycosides is the inhibition of T cell stimulation. antigen spread and inactivation of the innate immune system. It alsohindered the process of accelerated-onset of glomerulosclerosis.[60,61]
- Tripterygium glycosides restricted inflammatory responses and the release of related cytokines, concomitant with a reduction in the harmful lupus-associated autoantibodies. They also helped reduce the differential immune recognition of hemoglobin and B-cell precursor frequencies that participated in LN pathogenesis.[62,63] The TCM suppressed IL-6 and IL-10

levels, which promote the secretion of erythrocyte-reactive autoantibodies, and serum levels of TNFα.

- Tripterygium glycosides down-regulated the NFκB, AP-1 and the NFκB regulatory components, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα), and IκBkinaseα. These anti-inflammatory effects ultimately reduced AP-1- and NFκB-mediated transcription of the downstream inflammatory mediators.
- Tripterygium glycosides reduced renal injury by inducing the anti-apoptotic pathways marked by enhanced B-cell lymphoma 2 (Bcl-2) and decreased CD36, ADFP, BCL2 associated X, apoptosis regulator (Bax) and Cleaved caspase-3 in the nephritic cells. Additionally, a regulated lipid deposition also helped in alleviating problems associated with LN-induced renal damage, which regulated the infiltration of inflammatory cells in the glomeruli.
- Additionally, Tripterygium glycosides appeared protective against renal inflammatory lesion through reduced activation of p38MAPK signaling in the kidney.[65]

8. Total glucosides of paeony is another TCM known for its usage as a therapy for autoimmune diseases. This TCM undergoes extraction from *Radix Paeoniae Alba*whichbelongs to *Ranunculaceae* family.

- Total glucosides of paeony treatment helped reduce proteinuria, serum creatinine and anti-dsDNA antibody levels comprising a group of anti-nuclear antibodies and markers for the diagnosis of Lupus. Owing to these protective effects in the kidneys, Total glucosides of paeony down-regulated interstitial and glomerular cellular infiltration and reduced renal tissue injury.
- Total glucosides of paeony attenuated the renal macrophage infiltration and inactivated the STAT6 signaling mechanism in LN, hindering the phenotypic features and progression of the disease.
- The glycosides suppressed the serum creatinine and protein levels and reduced the Anti-dsDNA autoantibody that serves as a marker of the failed immune system, associated with loss in damaged genetic material and tissues.
- Furthermore, a balance between T helper type 17 (Th17) cells and peripheral Treg cells of the immune system has been observed in response to TCM treatment. In addition, it enhanced the F4/80+ Arg1+ and decreased F4/80+ iNOS+ macrophage infiltration, followed by a balanced M1/M2 polarization in the kidney[66]

9. Integrative medicine in SLE is generally a combination of conventional medicines (corticosteroids: prednisolone, methylprednisolone, methotrexate, sulfasalazine, azathioprine, hydroxychloroquine, mycophenolate mofetil or cyclophosphamide) with herbal medicines (with antioxidant, anti-inflammatory and immune-stimulating effects). The first nationwide study in SLE patients from Taiwan demonstrated that integrative medicine reduced the likelihood of LN. The effects were varied for the combination formulations.[67]

- The herbal formula mainly studied were Sheng-Di-Huang (raw Rehmanniaglutinosa), Mu-Dan-Pi (root bark of peony), and Dan-Shan (Salvia miltiorrhiza), which ameliorated LN-induced renal damage by protecting against kidney epithelial cell degeneration. This herbal formulation with a predominant amount of raw *Rehmanniaglutinosa*, which is rich in iridoid glycosides, down-regulated the binding affinity between eosinophil cationic protein (ECP) and epithelial cells and sustained the permeability of renal cells. The interactions further restricted the cellular entry of ECP, alleviating symptoms of inflammation.
- A few of these combinations, with a predominance of *Anemarrhenaasphodeloides* and *Phellodendronchinense* played a key role in reducing renal cell death. This was marked by attenuated caspase-3 and caspase-7 expression, and the inflammatory Receptor activator of nuclear factor kappa-B ligand. These herbal medicines also had a key etiological significance in improving the neuro-endocrine-immune mechanism of LN.
- Another widely used medicinal herb, *Radix Salivaemiltiorrhizae,* inhibited interstitial fibrosis in the renal tubular epithelial cells through a regulated c-myc protein expression and subsequent TGF-β/Smad signaling in fibroblasts, which improved the normal proliferation of these fibroblast cells. This medicinal herb involved the participation of a balanced NF-κB signaling, reducing the production of extracellular matrix components. The subsequent anti-inflammatory effects suppressed tubular atrophy ,interstitial inflammation and fibrosis, which improved renal survival in LN.[68]
- *Radix Salivaemiltiorrhizae* also sustained the proliferation of kidney cells through modulated IFNα level that directs the homeostasis between the endothelial progenitor cell survival, proliferation, apoptosis, differentiation, etc. These effects also had a key impact on angiogenesis and augmented vascular repair.
- A closely related Chinese herbal medicine, *Radix Paeoniae Rubra,* decreased blood stasis associated with SLE and renal failure, regulating normal blood flow and circulation. The herbal preparation induced protective effects against renal pathology associated with reduced infiltration of inflammatory cells in the glomeruli and interstitial cells. *Radix Paeoniae Rubra* also induced a significant suppression in the renal intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and platelet endothelial cell adhesion molecule 1 (PECAM-1) that correlated with proteinuria, serum creatinine, anti-dsDNA antibodies, leukocyte infiltration and fibrinoid necrosis/karyorrhexis scores and renal flare.[68]

- A retrospective analysis using the data obtained from a Taiwan National Health Insurance Research Database (NHIRD) from 1997 to 2011 showed that an Integrative medicine administration comprising conventional medicines, prednisolone, methylprednisolone, methotrexate, sulfasalazine, azathioprine, hydroxychloroquine, mycophenolate mofetil or cyclophosphamide, and herbal medicine (HM), Sheng-Di-Huang," "Mu-Dan-Pi," "Dan-Shan," "Zhi-Bo-Di-Huang-Wan," and "Chi-Shao" had a protective effect in the kidneys. The adjusted hazard ratio (HR) for LN, estimated using the Cox proportional regression model and the Kaplan-Meier method, was lower in SLE patients who received conventional medicines plus HM than in the group receiving only.[67]

10. Cordyceps, *Chinese caterpillar* (or Dong chongxiacao in Chinese), is a type of fungus that has been used in TCM for centuries to treat a variety of health conditions. The bioactive ingredients, including cordycepin, adenosine, polysaccharides, and ergosterol are primarily responsible for therapeutic functions and mainly as an adjuvant therapy.

- It has been shown that Treatment with Cordycepin reduced acute rejection of the transplanted kidney, improved renal function, prolonged graft survival, and reduced cyclosporine-induced aminoglycoside nephrotoxicity, mainly owing to its immunomodulatory potential.
- One of the bioactive ingredients in Cordyceps is cordycepin, which is a nucleoside analogue capable of significantly reducing the severity of renal fibrosis and increasing glomerular filtration rate in patients with kidney dysfunction.
- Cordyceps exhibits pharmacologic activity as aimmune response modulator by regulating the balance between Th1 and Th2 cells. The TCM reduced IL-1β, IL-4, and IL-6 levels and inflammatory immune cells' subsequent activation, proliferation, and pathogenesis. Cordyceps promoted immune responses through the inhibition of STAT3 in the immune cells.
- Cordyceps suppressed the activity of the mTOR and NF-κB signaling and regulated activation and proliferation of T cells and B cells and cellular metabolism, ultimately leading to reduced persistent inflammation. The above inflammatory pathways further reduced the abnormal activation of AKT signaling pathway, cytochrome c release from the mitochondria into cytoplasm, inflammasome activation, and balanced energy production in the various cell types of kidneys.
- Cordyceps extract could also reduce BAX, increase BCL-2, and maintain the homeostasis of these important molecules of the apoptotic pathway, attenuating the progression of LN.[69] Researchers also found the potential benefits of *Cordyceps sinensis* (a parasitic fungus that derives nourishment from the larvae of Lepidoptera) and *Artemisia annua* in preventing the recurrence of LN after three years in patients who had been successfully treated with immunosuppressive drugs (corticosterone and cyclophosphamide).
- The herbal Treatment showed improved blood creatinine, creatinine clearance rate, and antinuclear antibodies, and a significant improvement in kidney functioning.[70]
- A study investigating the potential therapeutic effects of a pure compound H1-A extracted from *Cordyceps sinensis* showed immunomodulatory effects in LN. It regulated the generation of IL-2 (from peripheral blood mononuclear cells) and antinuclear autoantibodies and the hyper-proliferation of the normal lymphocytic cells. In terms of LN, the study showed a reduction in mesangial proliferative glomerulonephritis and improved morphological pattern and numerical maintenance of the intercellular matrix in the mesangial cells of the glomerulus. The H1-A extract showed relatively selective action on T lymphocytes and peripheral T cell reactivity, with an overall improvement in the clinical manifestation of LN.[71]

11. Another TCM, Artemisinin, an antimalarial agent, functions as a natural compound extracted f*rom the herb Artemisia annua*, also known as sweet wormwood. This TCM has been used for centuries to treat fever and other ailments. Artemisinin and its derivatives, including artesunate and artemether, have been studied for their potential therapeutic effects in managing kidney diseases. The major mechanisms for the action of artemisinin included anti-inflammatory, anti-oxidative, anti-fibrotic, and anti-proliferative effects in acute kidney injury, CKD, and diabetic nephropathy. These mechanisms have been proposed for certain types of kidney cancer as well.[72]

- Findings (*in vivo*) demonstrated the ability of artemisinin to target the expression of the cell-surface glycoprotein, ICAM-1, that plays a key role in the adhesion and migration of immune cells, such as T cells and macrophages, to sites of inflammation in the kidneys. Related to the anti-inflammatory effects, the inhibition of NF-κB translocation by dihydroartemisinin led to a reduction in the expression of genes involved in inflammation, such as IL-6 and inducible nitric oxide synthase (iNOS), in immune cells.
- Additionally, dihydroartemisinin reduced the production of autoantibodies and ameliorated TNFα, NF-κB, IL-6, TGFβ (and down-stream Smad2/3) and kidney damage in BXSB mice model of Lupus.
- Dihydroartemisinin also suppressed the enzymatic activity of serum urine albumin, creatinine and BUN anti-ds-DNA, antinuclear antibodies, and IgG. A study investigating the immunosuppressive effects of hydroxychloroquine and artemisinin combination therapy in LN mice found that it reduced proteinuria, serum creatinine and immune complex deposition in the kidneys. The combination therapy also down-

regulated the expression of NF-κB, which decreased the expression of pro-inflammatory IL-1β and TNFα and increased the expression of anti-inflammatory IL-10 in the kidneys of LN mice.
- Furthermore, studies demonstrated a reduced activation of the MAPK/ERK signaling pathway, which participated in the pathogenesis of LN by promoting the production of pro-inflammatory cytokines and oxidative stress. The TCM restored the transcription factor Krüppel-like factor 15, which played a critical role in regulating gene expression in the kidneys. It also induced recovery from LN-induced glomerulus growth, asymmetrical glomerular basement membrane, and enhanced glomerular cell number.[73,74] It has been seen that artemisinin modulated the glucocorticoid receptor-alpha mRNA level in the peripheralblood mononuclear cells and transcriptional coactivator P300/CBP protein in LN.[75]

12. Curcumin treatment reduced the production of BAFF by macrophages that promote the survival and activation of autoreactive B cells. Researchers found that curcumin attenuated the severity of LN in MRL/lpr mice, as evidenced by decreased proteinuria and kidney damage.

- Curcumin reduced the activation of autoantibodies (including anti-dsDNA IgG), and signaling and expression of TLR4 in the kidneys of MRL/lpr mice. It also led to reduced generation of pro-inflammatory cytokines and chemokines in the human renal proximal tubular epithelial cells exposed to lupus sera.[76]
- Curcumin treatment inhibited the activation and expression of Proline-rich tyrosine kinase 2 (a cytoplasmic tyrosine kinase that has been implicated in the pathogenesis of LN by promoting inflammation, tissue damage, and fibrosis in the kidneys) and downstream signaling pathways in peripheral blood mononuclear cells. It reduced abnormalities in serum complement levels, resulting in reduced production of pro-inflammatory cytokines and chemokines in LN.
- Moreover, curcumin regulated the peripheral blood mononuclear cell levels of costimulatory molecules, CD40L and CTLA-4, that play important roles in the immune response and have been implicated in the pathogenesis of LN.[77]

13. Loquat leaf and Osmanthus extracts is a TCM whose leaves contain several bioactive compounds, including triterpenes, flavonoids, and polysaccharides. Loquat leaf and Osmanthus extracts exhibited anti-inflammatory and immunomodulatory properties.

- In terms of LN, Loquat leaf demonstrated potential for inhibiting Th17 differentiation and reducing IL-6, IL-1β, TGF-β,and IL-17 production.
- **Loquat leaf** could function as a therapeutic agent for LN by inhibiting retinoic acid-related orphan receptor gamma (RORγt) activity. By decreasing RORγt, the extract combination reduced the activation of Th17 cells and subsequently reduced kidney inflammation and damage in the mouse model of LN.[78]

14. Realgar: Realgar, a type of arsenic mineral, has been traditionally used in TCM for various therapeutic purposes.

- Realgar nanoparticles demonstrated immunomodulatory and anti-inflammatory properties in the MRL/Lpr mice.
- Furthermore, Realgar nanoparticles significantly improved kidney function and reduced proteinuria in the mice.
- The Treatment with Realgar reduced the expression of STAT1 and its downstream target genes, such as IFNγ and IL-6, infiltration of inflammatory cells, deposition of immune complexes in the kidneys, and the levels of anti-dsDNA antibodies, IgG, and IgM in the serum.
- Realgar down-regulated the BUN and creatinine levels, suggestive of improved kidney functioning and decreased inflammation.
- Treatment with Realgar nanoparticles decreased glomerular damage, as evidenced by decreased glomerular cell proliferation, mesangial expansion, and inflammatory cell infiltration in the renal tissue of the MRL/lpr mice model of LN.[79]

15. Acupuncture, cupping, and Dietary therapy: LN patients have been prescribed acupuncture as a form of complementary and alternative medicine.

- Pilot randomized controlled trial studies on SLE patients demonstrated a certain degree of pain reduction through acupuncture and minimal needling. The study showed that acupuncture was feasible and safe for participants with SLE.
- Moreover, acupuncture treatment demonstrated chances of ameliorating manifestations of LN and quality of life in the true acupuncture group compared to sham acupuncture. Acupuncture treatment was not associated with serious adverse events, unlike the long-term immunosuppressant usage in LN, which reported chronic dry intractable cough, throat irritation, fatigue, appetite loss, and low-back pain lingering for several years.
- Acupuncture therapy showed promise in reducing inflammation, improving joint mobility, and alleviating stress. Moreover, Space-time acupuncture (STA) involved acupoints at ST41, ST36, SP6, KI 3, and ST40, which nourished the spleen and kidney and attenuated cough and cold symptoms in patients with LN.
- Acupuncture improved the central nervous system functioning, and improved airway inflammation and sensitivity, which led to reduced LN-induced cough symptoms.[80]
- **Cupping** that involves cups (glass, plastic or bamboos) placed on skin tissue to create a suction effect has been considered an alternative therapy that helps promote blood flow, reduce pain, and reduce inflammation in

SLE patients.

- As a complementary therapy, alongside conventional medical treatments, cupping appeared effective in lowering pain and inflammation, added to its impact in reducing stress and anxiety and improving overall health and well-being associated with LN.[81]
- **Dietary therapy**, per the TCM concept, can be an important part of managing LN, where a healthy diet can help reduce inflammation and support overall health. A few dietary recommendations for people with LN included limited salt intake (within 2300 milligrams of sodium/day), which attenuated fluid retention and hypertension that are harmful to the kidneys. Reduced protein may also decrease undesired strain on the kidney, where a registered dietitian could help in determining the appropriate protein quantity based on an individual's needs.
- Food items that are high in antioxidants and anti-inflammatory compounds, such as fruits, vegetables, whole grains, herbs and spices (turmeric, ginger, and cinnamon), fatty fish, as well as black beans, kidney beans, sweet potatoes, goji berries, adzuki beans, mung beans, and lotus root are considered beneficial for the kidneys. They may help reduce inflammation in the body and hence, the progress of LN.
- TCM suggests a balance between a diet comprising fruits and vegetables and that of meats and grains as essential. The recommended diet also includes avoiding processed, spicy and greasy foods, usually rich in salt, sugar, and unhealthy fats that could contribute to inflammation and related health problems associated with SLE and LN. Hydration through water intake could also help to flush toxins out of the body and support kidney function.[82]

SAFETY, SIDE EFFECTS AND TOXICITY OF TCMS

A- contamination can lead to toxic effects of the TCM. The contaminants in the herbal ingredients include drugs (warfarin and diclofenac), heavy metals (arsenic and lead), pesticides or sulfites, and undesired herbs, which often pose health problems, such as allergies, asthma and generalized organ damage. Acupuncture is usually estimated safe with less serious adverse effects. However, there might be secondary complexities owing to the inappropriate use and delivery method of nonsterile needles, and serious unfavorable impact, such as inflammation, organ rupture, lung deflation and brain injury.

Key Considerations for Patients Exploring TCM Treatment Options

Procurement of the TCMs needs being done from registered and experienced TCM practioners. Moreover, pregnant women need to consult their physicians before the administration of TCMs. The response of a TCM may vary between the individual users, based on varied factors, such as age, preexisting health and medical conditions and prior drug usage. Hence, consulting a physician prior to the TCM administration appears essential. The TCM practitioners should also comply with the Regulations and Ethical standards specified for the particular country, and inform their patiets about the potential side effects being prescribed and the regulatory landscape. These safety considerations underscore the importance of proper training, hygiene, and adherence to guidelines when using TCM approaches.

CLINICAL INSIGHTS ON TCM AND THE NEED FOR FUTURE RESEARCH

Clinical applications of TCM include using these herbal medicines and combinations as alternatives or replacing conventional drugs to treat LN. The clinical execution not only targets reducing the pathological manifestations of TCM, but also aims at attenuating any significant adverse side effects. The clinical studies may include Randomized, controlled, and clinical trials, research-based Laboratory studies, and the diverse phases of the clinical trials towards improving the patient's longevity and quality of life. The clinical trials also oversee the concept of minimum toxic side effects and adverse impacts on the patients. Clinical trials and studies demonstrated the clinical applications of Huang-Lian Jie-Du decoction (HLJDD) and Zhenwu decoction, in patients suffering from LN and related immune diseases. The TCM targeted the prime pro-inflammatory key signaling pathways, protected the organs as additional beneficial effects while treating for LN. The combined treatment of Tripterygium wilfordii and Triptolide extract with steroids and immunosuppressants suppress proteinurea, inflammation-associated antibody levels and kidney damage in LN patients, with minimum side effects and chances of recurrence. A combination of Liuwei Dihuang pills, together with hormone therapy has also shown relevance in reducing the clinical manifestations of LN. It attenuated RAGE levels, inhibited generation of inflammatory mediators and recurrent risk for LN. Red peony rootis also a TCM used for clinical purposes in LN. The integrative impact of *Cordyceps sinensis* preparations with Western medicine ameliorated clinical symptoms of LN, and demonstrated reduced chances of infection and increased immune tolerance in LN patients. The artemisinin derivative, These TCMs had curative impact in LN patients. Overall, TCM treatments demonstrate their efficacy in improving clinical condition by inducing symptom relief in LN patients and enhancing their quality of life.[72] However, detailed studies on clinical applications of TCMs are essential for the wider use of TCMs.

SUMMARY

Potential advantages

TCM helps to improve renal functions by reducing LN-induced auto-immune responses that have detrimental effects on the kidneys. The TCMs aim to function as alternatives or as combinatorial treatments to conventional Western medicines, predominantly targeting the immunosuppressive

mechanisms of LN. The few well-known TCMs include LiuweiDihuang, Tripterygium wilfordii Hook, used by LN patients for their potential immunomodulatory role. The TCMs may target the inflammatory cytokines, Cox-2, NFκ B, TLR, MAPK, JAK-STAT, TGF-β/Smadand complement C3 and C4 pathways, Th1/Th2 balance in the cells of the kidney, renal ICAM-1, VCAM and PECAM, CD40L and CTLA levels towards reducing the pathogenesis and manifestations of LN. The TCMs have a comprehensive and integrated outlook, which address the symptoms and the key causes of LN. Unlike the Western therapies for LN that induce immunosuppression, enhanced risk of infections, and organ damage, TCM or thir combined treatment with the conventional therapies help in reducing these adverse side effects. This intergrated treatment strategy may concurrently reduce immune dysregulation and the symptoms of LN and avoid the potential disadvantages of immunesuppression. TCM may also function by an individualized approach, which requires the symptoms and constitution of the patients into consideration which may take into consideration the symptomswhich considers a patient's unique constitution and symptom pattern, can lead to more effective and targeted interventions in LN, addressing the variability of the disease in different individuals.

TCM

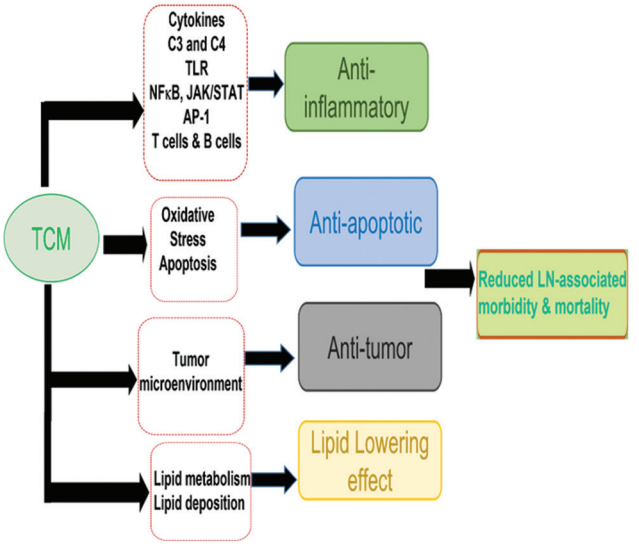
However, further research is needed to understand the side effects, toxicity profiling, regulatory and ethical issues, systemic impact, and clinical relevance of TCMs compared to conventional drugs. In summary, TCM approaches, including preparations, monomers, herbal extracts, and protein therapies, hold promise in managing LN by mitigating inflammation and improving renal function. Their advantages lie in their holistic nature and potential to reduce adverse effects when integrated with conventional treatments. However, limitations include the need for standardized dosages, monitoring for side effects, and further research to optimize these therapies. Additionally, research should delve deeper into the mechanisms of action and explore potential synergies between TCM and Western medicine for personalized LN treatment strategies. Future Research Directions: It is essential to underscore the imperative for continued research endeavors, including rigorous clinical trials and in-depth molecular studies, to gain a comprehensive understanding of the efficacy and safety of TCM interventions in the management of LN. These efforts will further solidify evidence-based practices and facilitate the integration of TCM into mainstream healthcare, offering a holistic and potentially more effective approach to treating this complex condition

CONCLUSION

Benefits of TCM

TCM is a holistic approach to health and wellness that has been practiced for thousands of years in China. LN can lead to kidney damage and dysfunction if left untreated; hence, TCM practitioners use this technique to help strengthen the kidneys, nourish the blood, and alleviate symptoms of LN (Figure 2).

Figure 2. Mechanism(s) targeted by TCM in reducing LN-associated pathogenesis. The pathways mainly include anti-inflammatory, anti-apoptotic, anti-tumor and lipid lowering properties that ultimately suppress LN-associated morbidity and mortality.



Mechanism of action of TCM

TCM functions as a natural healing process, reducing inflammation and improving blood flow to the kidneys. It may help to regulate the production of cytokines and reduce inflammation, sustaining the normal functions of the immune system. The mechanism primarily involves a regulated production of cytokines and chemokines, such as IL-1, IL-6, IL-12, TNFα, IFN-γ and TGFβ, decreased renal ICAM-1, VCAM-1, and PECAM-1 expression and reduced infiltration of immune cells to the site of inflammation in the kidney. The TCMs may target COX-2 expression, prostaglandin, NK cells, and TLR, JAK-STAT, and NF-(B, Akt/mTOR, and Fox O signaling pathways. It restricts the release of cytokines by immune cells, such as T cells, macrophages and endothelial cells. TCMs may also suppress production of IgG2a anti-dsDNA autoantibodies by B cells, regulate the associated functioning of genetic factors that influence cytokine levels and activity, and contribute to the development and severity of LN. This may lead to the decreased release of destructive enzymes and formation of immune complexes, restrict further exacerbation of the autoimmune response, and prevent kidney damage and dysfunction. A TCM-induced therapy also involves a reduction in oxidative stress, fibrosis, and abnormal cell growth and proliferation in the kidney tissues. TCM restores the balance between pro-apoptotic (caspases, Bax and p53) and anti-apoptotic factors (Bcl-2 and NF-κB) in the kidney tissues. TCM therapies can enhance the proliferation of kidney cells by activating signaling pathways that promote cell proliferation, growth, and survival.

Challenges

On the contrary, despite their long history of use and anecdotal evidence of their effectiveness, there is a lack of rigorous scientific research on the mechanisms of TCM therapies and their clinical effectiveness. Few TCM therapies may exert their effects through multiple mechanisms of action, and it can be difficult to isolate the specific mechanisms responsible for their therapeutic benefits. In addition, the complexity of LN and the heterogeneity of patients with the disease can make it challenging to identify the specific factors contributing to TCM therapies' efficacy. Like any other therapeutic intervention, TCM can also have toxic effects if used improperly or inappropriately. Some TCM herbs may contain toxic substances or interact with conventional medications, leading to adverse events such as liver or kidney damage, allergic reactions, or drug interactions. To ensure the safety and effectiveness of TCM therapies for LN, it is important to consult with qualified practitioners with extensive knowledge of TCM theory and practice. TCM practitioners can recommend appropriate therapies and dosages based on individual patient needs and can monitor for potential toxic effects or drug interactions. It is also important to inform conventional healthcare providers of any TCM therapies being used to ensure safe and coordinated care. Appropriate measures needs being taken to identify potential interactions between TCM and conventional medications, emphasizing on the safety of the TCMs and the health and safety of patients nedds. The integration of TCM with conventional treatments is vital, as TCM therapies generally complement the Western treatment approach for LN. Direct interaction between the patients, and the TCM and conventional healthcare practitioners may secure a comprehensive and coordinated approach to improve patient health and welfare.

ONGOING EFFORTS AND NEED FOR FURTHER RESEARCH

There are ongoing efforts to understand the mechanisms of action of TCM therapies for LN. Researchers use modern analytical techniques such as genomics, proteomics, and metabolomics to investigate the molecular and cellular pathways TCM therapies target. However, further research is needed for a rigorous understanding of the mechanisms of action of TCM therapies in LN and to determine their clinical effectiveness. Towards a progress on the concept of TCM research for LN, emphasizing and promoting the ongoing interdisciplinary collaborations between traditional practitioners, conventional practitioners and modern scientists may help revealing the mechanisms underlying the potential and safety of TCMs. These collaborations are critical for refining TCM therapies. Hence, future research directions may include properly framed clinical trials, molecular investigations, and identification of the active TCM ingredients for LN therapy. Importance may also be contributed to patient education, focusing on the potential benefits, gaps and risks of TCM therapies. A consultation with healthcare providers may be carried out for such treatments.

AUTHOR CONTRIBUTIONS

L. L.D., D. L. and D. L.performed the literature search and wrote the manuscript; X.Y. Z. conceptualized the theme of the review, finalized and completed the manuscript. X.Y. Z. takes responsibility for the integrity of the contentelaborated in the review as a whole as 'guarantor'.

CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest.

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