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Review article

Oral proprietary Chinese medicine for lupus nephritis: A bayesian network meta-analysis

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ABSTRACT

Objective: To analyze the efficacy and safety of proprietary Chinese medicines for the treatment of Lupus Nephritis (LN) based on the reticulated meta analysis. The study aim to provide evidence-based evidence for the clinical treatment of LN.

Methods: The studies related to the randomized controlled studies (RCTs) on the treatment of LN with oral proprietary Chinese medicines were obtained from China National Knowledge Infrastructure (CNKI), Database for Chinese Technical Periodicals (VIP), SinoMed, Wanfang, PubMed, Web of Science, Embase and Cochrane Library databases since its inception-August 2022. Cochrane tools were used for risk bias assessment, Stata 13.0 and ADDIS 1.16.5 software were used for net evidence analysis.

Results.

1) 41 RCTs with 3124 L N patients were included, involving 9 types of proprietary Chinese medicines.

2) The meta-analysis showed that in terms of efficacy, the top 3 Chinese patent medicine interventions were Xin Gan Bao Capsule (XGB) +western medicines (WM), Huang Kui Capsule (HK) + WM, Kun Xian Capsule (KX) + WM; in terms of reducing adverse event rate, the top 3 Chinese patent medicine interventions were Yi Shen Hua Shi Granules (YSHS) + WM, Jin Shui Bao Capsule (JSB) + WM, HK + WM; in terms of reducing 24 h urine protein, the top 3 Chinese patent medicine interventions were XGB + WM, YSHS + WM, Bai Ling Capsule (BL) + WM; in terms of reducing blood creatinine (Cr), the top 3 Chinese patent medicine interventions were Yi Shen Granules (YS) + WM, JSB + WM, KX + WM; in terms of reducing urea nitrogen (BUN), the top 3 Chinese patent medicine interventions were Shen Kang Capsule (SK) + WM, HK + WM, JSB + WM; in terms of reducing systemic lupus erythematosus disease activity index (SLEDAI) scores, the top 3 Chinese patent medicine interventions were JSB + WM, BL + WM, YSHS + WM; in terms of improving complement C3, the top 3 Chinese patent medicine interventions were HK + WM, XGB + WM, BL + WM; in terms of improving complement C4, the top 3 Chinese patent medicine interventions were KX + WM, YSHS + WM, BL + WM.

Conclusion: Xin Gan Bao Capsule has a good efficacy in improving efficiency and the level of complement C3, lowering 24 h urine protein. Jin Shui Bao Capsule and Huang Kui Capsule have a good efficacy in treating LN. However, more multicentre, large sample and high quality RCTs are needed for validation the results.

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1. Introduction

Lupus Nephritis (LN) is the most common and severe manifestation of Systemic Lupus Erythematosus (SLE), accounting for approximately 60% of patients diagnosed with SLE and leading to permanent and irreversible kidney damage. Clinically, LN is characterized by arthritis, fever, hematuria, or proteinuria caused by the glomerular deposition of immune complexes followed by the recruitment of an inflammatory response. LN has a heavy social and public health burden [1–4]. Currently, the main clinical drugs used to treat LN are glucocorticoids, immunosuppressive agents, and biological therapy [5]. However, they are prone to adverse events, such as osteoporosis and induced infections. Combinational Chinese medicine treatment can increase clinical efficacy and reduce the incidence of adverse events.

Proprietary Chinese medicines have good efficacy in treating kidney diseases [6]. Luo et al. concluded that Shenyan tablets combined with leflunomide and prednisone had a significant clinical effect in treating LN, improving the clinical remission rate and reducing the incidence of adverse reactions [7]. Clinically, tripterysium glycosides (TGs) were used as a treatment for LN, which could increase clinical efficacy [8]. Moreover, studies have shown that many proprietary Chinese medicines have clinical efficacy in treating LN [9]. However, direct or indirect comparative analyses of the effectiveness and safety of proprietary Chinese medicines in the clinical treatment of LN are lacking, which is not conducive to developing optimal clinical treatment plans. This study was based on the "Progress of integrated traditional Chinese medicine and Western medicine in lupus nephritis" (2018) to choose proprietary Chinese medicines [10], including Bai Ling capsule (BL), Huang Kui capsule (HK), TG, Jin Shui Bao capsule (JSB), and Kun Xian capsule (KX). Moreover, we included proprietary Chinese medicines commonly used in the clinical treatment of LN, such as Shen Kang capsule (SK), Xin Gan Bao capsule (XGB), Yi Shen Hua Shi granules (YSHS), Yi Shen granules (YS). After screening based on the inclusion and exclusion criteria, randomized controlled trials (RCTs) of nine kinds of proprietary Chinese medicines combined with Western medicine were selected as the research objects. Therefore, this study aimed to provide evidence-based for the efficacy and safety of proprietary Chinese medicines in treating LN.

2. Materials and methods

2.1. Sources of information

We collected the literature in several medical databases, which included: China National Knowledge Infrastructure (CNKI), Database for Chinese Technical Periodicals (VIP), SinoMed and Wanfang, PubMed, The Cochrane Library, Web of Science and Embase, since its inception - August 2022. In addition to, we also collected the relevant articles from conference abstracts and references. We used the following search strategy for the PubMed database: ((Lupus nephritis) or (Lupus Glomerulonephritis) or (Nephritis, Lupus) or (Lupus Nephritides) or (Nephritides, Lupus) or (Glomerulonephritis, Lupus) or (Glomerulonephritides, Lupus) or (Lupus Glomerulonephritides) or (LN)) and ((Medicine, Chinese Traditional) or (Traditional Chinese medicine) or (proprietary Chinese medicine) or (Chinese patent medicine) or (Chinese patent drug) or (TCM)) and ((randomized controlled trial) or (controlled clinical trial) or (random allocation) or (double-blind) or (placebo) or (randomly) or (randomized) or (clinical trial) or (RCT) or (random)).

2.2. Inclusion criteria

2.2.1. Object of study

Diagnostic criteria for LN or definitive diagnosis by renal puncture biopsy were met. The patient's gender, age, occupation, race and renal pathological staging were not restricted.

2.2.2. Interventions

The dosage requirements of proprietary Chinese medicines were strictly adhered to. In the treatment group, one proprietary Chinese medicine was administered orally alone, or proprietary Chinese medicines were combined with western medicines (WM) (e.g. glucocorticoids, biologics, immunosuppressants, etc.); in the control group, WM were administered alone. And no other treatments (e.g. prescriptions, Traditional Chinese Medicine (TCM) external treatment, etc.) were given to patients in both groups. On the one hand, we compared the different between 9 proprietary Chinese medicines + WM and WM alone in the treatment of LN. On the other hand, we compared the different between 9 proprietary Chinese medicines in the treatment of LN each other.

2.2.3. Types of research and language of publication

Randomized controlled trials (RCTs), English or Chinese language.

2.3. Exclusion criteria

① Other types of SLE.
② Non-RCT studies (e.g. reviews, case reports, animal and cell-based experiments, etc.), or RCT studies using their own before-and-after controls.
③ Repeatedly included literature, literature with incomplete data indicators or the information of studies was not available.

2.4. Ending indicators

Clinical effectiveness, 24 h urine protein quantification, complement C3, C4, BUN, Cr, SLEDAI scores, occurrence of adverse events (e.g. infections, cardiovascular disease, gastrointestinal reactions, etc.). Included studies contained at least one outcome indicator.

2.5. Data extraction

2.5.1. Literature screening and data extraction

Literature screening was done independently by 2 uniformly trained researchers (ZZY), (LXY). The literature was managed using NoteExpress software, and after eliminating duplicates for inclusion, the primary screening was done by reading the title and abstract of the literature. The secondary screening by reading the remaining full-text literature, resulting in the final study literature. If there was disagreement between the 2 researchers in the literature screening or data extraction process, the decision was submitted to a 3rd researcher (WJY).

2.5.2. Assessment of the quality of the literature

Two researchers independently assessed the quality of the included literature according to the Cochrane Risk of Bias Assessment Tool [11]. The risk of bias was assessed as Low risk, Unclear risk and High risk. If there was disagreement between the 2 researchers in the assessment, the decision was submitted to a 3rd researcher (WJY).

2.6. Statistical analysis

Stata 13.0 was used to plot the network evidence. The frequency-based framework of the network meta-analysis was analysed by the ADDIS 1.16.5 software [12].

3. Results

3.1. Protocol and registration

PROSPERO registration number: CRD42022377386.

Ethical approval

Our study did not involve human or animal experiments, which simply integrated results from other articles. Therefore, the study did not need to obtain ethical approval.

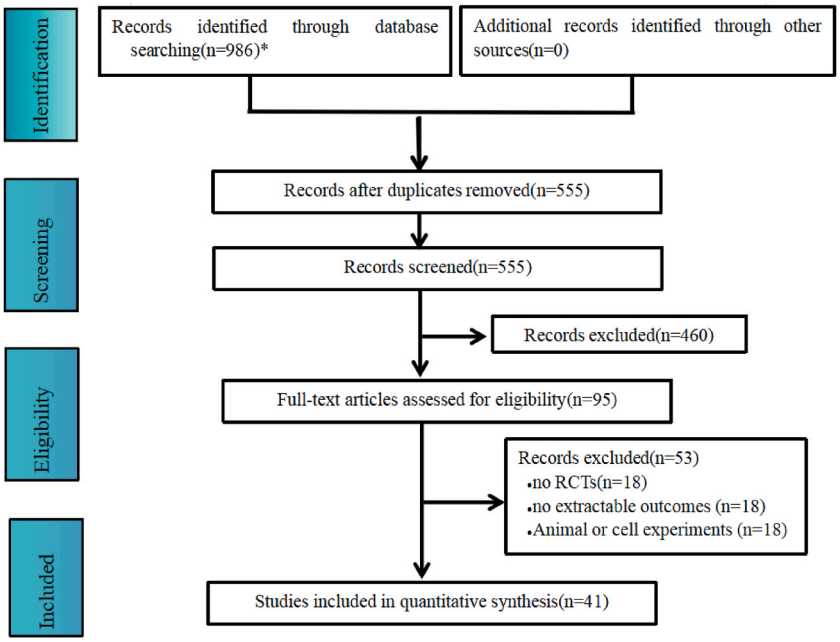

Fig. 1. Literature screening process and results. Note: *Databases searched and literature obtained are as follows: PubMed (n = 11), Web of Science (n = 9), The Cochrane Library (n = 11), Embase (n = 18), CNKI (n = 150), Wanfang (n = 393), VIP (124), SinoMed (n = 270).

Table 1
Basic characteristics of the included studies.

Inclusion in the study	n/case		Average age/year		Gender (T/C)/ case		Interventions		Treatment	Ending indicators
	T	C	T	C	Male	Female	T	C		
Zhu 2016	60	60	49.87 ± 16.34	50.03 ± 16.42	6/7	54/53	BL + Prednisone + CTX	Prednisone + CTX	1year	①②③⑤⑥⑦
Shu 2019	23	24	31.8 ± 9.4	30.6 ± 10.5	7/6	17/17	BL + Prednisone + CTX	Prednisone + CTX	1year	①③⑥
Pan 2021	46	46	45.27 ± 6.85	46.04 ± 7.24	5/7	41/39	BL + Prednisone + LEF	Prednisone + LEF	6months	①②③⑥⑦
He2013	21	20	31.8 ± 4.4	30.2 ± 5.3	2/3	19/17	BL + Prednisone + Heparin	Prednisone + heparin	8weeks	②③④
Bai 2019	30	30	31.42 ± 12.39	35.17 ± 14.21	7/15	23/15	BL + CTX	CTX	6months	①②③④⑤⑦
Liu 2022	50	50	35.44 ± 5.50	33.29 ± 15.13	27/ 28	23/22	BL + CTX	CTX	6months	①⑦
Huang 2021	32	32	33.37 ± 4.02	33.26 ± 3.96	19/ 18	13/14	BL + CTX	CTX	21 d	①②③⑦
Qi2020	34	34	49.16 ± 6.61	45.35 ± 8.28	8/5	26/29	BL + Prednisone + LEF	Prednisone + LEF	5months	①⑦
Li2019	63	63	38.20 ± 9.16	38.92 ± 12.75	28/ 29	35/34	BL + Prednisone + LEF	Prednisone + LEF	6months	①②③⑤⑦
Ma2019	30	30	35.90 ± 6.76	36.52 ± 6.84	7/9	23/21	BL + MMF	MMF	5months	①⑥
Wang 2019	55	55	44.88 ± 9.60	45.18 ± 9.46	30/ 32	25/23	BL + Prednisone	Prednisone	6months	③⑤⑦
Xu2018	60	60	46.95 ± 10.62	47.84 ± 11.56	5/6	55/54	BL + FK-506	FK-506	1year	①②③⑤⑥⑦
Wang 2017	59	59	31.39 ± 7.84	29.96 ± 8.02	11/9	48/50	BL + FK-506	FK-506	1year	①②③⑤⑥⑦
Sun 2022	41	41	43.18 ± 3.01	43.25 ± 2.89	20/ 18	21/23	BL + Prednisone	Prednisone	6months	①⑤⑦
Yang 2021	38	38	46.5 ± 4.2	42.1 ± 5.2	17/ 18	21/20	BL + CTX	CTX	21 d	②⑤⑥
Sun 2012	11	11	–	–	–	–	HK + Methylprednisolone	Methylprednisolone	1year	①⑦
Nong 2022	36	36	37.56 ± 1.58	35.50 ± 1.77	19/ 20	17/16	HK + AZA	AZA	8weeks	①②③④⑦
Wei 2014	28	28	–	–	–	–	HK + CT	CT	6months	① ③ ⑥
Wu2007	22	20	34.3 ± 12.2	32.6 ± 11.8	–	–	BL + Prednisone	Prednisone	2 months	②③④⑥
Liu 2019	29	29	28.1 ± 7.1	28.5 ± 6.9	3/4	26/25	JSB + MMF	MMF	6months	①②③⑥⑦
Guo 2022	40	40	33.8 ± 8.2	35.2 ± 8.6	7/4	33/36	JSB + Prednisone	Prednisone	6months	①②③④⑤⑦
Gao 2010	24	24	33.65 ± 10.33	34.56 ± 4.21	5/6	19/18	KX + CT	CT	5months	①②
Shi 2022	64	64	38.59 ± 6.15	38.54 ± 6.12	39/ 41	25/23	KX + CTX	CTX	12weeks	①②③④⑥⑦
Liu 2020	33	33	26.09 ± 5.96	25.06 ± 5.59	–	–	KX + Prednisone	CTX + Prednisone	24 weeks	②⑤⑥⑦
Li2019	33	33	26.09 ± 5.96	25.06 ± 5.59	–	–	KX	CTX	12weeks	②⑤⑥⑦
Dai 2018	46	45	–	–	–	–	TG + Prednisone	Prednisone + LEF	6months	①②③⑤⑥⑦
Hung 2018	41	41	30.14 ± 4.67	30.02 ± 4.71	10/ 11	31/30	TG + Prednisone	Prednisone	12weeks	⑥
Li2022	54	54	41.6 ± 13.7	41.4 ± 13.9	7/8	47/46	TG + LEF	LEF	6months	①③④⑦
Ding 2019	55	55	41 ± 17	41 ± 17	31/ 33	24/22	TG + Prednisone + LEF	Prednisone + LEF	6months	①③④⑦
Liu2018	68	68	31.06 ± 4.28	30.64 ± 4.81	13/ 15	55/53	TG + CTX	CTX	5months	①
Liu2018	31	31	37.9 ± 3.4	36.6 ± 3.5	3/5	28/26	TG + prednisone	Prednisone	8weeks	①②③⑤⑥⑦
Shi 2016	28	27	31.04 ± 4.17	30.15 ± 4.37	3/4	25/23	TG + AZA	AZA	–	①②③④⑥⑦
Liu 2002	27	21	–	–	2/1	25/20	TG + prednisone + CTX	Prednisone + CTX	18 months	①⑦
Huang 2020	19	19	35.8 ± 3.6	36.2 ± 4.5	10/9	9/10	BL + CTX	CTX	21 d	①②③④

(*continued on next page*)

Table 1 (*continued*)

Inclusion in the study	n/case		Average age/year		Gender (T/C)/ case		Interventions		Treatment	Ending indicators
	T	C	T	C	Male	Female	T	C		
Gong 2007	27	25	36.3 ± 11.3	34.6 ± 10.5	4/3	23/22	SK + CT	CT	5months	①③④⑦
Cai 2019	39	39	37.5 ± 4.3	37.5 ± 4.3	10/9	29/30	XGB + FK-506 + MMF	Methylprednisolone	6months	①②③④⑤⑥⑦
Xu2019	68	68	40 ± 16	41 ± 16	8/9	60/59	YSHS + methylprednisolone + prednisone	Methylprednisolone + Prednisone	6months	①⑤⑥⑦
Ma2017	26	26	–	–	–	–	YSHS + MMF + prednisone	MMF + prednisone	6months	①⑥⑦
Lan 2007	30	30	36 ± 10.8	34 ± 11.0	4/5	26/25	YS + Prednisone	Prednisone	8weeks	②③④
Zhou 2007	20	20	31 ± 10.2	30 ± 10.3	2/1	18/19	YS + Prednisone	Prednisone	4 weeks	②③④
Zhou 2011	26	28	–	–	2/2	24/26	YS + MMF	MMF	1 month	①②③④

Note: ①Effective rate; ②24 h urine protein quantification; ③blood creatinine; ④urea nitrogen; ⑤SLEDAI score; ⑥complement C3 and C4; ⑦adverse reactions.
CTX: cyclophosphamide; AZA: azathioprine; LEF: leflunomide; TG: tripterysium glycosides; FK-506: tacrolimus; MMF: mycophenolate mofetil; CT: conventional therapy.

3.2. Literature search results

986 relevant literature were obtained through database search, and 41 RCTs were finally included for quantitative analysis in strict accordance with the inclusion and exclusion criteria of this study. The specific literature screening process is shown in Fig. 1.

3.3. Basic characteristics of the included studies

41 RCTs were included in the study [13–53], 3124 patients with LN, including 1568 in the trial group and 1556 in the control group. The literature information is detailed in Table 1.

3.4. Assessment the quality of the literature for the included studies

In the study, 40 RCTs mentioned random allocation methods, which 19 RCTs used the random number table method. While, the remaining 21 RCTs mentioned random grouping only which were rated as “unknown risk”. 1 RCT study did not mention the grouping method which was rated as “high risk”. 4 studies had incomplete data and reporting bias which were rated as “high risk”. None of the included studies stated whether the allocation scheme was concealed or blinded, and were rated as “risk unknown”. Other risks of bias were also assessed as “risk unknown”. This is shown in Fig. 2.

3.5. Consistency test

We did the consistency test of outcome indicators. The dot size represented the sample size of intervention measures, and the line thickness represents the number of literatures using intervention measures. There is no closed loop in the diagram, so no inconsistency

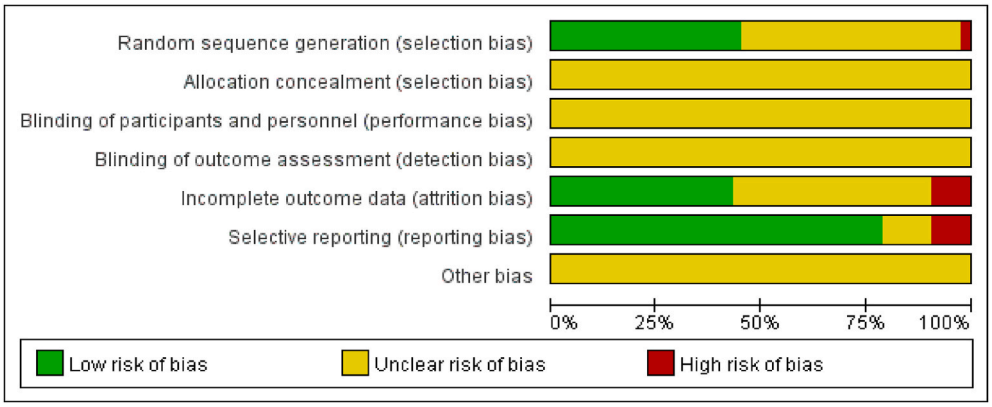

Fig. 2. Literature risk bias assessment chart.

test is required. This is shown in Fig. 3 (A-E).

3.6. Efficient

3.6.1. Evidence grid diagram

32 studies mentioned the clinical efficacy. The network evidence was shown in Fig. 4. The dot size represented the sample size of intervention measures, and the line thickness represents the number of literatures using intervention measures. Among them, the largest number of study was BL + Western medicine, with a total of 13 literatures.

3.6.2. Reticulated meta-analysis

Table 2 showed a network meta-analysis of effective rate of the included RCTs literature. The meta-analysis results showed that the differences between BL + WM, HK + WM, TG + WM, JSB + WM, KX + WM, YSHS + WM and WM group were statistically significant ($P < 0.05$). While, the differences between SK + WM, XGB + WM, YS + WM and WM group were not significant ($P > 0.05$). The information is detailed in Table 2.

3.6.3. Ranking of network meta-analysis

We ranked the efficacy and safety of the 9 proprietary Chinese medicines in the treatment of LN based on bayesian statistical methods.

The meta-analysis showed that: 1) in terms of efficacy, the top 3 Chinese patent medicine interventions were XGB + WM, HK + WM, KX + WM (Fig. 5A). 2) in terms of reducing adverse event rate, the top 3 Chinese patent medicine interventions were YSHS + WM, JSB + WM, HK + WM (Fig. 5B). 3) in terms of reducing 24 h urine protein, the top 3 Chinese patent medicine interventions were XGB + WM, YSHS + WM, BL + WM (Fig. 5C). 4) in terms of reducing Cr, the top 3 Chinese patent medicine interventions were YS + WM, JSB + WM, KX + WM (Fig. 5D). 5) in terms of reducing BUN, the top 3 Chinese patent medicine interventions were SK + WM, HK + WM, JSB + WM (Fig. 5E). 6) in terms of reducing SLEDAI scores, the top 3 Chinese patent medicine interventions were JSB + WM, BL + WM, YSHS + WM (Fig. 5H). 7) in terms of improving complement C3, the top 3 Chinese patent medicine interventions were HK + WM, XGB + WM, BL + WM (Fig. 5F). 8) in terms of improving complement C4, the top 3 Chinese patent medicine interventions were KX + WM, YSHS + WM, BL + WM (Fig. 5G). The information is detailed in Table 3 and Fig. 5.

3.6.4. 24 h urine protein reticulation meta-analysis

As shown in Table 4, the meta-analysis results of reducing 24 h urine protein showed that the differences between BL + WM, HK + WM, and WM group were statistically significant ($P < 0.05$). While the differences between the other Chinese patent medicine

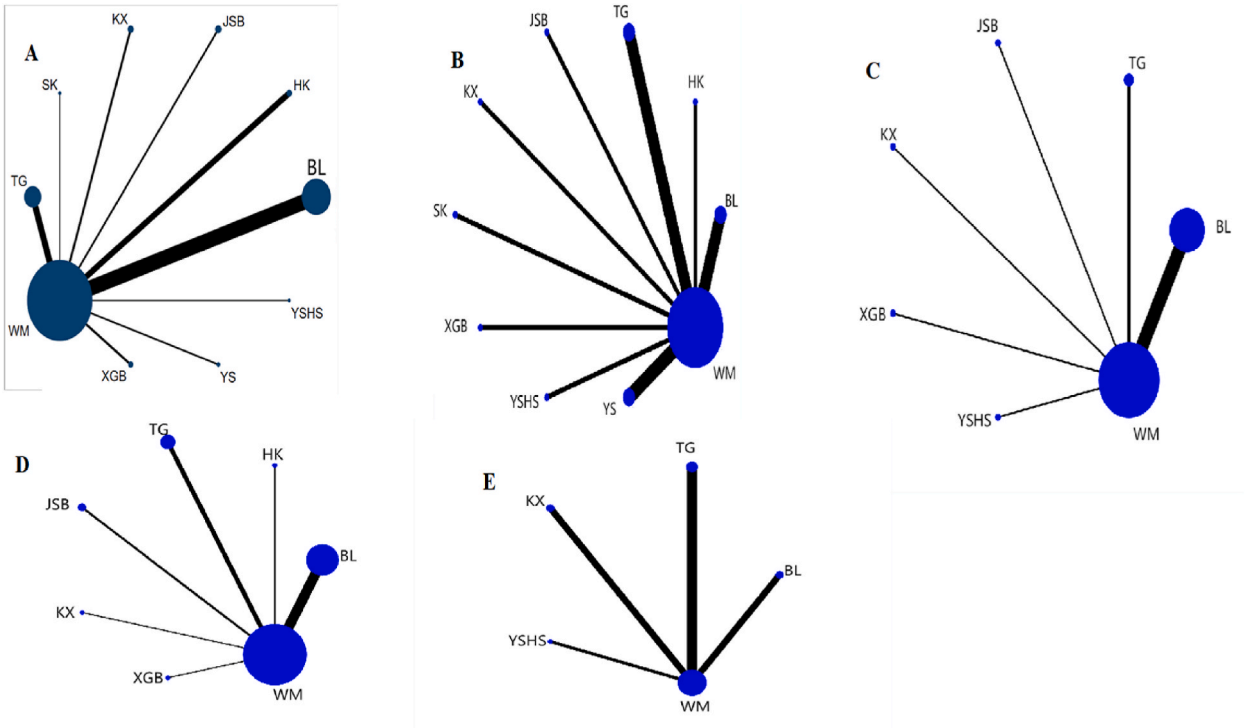

Fig. 3. Clinical effectiveness (A), urea nitrogen (B), SLEDAI scores (C), complement C3 (D), complement C4 (E).

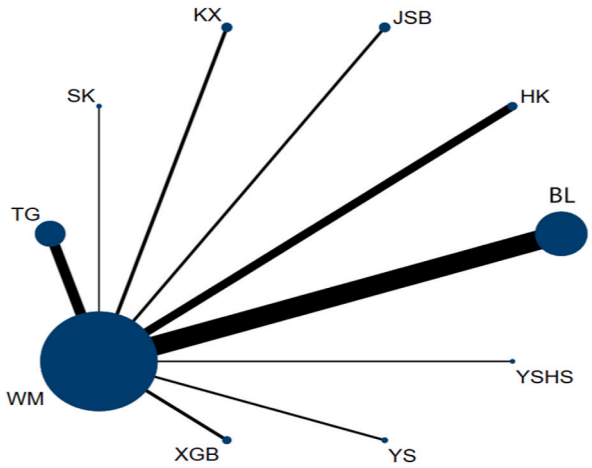

Fig. 4. Network diagram of effective rate.

interventions and WM group were not statistically significant ($P > 0.05$).

3.6.5. Urea nitrogen reticulation meta-analysis

The meta-analysis results of reducing urea nitrogen showed in Table 5, obtaining: 1) the differences between BL + WM, HK + WM, TG + WM, JSB + WM, KX + WM, SK + WM, XGB + WM, YHSH + WM and WM group were statistically significant ($P < 0.05$). While the differences between YS + WM and WM group was not statistically significant ($P > 0.05$). 2) The differences between BL + WM, HK + WM, JSB + WM, KX + WM, SK + WM, XGB + WM and YS + WM group were all statistically significant ($P < 0.05$). 3) Moreover, the differences between JSB + WM, SK + WM, XGB + WM and TG + WM group were all statistically significant ($P < 0.05$). As shown in Table 5.

3.6.6. Complement C3 and C4 reticulum meta-analysis

As shown in Tables 6 and in complement C3, the differences in BL + WM, HK + WM, TG + WM and JSB + WM were statistically significant compared to WM ($P < 0.05$). In complement C4, the difference between HK + WM and WM was statistically significant ($P < 0.05$).

3.6.7. SLEDAI score reticulum meta-analysis

Table 7 showed that the differences between BL + WM, JSB + WM, XGB + WM and WM group were statistically significant ($p < 0.05$). And

The differences between BL + WM, JSB + WM and TG + WM were statistically significant ($p < 0.05$).

3.7. Adverse event occurrence

As shown in Table 8, the differences in the occurrence of adverse events between BL + WM, JSB + WM, KX + WM, YSHS + WM and WM group were statistically significant ($P < 0.05$). In contrast, the differences between HK + WM, TG + WM, XGB + WM and WM group were not statistically significant ($P > 0.05$).

3.8. Publication bias

As shown in Fig. 6 (A-E). It can be seen that most of the studies were distributed on both sides of the inverted triangle, indicating a low publication bias in the inclusion of RCTs.

4. Discussion

LN is a common complication of SLE characterized by hypoproteinemia, proteinuria, blood urea nitrogen, and reduced creatinine clearance. About 5%–20% of patients can progress to end-stage renal disease within 10 years, with a heavy public health burden on society [54,55]. With the development of reticulated meta-analysis, many studies have been conducted to analyze the efficacy and safety of proprietary Chinese medicines in treating diseases, aiming to provide evidence-based clinical diagnosis and treatment [56, 57]. This study was the first to use reticulated meta-analysis to compare the efficacy and safety of nine proprietary Chinese medicines for treating LN, intending to provide the best treatment options for patients.

Our study results showed that XGB had good efficacy in terms of reducing 24-h urine protein levels. JSB effectively reduced the rate of adverse events rate and the levels of blood creatinine and urea nitrogen. Furthermore, it could reduce the SLEDAI scores. Moreover,

Table 2
Network Meta-analysis of effective rate.

OR (95% CI)										
	BL + WM	HK + WM	TG + WM	JSB + WM	KX + WM	SK + WM	XGB + WM	YSHS + WM	YS + WM	WM
BL + WM	0									
HK + WM	0.68 (0.19,2.48)	0								
TG + WM	1.77 (0.98,3.20)	2.60 (0.69,9.82)	0							
JSB + WM	0.88 (0.29,2.70)	1.30 (0.25,6.63)	0.50 (0.16,1.58)	0						
KX + WM	1.15 (0.36,3.66)	1.69 (0.32,8.89)	0.65 (0.20,2.15)	1.30 (0.28,6.00)	0					
SK + WM	1.57 (0.33,7.44)	2.31 (0.33,16.36)	0.89 (0.18,4.32)	1.78 (0.28,11.28)	1.37 (0.21,8.86)	0				
XGB + WM	0.58 (0.06,5.18)	0.85 (0.07,10.29)	0.32 (0.04,2.98)	0.65 (0.06,7.28)	0.50 (0.04,5.69)	0.37 (0.03,5.14)	0			
YSHS + WM	1.06 (0.43,2.61)	1.56 (0.35,6.94)	0.60 (0.23,1.55)	1.21 (0.32,4.61)	0.92 (0.23,3.65)	0.68 (0.12,3.78)	1.85 (0.18,18.79)	0		
YS + WM	2.00 (0.54,7.39)	2.94 (0.50,17.20)	1.13 (0.29,4.32)	2.27 (0.44,11.71)	1.74 (0.33,9.23)	1.27 (0.18,9.06)	3.47 (0.28,42.55)	1.88 (0.42,8.44)	0	
WM	**3.98 (2.78,5.70)***	**5.85(1.69,20.24)***	**2.24 (1.40,3.59)***	**4.51 (1.57,12.98)***	**3.46(1.15,10.38)***	2.53 (0.56,11.45)	6.91 (0.79,60.36)	**3.74(1.64,8.52)***	1.99 (0.57,6.99)	0

Note: * Differences are statistically significant, same as in Tables 4 and 7.

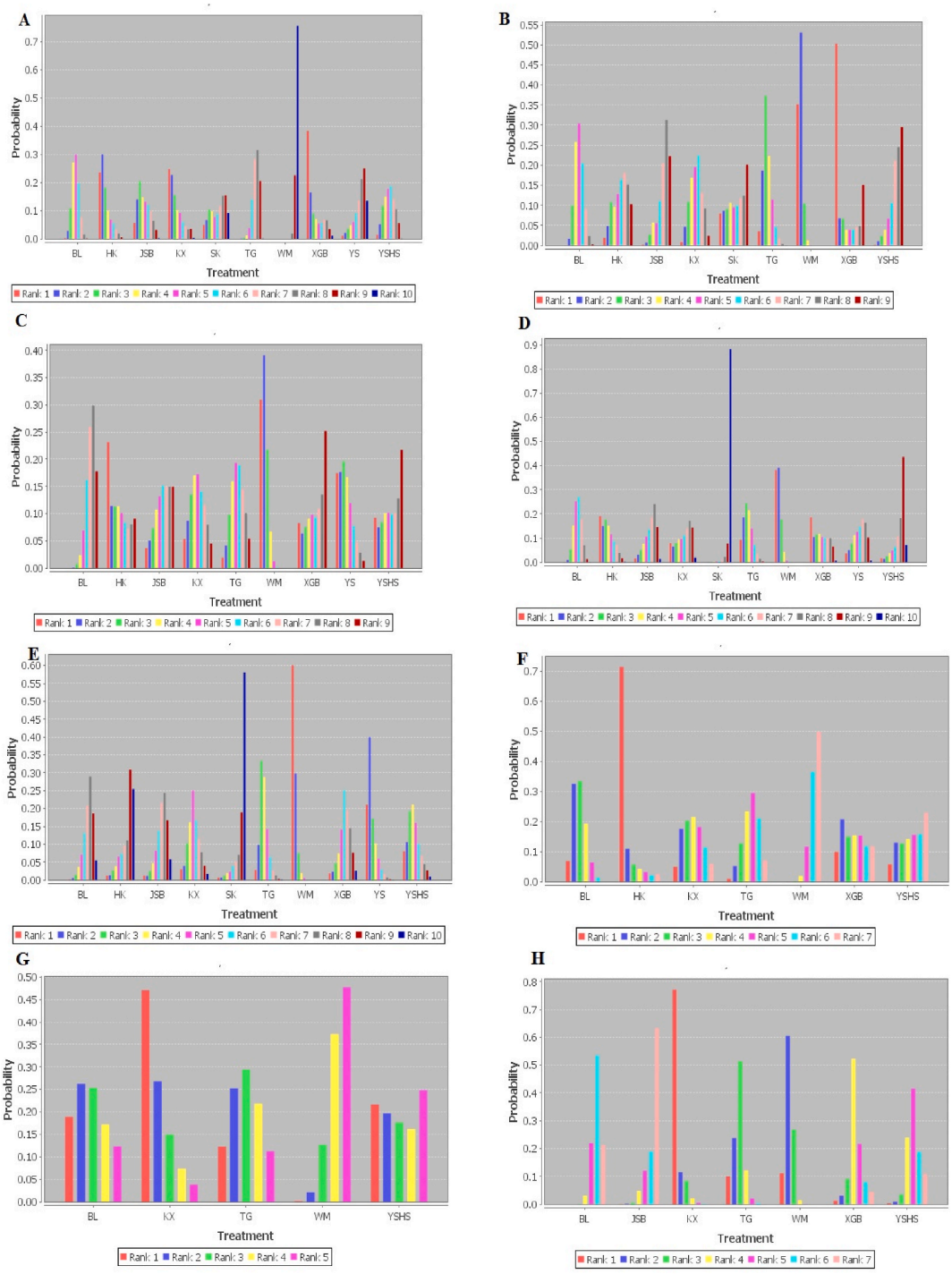

Fig. 5. Clinical effectiveness (A), adverse event rate (B), 24 h urine protein quantification (C), blood creatinine (D), urea nitrogen (E), complement C3 (F), complement C4 (G), SLEDAI scores (H).

HK had good efficacy in improving complement C3 levels and reducing urea nitrogen levels. By exploring several indicators for treating LN with proprietary Chinese medicines, it is clear that proprietary Chinese medicines combined with Western medicines have better efficacy and safety than Western medicines alone in treating LN.

Many studies have shown that proprietary Chinese medicines are effective in treating LN. XGB, JSB, and BL are composed of *Cordyceps sinensis* hyphae. Previous studies reported that *C sinensis* hyphae had the effect of immune regulation and also enhanced the of cellular immune function. Besides, Zhang et al. found that *C sinensis* hyphae also inhibited the formation of immune complexes in

Table 3
Ranking results of the reticulated Meta-analysis.

Interventions	Efficient		Adverse reactions		24 h urine protein		Blood creatinine		Urea nitrogen		Complement C3		Complement C4		SLEDAI Rating	
	Rank1	Sort by	Rank 9	Sort by	Rank1	Sort by	Rank1	Sort by	Rank1	Sort by	Rank1	Sort by	Rank1	Sort by	Rank1	Sort by
BL + WM	0.00	7	0.00	7	0.18	**3**	0.01	8	0.05	4	0.07	**3**	0.19	**3**	0.21	**2**
HK + WM	0.24	**2**	0.13	**3**	0.10	5	0.02	7	0.25	**2**	0.71	**1**	0.47	**1**	–	–
JSB + WM	0.04	4	0.21	**2**	0.15	4	0.15	**2**	0.06	**3**	–	–	–	–	0.63	**1**
KX + WM	0.23	**3**	0.03	6	0.04	7	0.14	**3**	0.02	6	0.05	5	–	–	0.00	5
SK + WM	0.03	5	0.13	3	0.06	6	0.08	5	0.58	**1**	–	–	–	–	–	–
TG + WM	0.00	7	0.00	7	0.00	9	0.00	9	0.00	8	0.01	6	0.12	4	0.00	5
WM	0.00	7	0.00	7	0.26	**1**	0.00	9	0.00	8	0.00	7	0.00	5	0.00	5
XGB + WM	0.43	**1**	0.13	3	0.01	8	0.06	6	0.03	5	0.10	**2**	–	–	0.04	4
YSHS + WM	0.00	7	0.36	**1**	0.21	**2**	0.10	4	0.00	8	–	–	0.22	**2**	0.11	**3**
YS + WM	0.02	6	–	–	0.00	9	0.44	**1**	0.01	7	0.06	4	–	–	–	–

Table 4
Network Meta-analysis of 24 h urinary protein quantification.

Interventions	OR (95% CI)									
	BL + WM	HK + WM	TG + WM	JSB + WM	KX + WM	SK + WM	XGB + WM	YSHS + WM	YS + WM	WM
BL + WM	0									
HK + WM	0.69 (0.27,1.73)	0								
TG + WM	0.82 (0.49,1.37)	1.19 (0.44,3.19)	0							
JSB + WM	0.88 (0.45,1.73)	1.28 (0.44,3.76)	1.08 (0.50,2.30)	0						
KX + WM	0.75 (0.42,1.36)	1.10 (0.39,3.06)	0.92 (0.47,1.82)	0.86 (0.38,1.92)	0					
SK + WM	0.89 (0.35,2.25)	1.30 (0.37,4.52)	1.09 (0.41,2.92)	1.01 (0.34,2.98)	1.18 (0.42,3.29)	0				
XGB + WM	0.91 (0.37,2.24)	1.32 (0.39,4.54)	1.11 (0.42,2.93)	1.03 (0.36,2.98)	1.20 (0.44,3.30)	1.02 (0.30,3.51)	0			
YSHS + WM	0.86 (0.35,2.14)	1.26 (0.37,4.33)	1.06 (0.40,2.79)	0.98 (0.34,2.84)	1.15 (0.42,3.14)	0.97 (0.28,3.35)	0.95 (0.28,3.23)	0		
YS + WM	0.64 (0.35,1.15)	0.93 (0.33,2.59)	0.78 (0.39,1.54)	0.72 (0.32,1.63)	0.84 (0.40,1.77)	0.71 (0.26,2.00)	0.70 (0.25,1.92)	0.74 (0.27,2.03)	0	
WM	**0.55 (0.42,0.71)***	**0.79 (0.33,0.92)***	0.67 (0.43,1.04)	0.62 (0.33,1.15)	0.72 (0.43,1.22)	0.61 (0.25,1.48)	0.60 (0.25,1.42)	0.63 (0.27,1.50)	0.86 (0.51,1.45)	0

Table 5
Network meta-analysis of BUN.

Interventions	OR (95% CI)									
	BL + WM	HK + WM	TG + WM	JSB + WM	KX + WM	SK + WM	XGB + WM	YSHS + WM	YS + WM	WM
BL + WM	0									
HK + WM	2.08 (0.34,12.63)	0								
TG + WM	0.45 (0.20,1.00)	0.22 (0.04,1.12)	0							
JSB + WM	1.17 (0.47,2.92)	0.56 (0.10,3.09)	**2.58 (1.50,4.46)***	0						
KX + WM	0.66 (0.27,1.64)	0.32 (0.06,1.74)	1.46 (0.86,2.49)	0.57 (0.28,1.14)	0					
SK + WM	3.64 (0.46,28.58)	1.75 (0.14,21.62)	**8.07 (1.18,55.28)***	3.13 (0.43,22.58)	5.53 (0.77,39.79)	0				
XGB + WM	0.87 (0.38,2.03)	0.42 (0.08,2.22)	**1.93 (1.28,2.92)***	0.75 (0.40,1.38)	1.32 (0.72,2.42)	0.24 (0.03,1.67)	0			
YSHS + WM	0.47 (0.15,1.43)	0.23 (0.04,1.39)	1.04 (0.45,2.40)	0.40 (0.16,1.04)	0.71 (0.28,1.83)	0.13 (0.02,1.03)	0.54 (0.22,1.30)	0		
YS + WM	**0.25 (0.08,0.76)***	**0.12 (0.02,0.74)***	0.55 (0.24,1.28)	**0.21 (0.08,0.56)***	**0.38 (0.14,0.97)***	**0.07 (0.01,0.54)***	**0.28 (0.12,0.69)***	0.53 (0.17,1.67)	0	
WM	**0.19 (0.09,0.41)***	**0.09 (0.02,0.47)***	**0.42 (0.34,0.52)***	**0.16 (0.10,0.27)***	**0.29 (0.18,0.47)***	**0.05 (0.01,0.35)***	**0.22 (0.15,0.31)***	**0.41 (0.18,0.91)***	0.77 (0.34,1.74)	0

Table 6
Network meta-analysis of C3, C4.

InterventionsA	OR (95% CI) B									
	BL + WM	HK + WM	TG + WM	JSB + WM	KX + WM	SK + WM	XGB + WM	YSHS + WM	YS + WM	WM
BL + WM	0	–	1.00 (0.90,1.12)	–	0.97 (0.86,1.09)	–	–	1.01 (0.87,1.16)	–	1.05 (0.97,1.14)
HK + WM	0.81 (0.55,1.21)	0	0.96 (0.86,1.07)	–	–	–	–	–	–	–
TG + WM	1.04 (0.89,1.21)	1.28 (0.85,1.91)	0	–	–	–	–	1.00 (0.88,1.15)	–	1.04 (0.97,1.12)
JSB + WM	–	–	-	0	–	–	–	–	–	–
KX + WM	1.05 (0.87,1.28)	1.29 (0.85,1.97)	1.01 (0.82,1.26)	0.57 (0.28,1.14)	0	–	–	1.04 (0.90,1.20)	–	**1.09 (1.00,1.18)***
SK + WM	–	–	-	–	–	–	–	–	–	–
XGB + WM	1.05 (0.81,1.36)	1.29 (0.82,2.03)	1.01 (0.77,1.33)	0.75 (0.40,1.38)	1.00 (0.74,1.34)	–	0	–	–	–
YSHS + WM	1.11 (0.85,1.45)	1.36 (0.86,2.16)	1.07 (0.80,1.42)	0.40 (0.16,1.04)	1.05 (0.77,1.44)	–	1.06 (0.74,1.50)	0	–	1.04 (0.93,1.17)
YS + WM	-	-	–	-	-	-	-	–	–	
WM	**1.21 (1.11,1.32)***	**1.49 (1.02,2.19)***	**1.17 (1.03,1.33)***	**0.16 (0.10,0.27)***	1.15 (0.97,1.37)	-	1.16 (0.91,1.48)	1.09 (0.85,1.41)	–	0

Note: A is complement C3 reticulum Meta-analysis, B is complement C4 reticulum Meta-analysis.

Table 7
Network meta-analysis of SLEDAI.

Interventions	OR (95% CI)						
	BL + WM	TG + WM	JSB + WM	KX + WM	SK + WM	XGB + WM	WM
BL + WM	0						
TG + WM	**0.12 (0.02,0.67)***	0					
JSB + WM	2.16 (0.23,20.80)	**18.73 (1.32,265.89)***	0				
KX + WM	0.19 (0.02,1.87)	1.63 (0.11,23.77)	0.09 (0.00,1.81)	0			
SK + WM	0.42 (0.04,4.00)	3.60 (0.25,51.09)	0.19 (0.01,3.89)	2.20 (0.11,45.66)	0		
XGB + WM	0.76 (0.09,6.34)	6.62 (0.53,82.99)	0.35 (0.02,6.42)	4.05 (0.22,75.39)	1.84 (0.10,33.45)	0	
WM	**0.08 (0.04,0.17)***	0.66 (0.14,3.24)	**0.04 (0.00,0.30)***	0.41 (0.05,3.52)	0.18 (0.02,1.55)	**0.10 (0.01,0.72)***	0

Table 8
Network Meta-analysis of adverse events.

Interventions	OR (95% CI)							
	BL + WM	HK + WM	TG + WM	JSB + WM	KX + WM	XGB + WM	YSHS + WM	WM
BL + WM	0							
HK + WM	1.26 (0.41,3.93)	0						
TG + WM	0.79 (0.41,1.51)	0.63 (0.19,2.08)	0					
JSB + WM	1.98 (0.75,5.22)	1.56 (0.38,6.35)	2.50 (0.88,7.10)	0				
KX + WM	1.16 (0.52,2.59)	0.92 (0.25,3.34)	1.47 (0.61,3.55)	0.59 (0.19,1.85)	0			
XGB + WM	0.52 (0.03,9.06)	0.41 (0.02,8.52)	0.66 (0.04,11.75)	0.26 (0.01,5.15)	0.45 (0.02,8.30)	0		
YSHS + WM	2.19 (0.79,6.08)	1.73 (0.41,7.29)	2.77 (0.93,8.25)	1.11 (0.30,4.12)	1.88 (0.57,6.19)	4.21 (0.21,83.80)	0	
WM	**0.52 (0.36,0.75)***	0.41 (0.14,1.20)	0.66 (0.39,1.11)	**0.26 (0.11,0.65)***	**0.45 (0.22,0.91)***	1.00 (0.06,17.02)	**0.24 (0.09,0.62)**	0

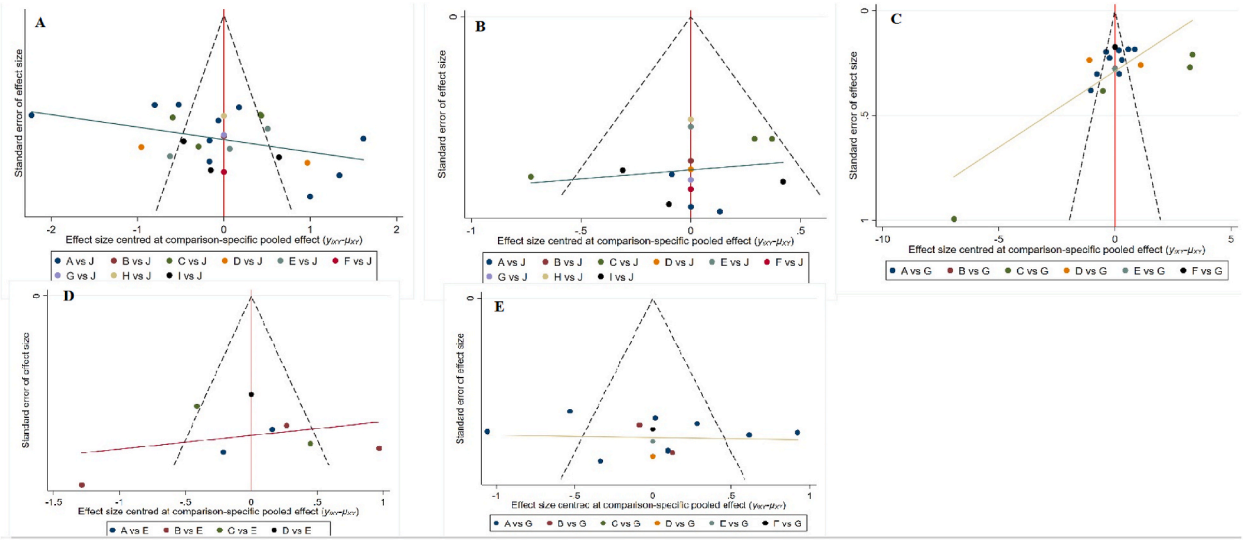

Fig. 6. Comparison of Cr (A), BUN (B), C3 (C), C4 (D) and SLEDAI (E) corrected funnel plot.

glomerular epithelial cells and reduced interstitial inflammatory cell infiltration and interstitial fibrosis [58]. The main component of HK is *Abelmoschus manihot*, which clears heat and reduces dampness. Modern studies have shown that HK reduces inflammatory response, inhibits oxidative stress, promotes immune complex clearance, and reduces renal tubulointerstitial injury [59]. Similarly, WU et al. concluded that HK might alleviate early glomerular pathological changes, including glomerular hypertrophy and glomerular basement membrane thickening, by inhibiting Akt/mTOR/p70S6K signal transduction activity [60].

Besides, TG is extracted from the traditional Chinese medicine *Tripterygium wilfordii,* which has strong anti-inflammatory and immunosuppressive effects [61]. Song et al. found that TG reduced the activity of inflammatory factors and renal cell damage,

improving renal function [62]. KX comprises four kinds of traditional Chinese medicines, including Kunmingshanhaitang, *Cuscuta chinensis* Lam, Yinyanghuo and matrimonyvine. Studies have shown that KX can improve the level of complements C3 and C4 in patients with LN. Clinically, SK, YSHS and YS are traditional Chinese medicine preparations for treating LN. Studies have reported that YSHS can increase Na^{+}-K^{+}-ATPase (ATP) activity in renal proximal tubules, reduce proteinuria, and improve renal function damage [63].

Besides the findings of this study, XGB can reduce 24-h urine protein levels and adverse events and improve complement C4 levels. YSHS can improve complement C3 levels and reduce urea nitrogen levels. HK can also be chosen. Clinicians should choose the best treatment plan according to the patient's conditions.

This study had some limitations. First, the included studies were almost single center, and the sample size was small. Second, the search literature was restricted to studies published in English or Chinese. Many studies from other languages and regions were not included in this study. Hence, more multi-center, large-sample, and high-quality RCTs are still needed to validate the findings.

5. Conclusions

Xin Gan Bao Capsule has a good efficacy in improving efficiency and the level of complement C3, lowering 24 h urine protein. Jin Shui Bao Capsule and Huang Kui Capsule have a good efficacy in treating LN. However, more multicentre, large sample and high quality RCTs are needed for validation the results.

Author contributions

Aitao LIN, zhiying ZHANG performed the data analysis and wrote the manuscript. Xiaoyu LIU participated in the data collection. Jinyu WU provided intellectual input and supervision during the study process and made a substantial contribution to manuscript drafting. All authors contributed to the article and approved the submitted version.

Data availability statement

Data associated with this study has been deposited at PROSPERO registration number: CRD42022377386.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations Full name

LN	lupus nephritis
SLE	Systemic Lupus Erythematosus
RCTs	randomized controlled studies
SLEDAI	systemic lupus erythematosus disease activity index
BL	Bai Ling Capsule
HK	Huang Kui Capsule
TG	Tripterysium Glycosides
JSB	Jin Shui Bao Capsule
KX	Kun Xian Capsule
SK	Shen Kang Capsule
XGB	Xin Gan Bao Capsule
YSHS	Yi Shen Hua Shi Granules
YS	Yi Shen Granules
CNKI	China National Knowledge Infrastructure
VIP	Chinese Technical Periodicals
TCM	Traditional Chinese Medicine
BUN	Urea nitrogen
Cr	blood creatinine
CTX	cyclophosphamide
AZA	azathioprine
LEF	leflunomide
FK-506	Tacrolimus
MMF	Morte-macrolimus
CT	Conventional therapy

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