Original Article

Efficacy and safety of *Tripterygium* glycosides in Sjögren's syndrome treatment: evidence from 12 randomized controlled trials

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Background: *Tripterygium* glycosides (TGs) has been widely used in the treatment of Sjögren's syndrome (SS).

Methods: Seven databases, PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Wanfang Medical Database, China Science and Technology Journal Database, and the Chinese Biomedicine database, were selected to collect randomized controlled trials (RCTs) related to the treatment of SS with TGs alone or in combination. The participants, intervention, comparison, outcome, and study design principle were adopted for the inclusion of related studies. The risk of bias was assessed using the Cochrane Collaboration's tool. Meta-analysis was conducted using RevMan 5.3, with risk ratios (RRs) or standard mean differences (SMDs) and 95% confidence intervals (CIs).

Results: Overall, 12 trials involving 668 patients were analyzed. The results of the meta-analysis showed that TGs in combination with total glucosides of paeony (TGP) had significantly lower symptom scores than TGs alone on dry eyes (SMD =–0.61, 95% CI: –1.12 to –0.10, P=0.02) or dry mouth (SMD =–1.29, 95% CI: –1.84 to –0.74, P<0.00001). The efficacy rates of TG + TGP *vs.* TGs (P<0.00001) and TG + HM *vs.* TGs (P=0.01) were significantly different. In addition, compared to hydroxychloroquine (HCQ), TGs could induce expression of C-reactive protein (P=0.007), globulin (P<0.00001), and immunoglobulin A (IgA) (P=0.006), whereas the TG + TGP group had lower levels of immunoglobulin G (IgG) (P<0.00001), immunoglobulin M (IgM) (P=0.02), and IgA (P<0.00001), as well as saliva flow rate (P<0.00001) and lacrimal gland function (P<0.00001). The adverse events between TGs and HCQ were not evident, and there was no increase in the risk of adverse reactions when combined with other drugs.

Discussion: TGs are potentially effective for treating SS without increasing the risk of adverse events. High-quality, multi-center, and large-scale RCTs are required.

Keywords: Sjögren's syndrome (SS); *Tripterygium* glycosides (TGs); meta-analysis

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Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease characterized by progressive exocrine gland damage (1), affecting 0.4% people in China (2) and 0.1–0.4% people in the UK (3). Patients with SS are categorized into having primary or secondary SS. Decreased function of the salivary and lacrimal glands commonly causes dry mouth and eyes. Furthermore, SS has been reported to cause multiple organ damage, including immune thrombocytopenia, interstitial lung disease, and a 5–10% lifetime risk of B-cell lymphoma (4). The histological characteristics of SS include focal lymphocytic infiltration of exocrine glands (5), with a plethora of autoantibodies, cryoglobulins, hypocomplementemia, and hypergammaglobulinemia present in the serum of patients (6,7). Physical limitations and life-shortening complications (e.g., lymphoma) caused by SS result in a significant financial burden on the patient's family and healthcare services (8).

The etiology and pathogenesis of SS are not fully understood (5); therefore, therapeutic regimens are focused on symptom relief and broad-spectrum immunosuppression. According to the European League Against Rheumatism (EULAR) guidelines for SS (9), symptomatic treatments with of topical oral (e.g., saliva substitutes) and ocular (e.g., artificial tear drops) therapies only transiently relieve symptoms, which ultimately reoccur after therapeutic withdrawal. Furthermore, EULAR guidelines recommend immuno-directed therapies, such as hydroxychloroquine (HCQ) and oral glucocorticoids, as well as synthetic immunosuppressive and biologic agents, which have elevated incidences of serious adverse events (9). As such, efficacious and feasible interventions to treat SS, an orphan disease (10), are warranted.

In China, *Tripterygium* glycosides (TGs), extracted from *Tripterygium wilfordii Hook F.* of euonymus (11), are increasingly being used for the treatment of SS. TG, known as a "herbal hormone", is a fat-soluble mixture of active compounds, including diterpene lactones, alkaloids, and triterpenes, with bioactive and toxic constituents such as triptolide and celastrol (12,13). TGs can elicit immunosuppressive, anti-inflammatory, and anticancer effects (14), and exhibit significant clinical therapeutic potential, as highlighted in systematic reviews (15-18). Furthermore, guidelines on rheumatoid arthritis (RA) from the China Association of Chinese Medicine (CACM) (19) and Royal Australian College of General Practitioners (RACGP) (20) state that *T. wilfordii* effectively relieves the symptoms of RA, whereas TGs have been more commonly used for the treatment of autoimmune or inflammatory diseases including systemic lupus erythematosus and SS (21). However, one of our previous reviews indicated that the toxic side effects and adverse events of TGs include hepatotoxicity, reproductive toxicity, nematotoxicity, and intestinal toxicity (17), which may limit their clinical application.

However, systematic reviews have shown that combination therapies using TGs may be used to increase potency without increasing the risk of adverse events (18), which will enhance rational drug use and promote clinical therapy using TGs. It has been reported that the clinical effectiveness rate is significantly higher while using TGs in combination with topical glucocorticoids than that while using topical glucocorticoids alone ($P<0.00001$); additionally, the combination did not increase the occurrence or severity of adverse reactions (15). After primary literature research, it was found that literature on SS treated with TGs alone is limited; thus, the present study provides evidence on combination therapies using TGs.

Therefore, a meta-analysis of randomized controlled trials (RCTs) was performed in the current study to assess the therapeutic effectiveness of using TGs alone and in combination, as well as the associated adverse events, in the treatment of SS. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-256).

Methods

The main components of TGs

High-performance liquid chromatography (HPLC) analysis (22) was used to determine the main components of TGs (Lot No. 20160701), which included triptonide (0.2451 mg/g), triptolide (0.0806 mg/g), triptophenolide (0.3645 mg/g), celastrol (0.2619 mg/g), wilforine (0.2941 mg/g), and wilforlide A (0.3557 mg/g). The molecular structures of the main components of TGs are shown in Table S1.

Procedures

The procedures of the study followed a previously established protocol registered with PROSPERO (CRD42020185678), according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (23).

Table 1 Characteristics of the included studies on the efficacy and safety of *Tripterygium* glycosides in Sjögren's syndrome treatment

Study	Sample size		Patients (M/F)		Average age (years)		Average course duration of disease (years)		Interventions	
	E	C	E	C	E	C	E	C	E	C
Lan 2019	31	31	2/29	1/30	48.56 (6.97)	48.00 (7.31)	4.09 (3.67)	4.49 (3.07)	Zhibai Dihuang Decoction + TGs	TGs
Zhao 2019	42	42	18/24	17/25	51.52 (6.22)	50.53 (6.24)	6.51 (1.54)	5.52 (1.56)	TGs + TGP	TGs
Su 2019	30	30	16/14	17/13	37.1 (2.45)	34.2 (2.45)	7.23 (1.35)	7.23 (1.84)	TGs + TGP	TGs
Jiang 2018	35	35	7/28	6/29	45.21 (6.07)	45.32 (6.11)	4.06 (2.17)	3.97 (2.06)	TGs + TGP	TGs
Qiang 2018	37	38	3/35	2/35	51.95 (11.23)	50.86 (8.75)	6.12 (4.59)	5.83 (6.12)	TGs	Huoxue Jiedu Decoction
Wang 2017	49	49	20/29	18/31	49.7 (5.8)	50.1 (5.6)	NR	NR	TGs + TGP	TGs
Zhou 2015	30	30	2/28	3/27	57.3	56.6	NR	NR	Shengmai Yin + Yuye Decoction + TGs	TGs
Song 2014	30	30	NR	NR	50.83 (6.56)	50.67 (5.38)	NR	NR	TGs	Zaobiqing
Ma 2012	22	22	1/21	1/21	50 (7.14)	51 (7.82)	19 (6.46)	18 (6.72)	TGs	HCQ
Guo 2012	15	15	NR	NR	51.9 (7.1)	52.3 (7.2)	3.9 (5.7)	3.4 (5.8)	TGs	HCQ
Cui 2012	18	17	1/16	1/17	59.39 (10.98)	60.60 (10.07)	8.51 (6.54)	7.44 (5.63)	TGs	Huoxue Jiedu Yangyin Shengjin Decoction
Zhu 2010	31	32	2/30	1/30	52.00 (10.37)	51.06 (9.39)	6.03 (5.17)	5.94 (5.25)	TGs	Huoxue Jiedu Decoction

E, experimental group; C, control group; NR, not reported; RCT, randomized control trial; M, male; F, female; AEs, adverse events; TGs, Tripterygium glycosides; TGP, total glucosides of paeony; HCQ, hydroxychloroquine.

Search trials

Using the subject terms and free terms as search terms (Table S2), we systematically searched PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Medical Database, China Science and Technology Journal Database (CQVIP), and the Chinese Biomedicine (CBM) database, from the start date to March 12, 2020. The language conditions for retrieving literature were English and Chinese.

Study selection

Subsequently, the title, abstract, and full text were screened to identify articles using the following inclusion criteria: RCTs including patients diagnosed with SS; the intervention groups including TGs alone or combined therapies; the control groups including raw Chinese herbal medicine (HM), Chinese patent medicine, or western medicine; reporting outcome data regardless of efficacy rate, symptom scores, serum index, or adverse events. The criteria were followed by participants, intervention, comparison, outcome, and study design (PICOS) principle, which is presented in the supplementary material (Table S3).

Data extraction

The two authors independently extracted data by reading the titles, abstracts, and full texts of the included studies. The characteristics of the included studies are summarized in *Tables 1*,*2*, including the year of publication, first author, location, sample size, age and sex of patients, average course duration of disease, interventions, dosage, course of treatment, adverse events, efficacy rate, symptom scores, serum index, and physical index.

Risk of bias assessments

Risk assessments were performed using Cochrane bias risk tools, including random sequence generation (selection bias), allocation concealment (selection bias),

Table 2 Characteristics of the included studies on the efficacy and safety of *Tripterygium* glycosides in Sjögren's syndrome treatment

Study	Dosage	Course of treatment	Adverse events		Main outcomes
			E	C	
Lan 2019	20 mg, tid	8 w	Gastrointestinal symptom [2], menstrual disorder [1], abnormal liver function [2]	Gastrointestinal symptom [2], menstrual disorder [3], abnormal liver function [2]	Efficacy rate; symptom scores; saliva flow rate; Schirmer's test; AEs
Zhao 2019	1 mg/kg/d, tid	12 w	Gastrointestinal symptom [3], cardiovascular [1]	Gastrointestinal symptom [6], cardiovascular [6]	Efficacy rate; AEs
Su 2019	1 mg/kg/d, tid	12 w	Gastrointestinal symptom [2]	gastrointestinal symptom [3]	Efficacy rate; AEs
Jiang 2018	1 mg/kg/d, tid	12 w	NR	NR	Th17/Treg; IgM/IgM/IgA
Qiang 2018	20 mg, tid	12 w	NR	NR	Efficacy rate; ESR/CRP/IgG/IgM/IgA; saliva flow rate; Schirmer's test; BUT
Wang, 2017	1 mg/kg/d, tid	12 w	Gastrointestinal symptom [4]	Gastrointestinal symptom [2]	Efficacy rate, saliva flow rate; AEs
Zhou 2015	20 mg, tid	12 w	NR	NR	Efficacy rate
Song 2014	20 mg, tid	12 w	NR	NR	Efficacy rate; ESR/IgM/IgA/IgG; symptom scores
Ma 2012	20 mg, tid	12 w	Menstrual disorder [2], abnormal blood routine [2], abnormal liver function [2]	Abnormal blood routine [1], abnormal liver function [1], ocular form [1]	Symptom scores; ESR/CRP/IgG/IgA/IgM/globulin; AEs
Guo 2012	20 mg, tid	12 w	Menstrual disorder [1], abnormal liver function [2]	0	ESR/CRP/IgG/RF/globulin; AEs
Cui 2012	20 mg, tid	8 w	0	0	Efficacy rate, anti-SSA/anti-SSB/RF/ESR/CRP/IgA/IgM/IgG; symptom scores; AEs
Zhu 2010	20 mg, tid	4w	NR	NR	Efficacy rate; ESR/CRP; symptom scores; Schirmer's test

E, experimental group; C, control group; NR, no report; RCT, randomized controlled trial; M, male; F, female; w, weeks; d, days; tid, three times a day; AEs, adverse events; Th17, T helper 17; Treg, regulatory T; IgM/G/A, immunoglobulin M/G/A; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUT, break-up time; RF, rheumatoid factor; anti-SSA/B antibody, anti-Sjögren's syndrome A/B antibody.

blindness of participants and personnel (implementation bias), blindness of outcome assessment (monitoring bias), no complete result data (wear bias), selective reporting (reporting bias), and other biases. We used the method of low risk of bias, unclear risk of bias, or high risk of bias. In case of a disagreement between the two authors, we negotiated with a third reviewer. A funnel plot was used to analyze the publication bias across studies.

Statistical analysis

We used RevMan (version 5.3) to calculate the risk ratio (RR) in counting data or mean difference (MD) in quantitative data with a 95% confidence interval (CI). The standard mean difference (SMD) was used when the measurement standard differed among studies. Clinical heterogeneity was evaluated using the I^2 method. Summary statistics were produced at first, and when I^2 was >50%, subgroup analysis was used for clinical heterogeneity. If the value of the heterogeneity I^2 (tested by the I^2 statistic) was <50%, the fixed-effect model was selected; otherwise, the random effects model was used. A sensitivity analysis was performed if necessary. The inconsistent data extracted from the included studies are displayed in the Results section.

Outcome measures

The primary outcome comprised symptom scores, including the EULAR Sjögren's syndrome disease activity index (ESSDAI), dry eyes, dry mouth, dry skin, and joint pain. The therapeutic evaluation was based on the standard formulated by the EULAR, which developed the ESSDAI scores in 2010 that are now widely used both clinically and in research (24).

The secondary outcomes were as follows: efficacy rate; serum index of immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-SS A/B antibody (anti-SSA/B antibody), T helper 17 (Th17) cells, regulatory T (Treg) cells; physical index of saliva flow rate; Schirmer's test and break-up time (BUT); and adverse events.

Results

Characteristics of included studies

A total of 125 studies were retrieved from 7 databases, and 61 duplicate reports were eliminated. Overall, 34 records were excluded after the title and summary scanning, leaving 30 records. Finally, 12 articles (25-36) met the inclusion criteria based on PICOS, which were included in the current systematic review (*Figure 1*), including three (32,33,35) unofficially published dissertations.

Summary

A total of 668 patients were included in the 12 studies. The characteristics of the included trials are listed in *Tables 1,2*. All trials met the diagnostic criteria, and 10 trials mentioned the diagnostic criteria used, of which two (27,30) were confirmed by the hospital.

Interventions

This review involved 17 interventions, and we established subgroups based on different interventions. Two RCTs (33,34) compared TGs alone with HCQ, whereas four trials (29,32,35,36) compared TGs alone with HM. Five trials compared TGs in combination with total glucosides of paeony (TGP) and TGs alone (26,27,30), and two trials compared TG + HM and TGs alone (25,31). The duration of treatment ranged from 4 to 12 weeks with a dosage of 60 mg/d or 1 mg/kg/d.

Outcome indicators

Five trials measured symptom scores (25,32,33,35,36). Nine trials (25-27,29-32,35,36) used efficacy rate as an outcome, seven trials measured serum index (28,29,32-36), and four trials reported physical index (25,29,30,36). Seven trials reported adverse events (25,26,27,30,33-35).

Risk of bias assessment

Although all 12 trials were randomized trials, only three trials (26,27,30) documented the generation of random sequences (*Figure 2*). The risk of bias in one study (30) was considered as "high risk" because the integrated balance method was used for grouping. One study (33) reported the implementation and monitoring of blindness, while it considered the risk of breaking blindness as "high risk." According to data loss, four experiments (28,32,34,35) had little data loss but did not report the reason, which was considered as "unclear risk." The protocols of three studies (32,33,35) were accessible, and the established primary and secondary outcomes were reported according to the established plan. Therefore, we performed a low-risk evaluation. None of the studies described other biases. The risk of publication bias across studies has been presented in a funnel plot (Figure S1), implying a low-quality methodology and indicating that a publication bias may exist. The small sample size may be the main reason for this bias.

Primary outcome: symptom scores

One trial reported symptom scores of TGs in combination with TGP compared with TGs alone, and the combined therapies significantly reduced the scores of dry eyes (SMD =−0.61, 95% CI: −1.12 to −0.10, P=0.02) and dry mouth (SMD =−1.29, 95% CI: −1.84 to −0.74, P<0.00001). However, we found that TGs were as effective as the HM in terms of ESSDAI (SMD =0.12, 95% CI: −0.97 to 1.21, I^2 =85%, P=0.83) (*Table 3*) and relieving the symptoms of dry eyes (SMD =0.00, 95% CI: −0.31 to 0.31, I^2 =0%, P=0.99), joint pain (SMD =0.01, 95% CI: −0.92 to 0.95, I^2 =88%, P=0.98), and dry skin (SMD =0.20, 95% CI: −0.58 to 0.98, I^2 =83%, P=0.62), whereas the HM group seemed to have a better effect on relieving the symptom of dry mouth (SMD =0.73, 95% CI: 0.13 to 1.33, I^2 =69%, P=0.02). The clinical heterogeneity could not be solved by subgroup analysis, which may be related to the inconsistency of Chinese HM compound preparations.

Secondary outcomes

Efficacy rate

Subgroup analysis demonstrated that the efficacy of TGs

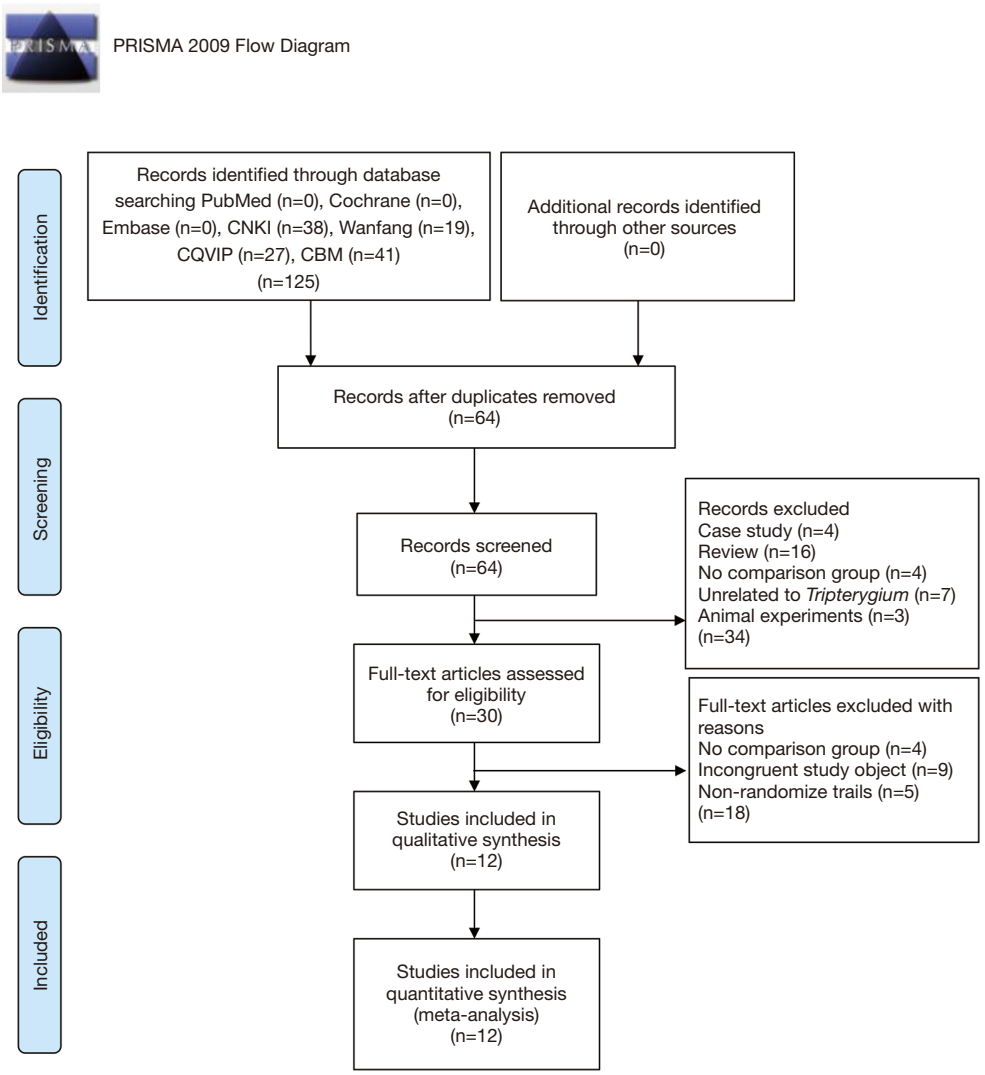

Figure 1 Flowchart of search strategy and study selection, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. EMBASE, Excerpta Medica database; CNKI, Chinese National Knowledge Infrastructure database; Wanfang, Wanfang Data Knowledge Service Platform; VIP, China Science and Technology Journal Database; CBM, Chinese Biomedicine Database.

vs. HM group did not have a significant difference (RR =0.90, 95% CI: 0.79 to 1.01, I^2 =0%, P=0.07; *Table 4*), and the TGs *vs*. HCQ group lacked sufficient data. The efficacy rate of combined medication with TGs was significantly higher that TGs alone (TG + TGP *vs*. TGs: RR =1.23, 95% CI: 1.11 to 1.36, I^2 =0%, P<0.00001; TG + HM *vs*. TGs: RR =1.27, 95% CI: 1.05 to 1.54, I^2 =0%, P=0.01). The clinical heterogeneity was solved by subgroup analysis, which indicated that the sources were interventions among subgroups.

Serum index

Subgroup analysis (*Table 5*) revealed that there was a significant difference between the HCQ and TG groups in reducing levels of CRP (MD =–0.41, 95% CI: –0.71 to –0.11, I^2 =0%, P=0.007), globulin (MD =–6.54, 95% CI: –9.20 to –3.88, I^2 =0%, P<0.00001), and IgA (MD =–0.64, 95% CI: –1.10 to –0.18, P=0.06); however, other indices were not significant (ESR: MD =–6.67, 95% CI: –13.27 to –0.08, I^2 =72%, P=0.05; IgG: MD =–3.11, 95% CI: –8.00 to 1.78, I^2 =88%, P=0.21; IgM: MD =0.05, 95% CI: –0.16

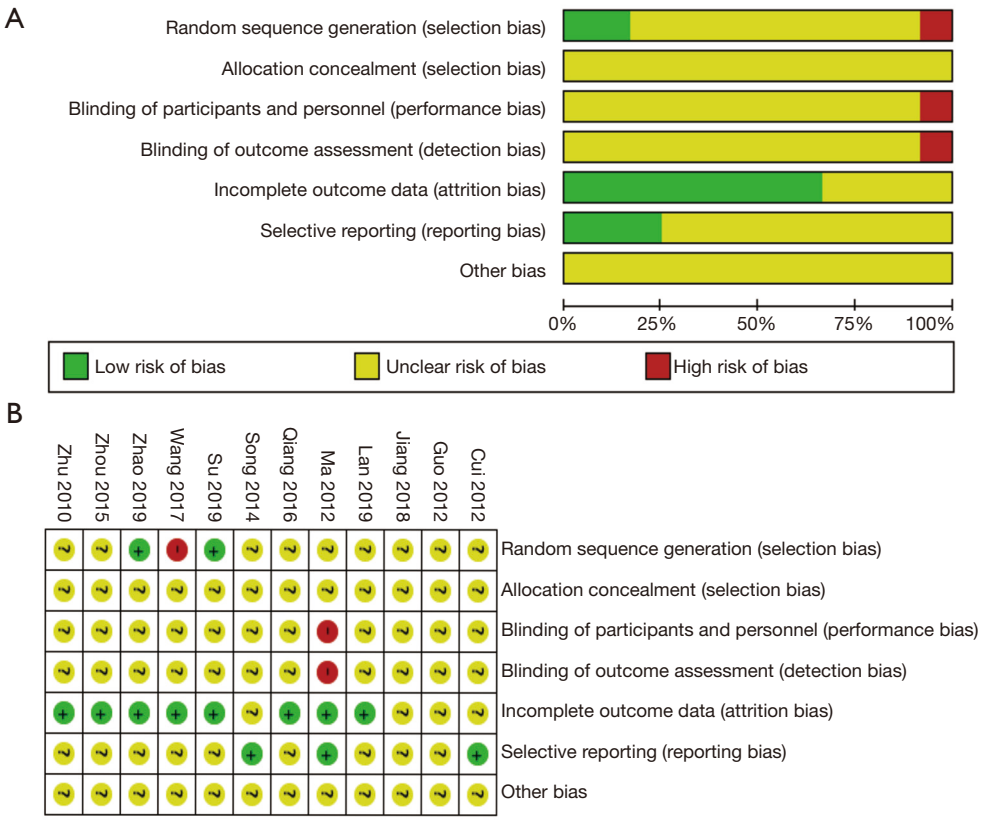

Figure 2 Risk of bias in the included studies on the safety and efficacy of *Tripterygium* glycosides for Sjögren's syndrome. (A) Risk of bias graph; (B) risk of bias summary.

to −0.26, P=0.65; RF: MD =−6.60, 95% CI: −16.31 to 3.11, P=0.18).

The CRP level of TG group was significantly higher than that of HM group (MD =2.48, 95% CI: 0.21 to 4.75, I^2 =24%, P=0.03). TGs had similar results with HM in terms of ESR (MD =2.28, 95% CI: −0.95 to 5.51, I^2 =10%, P=0.17), IgG (MD =1.06, 95% CI: −1.43 to 3.56, I^2 =72%, P=0.40), IgM (MD =0.10, 95% CI: −0.16 to −0.09, I^2 =72%, P=0.45), IgA (MD =0.15, 95% CI: −0.14 to −0.44, I^2 =51%, P=0.31), RF (RR =3.78, 95% CI: 0.47 to 30.5, P=0.21), anti-SSA antibody (RR =1.35, 95% CI: 0.67 to 2.72, P=0.40), and anti-SSB antibody (RR =1.51, 95% CI: 0.61 to 3.71, P=0.37).

The comparison between TG + TGP and TGs indicated strong synergistic effects of the combination on production of IgG (MD =−0.51, 95% CI: −0.67 to −0.35, P<0.00001), IgM (MD =−0.63, 95% CI: −1.17 to −0.09, P=0.02), IgA (TG + TGP *vs*. TGs: MD =−3.43, 95% CI: −4.71 to −2.15, P<0.00001), Th17 cells (MD =−0.21, 95% CI: −0.36 to 0.06, P=0.006), and Treg cells (MD =0.59, 95% CI: 0.09 to 1.09, P=0.02). Clinical heterogeneity may correspond to differences in the method of administration and duration of follow-up.

Physical index

Compared with HM, TGs alone exhibited a significant difference in saliva flow rate (SMD =−1.40, 95% CI: −1.91 to 0.90, P<0.00001; *Table 5*) and BUT (SMD =−0.59, 95% CI: −1.05 to −0.13, P=0.01), whereas Schirmer's test results were not significant (SMD =−0.14, 95% CI: −0.71, 0.44, I^2 =76%, P=0.64).

The results showed that TGs in combination with TGP or HM increased the saliva flow rate (SMD =1.73, 95% CI: 1.36 to 2.10, I^2 =0%, P<0.00001), and TGs in combination with TGP performed better in Schirmer's test of two eyes (SMD =1.34, 95% CI: 0.95 to 1.73, I^2 =0%, P<0.00001) than the groups treated with TGs alone. The clinical heterogeneity of Schirmer's test could not be solved by subgroup analysis, which may be related to differences in the specific operation methods.

Table 3 Symptom scores of *Tripterygium* glycosides in Sjögren's syndrome treatment

Trials	Comparisons	Effect estimates, SMD (95% CI)	P value
1. *Tripterygium* glycosides versus hydroxychloroquine			
1.1 Dry mouse			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	–0.12 (–0.71, 0.47)	0.69
2. *Tripterygium* glycosides versus herbal medicine			
2.1 ESSDAI			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	–0.46 (–1.13, 0.21)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	0.65 (0.13, 1.17)	
Meta-analysis		0.12 (–0.97, 1.21)	0.83
2.2 Dry eyes			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	0.14 (–0.35, 0.64)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	0.14 (–0.53, 0.80)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	–0.23 (–0.74, 0.27)	
Meta-analysis		–0.00 (–0.31, 0.31)	0.99
2.3 Dry mouse			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	1.27 (0.73, 1.82)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	0.62 (–0.06, 1.30)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	0.31 (–0.20, 0.82)	
Meta-analysis		0.73 (0.13, 1.33)	0.02
2.4 Dry skin			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	–0.41 (–0.91, 0.08)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	0.16 (–0.51, 0.82)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	0.85 (0.32, 1.38)	
Meta-analysis		0.20 (–0.58, 0.98)	0.62
2.5 Joint pain			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	–0.18 (–0.68, 0.31)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	1.06 (0.35, 1.78)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	–0.75 (–1.27, –0.22)	
3. *Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides			
3.2 Dry eyes			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	0.61 (–1.12, –0.10)	0.02
3.3 Dry mouse			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	–1.29 (–1.84, 0.74)	<0.00001

SMDs, standard mean differences; CI, confidence interval.

Table 4 Symptom scores of *Tripterygium* glycosides in Sjögren's syndrome treatment

Trials	Comparisons	Effect estimates, RR (95% CI)	P value
1. *Tripterygium* glycosides versus herbal medicine			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	0.93 (0.77, 1.12)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	0.94 (0.72, 1.24)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	0.78 (0.58, 1.04)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	0.89 (0.70, 1.15)	
Meta-analysis		0.90 (0.79, 1.01)	0.07
2. *Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides			
Wang 2017	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	1.18 (1.02, 1.36)	
Zhao 2019	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	1.29 (1.06, 1.56)	
Su 2019	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	1.27 (1.01, 1.61)	
Meta-analysis		1.23 (1.11, 1.36)	0.0001
3. *Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides			
Zhou 2015	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	1.39 (1.00, 1.94)	
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	1.22 (0.96, 1.54)	
Meta-analysis		1.27 (1.05, 1.54)	0.01

RR, risk ratio; CI, confidence interval.

Adverse events

By comparing TGs and HCQ, we found that their adverse events were not significantly different (abnormal liver function: RR =3.00, 95% CI: 0.50 to 18.06, I^2 =0%, P=0.23; abnormal blood routine: RR =2.00, 95% CI: 0.20 to 20.49, P=0.56; ocular form: RR =0.33, 95% CI: 0.01 to 7.76, P=0.49; menstrual disorder: RR =4.00, 95% CI: 0.47 to 34.22, I^2 =0%, P=0.21).

Table 5 shows that there was no significant difference in adverse effects between the TG + TGP and TG groups (gastrointestinal symptom: RR =0.82, 95% CI: 0.35 to 1.91, I^2 =0%, P=0.64; cardiovascular: RR =0.17, 95% CI: 0.02 to 1.33, P=0.09). In addition, the adverse events of TGs in combination with HM were similar to those of TGs alone (gastrointestinal symptom: RR =2.00, 95% CI: 0.19 to 20.93, P=0.56; menstrual disorder: RR =0.33, 95% CI: 0.04 to 3.03, P=0.33; abnormal liver function: RR =1.00, 95% CI: 0.15 to 6.66, P=1.00). The clinical heterogeneity in adverse events was solved by subgroup analysis, which indicated that its sources are interventions among subgroups.

Discussion

This systematic review included 12 RCTs to evaluate the effectiveness and safety of TGs in the treatment of SS. According to the EULAR guidelines (9), relieving SS symptoms should be the priority of first-line therapies. In accordance with HM, we demonstrated, to a limited extent, that combination therapy including TGs was effective at reducing dry eye or mouth as determined by the results of symptom score. Furthermore, TGs in combination with other treatments resulted in a synergistic benefit for the secretion function of the lacrimal gland (Schirmer's test) or salivary gland (saliva flow rate). As such, it appears that the underlying immunological mechanism of TGs is unclear, although previous reports have postulated that it is similar to steroids (37). Nonetheless, combinatorial treatments for SS that include TGs are beneficial for symptom relief.

Table 5 Serum and physical indices of *Tripterygium* glycosides and associated adverse events in Sjögren's syndrome treatment

Trials	Comparisons	Effect estimates, MD/RR/SMD (95% CI)	P value
1. *Tripterygium* glycosides versus hydroxychloroquine			
1.1 Serum index			
1.1.1 C-reactive protein			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –0.41 (–0.71, –0.11)	
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –1.90 (–7.90, 4.10)	
Meta-analysis		MD: –0.41 (–0.72, –0.11)	0.007
1.1.2 Erythrocyte sedimentation rate			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –3.05 (–8.59, 2.49)	
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –9.80 (–14.02, –5.58)	
Meta-analysis		MD: –6.67 (–13.27, –0.08)	0.05
1.1.3 Globulin			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –7.30 (–10.80, –3.80)	
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –5.50 (–9.60, –1.40)	
Meta-analysis		MD: –6.54 (–9.20, –3.88)	<0.00001
1.1.4 Immunoglobulin G			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –0.61 (–3.00, 1.78)	
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –5.60 (–7.95, –3.25)	
Meta-analysis		MD: –3.11 (–8.00, 1.78)	0.21
1.1.5 Immunoglobulin M			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: 0.05 (–0.16, 0.26)	0.65
1.1.6 Immunoglobulin A			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: –0.64 (–1.10, –0.18)	0.006
1.1.7 Rheumatoid factor			
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	MD: 6.60 (–16.31, 3.11)	0.18
1.2 Adverse events			
1.2.1 Abnormal liver function			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	RR: 2.00 (0.20, 20.49)	
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	RR: 5.00 (0.26, 96.13)	
Meta-analysis		RR: 3.00 (0.50, 18.06)	0.23
1.2.2 Abnormal blood routine			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	RR: 2.00 (0.20, 20.49)	0.56
1.2.3 Ocular form			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	RR: 0.33 (0.01, 7.76)	0.49

Table 5 (*continued*)

Table 5 (*continued*)

Trials	Comparisons	Effect estimates, MD/RR/SMD (95% CI)	P value
1.2.4 Menstrual disorder			
Ma 2012	*Tripterygium* glycosides versus hydroxychloroquine	RR: 5.00 (0.25, 98.52)	
Guo 2012	*Tripterygium* glycosides versus hydroxychloroquine	RR: 3.00 (0.13, 68.26)	
Meta-analysis		RR: 4.00 (0.47, 34.22)	0.21
2. *Tripterygium* glycosides versus herbal medicine			
2.1 Serum index			
2.1.1 C-reactive protein			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	MD: 2.73 (–2.32, 7.78)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	MD: –3.22 (–10.48, 4.04)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	MD: 3.20 (0.49, 5.91)	
Meta-analysis		MD: 2.48 (0.21, 4.75)	0.03
2.1.2 Erythrocyte sedimentation rate			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	MD: 1.07 (–6.81, 8.95)	
Cui 2012	*Tripterygium* glycosides versus herbal medicine	MD: –4.27 (–15.76, 7.22)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	MD: 1.36 (–2.85, 5.57)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	MD: 6.08 (0.53, 11.63)	
Meta-analysis		MD: 2.28 (–0.95, 5.51)	0.17
2.1.3 Immunoglobulin G			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	MD: –1.70 (–4.59, 1.19)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	MD: 1.41 (–1.01, 3.83)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	MD: 2.83 (1.14, 4.52)	
Meta-analysis		MD: 1.06 (–1.43, 3.56)	0.40
2.1.4 Immunoglobulin M			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	MD: –0.04 (–0.32, 0.24)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	MD: 0.35 (0.14, 0.56)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	MD: –0.03 (–0.28, 0.22)	
Meta-analysis		MD: 0.10 (–0.16, 0.37)	0.45
2.1.5 Immunoglobulin A			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	MD: 0.04 (–0.37, 0.45)	
Song 2014	*Tripterygium* glycosides versus herbal medicine	MD: –0.04 (–0.39, 0.31)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	MD: 0.41 (0.10, 0.72)	
Meta-analysis		MD: 0.15 (–0.14, 0.44)	0.31
2.1.6 Rheumatoid factor			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	RR: 3.78 (0.47, 30.5)	0.21

Table 5 (*continued*)

Table 5 (*continued*)

Trials	Comparisons	Effect estimates, MD/RR/SMD (95% CI)	P value
2.1.7 Anti-Sjögren's syndrome A antibody			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	RR: 1.35 (0.67, 2.72)	0.40
2.1.8 Anti-Sjögren's syndrome B antibody			
Cui 2012	*Tripterygium* glycosides versus herbal medicine	RR: 1.51 (0.61, 3.71)	0.37
2.2 Physical index			
2.2.1 Saliva flow rate			
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	SMD: –1.40 (–1.91, –0.90)	<0.00001
2.2.2 Schirmer's test			
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	SMD: –0.26 (–0.76, 0.24)	
Zhu 2010	*Tripterygium* glycosides versus herbal medicine	SMD: 0.43 (–0.07, 0.93)	
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	SMD: –0.56 (–1.02, –0.10)	
Meta-analysis		SMD: –0.14 (–0.71, 0.44)	0.64
2.2.3 Break-up time			
Qiang 2018	*Tripterygium* glycosides versus herbal medicine	SMD: –0.59 (–1.05, –0.13)	
3. *Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides			
3.1 Serum index			
3.1.1 Immunoglobulin G			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	MD: –0.51 (–0.67, –0.35)	<0.00001
3.1.2 Immunoglobulin M			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	MD: –0.63 (–1.17, 0.09)	0.02
3.1.3 Immunoglobulin A			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	MD: –3.43 (–4.71, –2.15)	<0.00001
3.1.4 T helper 17 cell			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	MD: –0.21 (–0.36, 0.06)	0.006
3.1.5. Regulatory T cell			
Jiang 2018	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	MD: 0.59 (0.09, 1.09)	0.02
3.2 physical index			
3.2.1 Saliva flow rate			
Wang 2017	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	SMD: 1.59 (1.14, 2.05)	<0.00001

Table 5 (*continued*)

Table 5 (*continued*)

Trials	Comparisons	Effect estimates, MD/RR/SMD (95% CI)	P value
3.3 Adverse events			
3.3.1 Gastrointestinal symptom			
Wang 2017	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	RR: 2.00 (0.38, 10.42)	
Zhao 2019	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	RR: 0.50 (0.13, 1.87)	
Su 2019	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	RR: 0.67 (0.12, 3.71)	
Meta-analysis		RR: 0.82 (0.35, 1.91)	0.64
3.3.2 Cardiovascular			
Zhao 2019	*Tripterygium* glycosides combined with total glucosides of paeony versus *Tripterygium* glycosides	RR: 0.17 (0.02, 1.33)	0.09
4. *Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides			
4.1 Physical index			
4.1.1 Saliva flow rate			
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	SMD: 1.97 (1.36, 2.59)	<0.00001
4.1.2 Schirmer's test			
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	SMD: 1.37 (0.81, 1.93)	
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	SMD: 1.31 (0.76, 1.86)	
Meta-analysis		SMD: 1.34 (0.95, 1.73)	<0.00001
4.2 Adverse events			
4.2.1 Gastrointestinal symptom			
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	RR: 2.00 (0.19, 20.93)	
4.2.2 Menstrual disorder			
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	RR: 0.33 (0.04, 3.03)	0.33
4.2.3 Abnormal liver function			
Lan 2019	*Tripterygium* glycosides combined with herbal medicine versus *Tripterygium* glycosides	RR: 0.17 (0.02, 1.33)	1.00

SMDs, standard mean differences; RR, risk ratio; MD, mean difference; CI, confidence interval.

TGs reportedly reduce systemic inflammation in SS patients by reducing CRP levels, which are independently associated with functional impairment in SS patients (38). The results of the present review provide evidence that TGs have a stronger therapeutic effect on reducing the level of CRP than HCQ or HM in patients with SS.

Therapeutics that reduce the proliferation of B cells, including TGs (39) and HCQ (40), have been used to

treat SS. Indeed, SS is considered an autoimmune disease associated with hyperactivity, a pathologic autoantibody response of B cells (41), and elevated levels of serum IgG (42). Therefore, the levels of immunoglobulins in peripheral blood are considered to be important indicators of SS activity (7). Our results demonstrated that TGs reduced the level of globulin or IgA to an extent greater than HCQ. A previous experiment in animals (39) demonstrated that TGs and HCQ effectively reduced the expression of genes related to inflammation and autoimmunity. Therefore, combination therapy including TGs with other therapies may be more effective than single treatment interventions. The present meta-analysis demonstrated that TGs combined with TGP significantly reduced the levels of CRP and immunoglobulins (IgG, IgM, and IgA) to an extent greater than TGs alone, which may be related to the synergistic effect of TGP on reducing immunoglobulins (43) or regulating immune homeostasis by modulating the Th17/Treg ratio (28).

Despite the promising therapeutic potential of TGs for patients with SS, the incidence of adverse events is worthy of discussion. This review demonstrated that the administration of TGs alone or in combination with other therapies resulted in gastrointestinal symptoms in four studies (23 cases), menstrual disorder in three studies (six cases), abnormal liver function in three studies (eight cases), cardiovascular events in one study (seven cases), abnormal blood function in one study (three cases), and ocular form in one study (one case) (see Figure S2). The results of the present review demonstrate that patients in the studies involving optimal dosage and duration of TG administration did not experience more adverse events compared to HCQ, which is in line with a previous study that reported that TGs resulted in fewer adverse events than HCQ in an animal model of SS (39). However, suboptimal treatment courses, combined interventions, and dosages of previous studies have resulted in an elevated incidence of TGs in previous trials, including the presence of intestinal toxicity, reproductive toxicity, hepatotoxicity, and hematotoxicity (17). As such, future studies should prevent TG-related toxicity by controlling drug dosage and clinical use time (44), as well as improving the mode of delivery (45) and compatibility in glycyrrhiza (46).

This study had several inherent limitations. First, the quality of the trials included in this review was low. For instance, only four trials reported random methods, one trial reported blinding methods, and no other biases were reported. Second, the baseline management of children with SS or secondary SS was not specifically reported. Third, the sample sizes of the included studies were often insufficient to provide adequate conclusions. Future studies are warranted incorporating a larger sample size with multi-center RCT methodologies, more comprehensively and objectively evaluating the efficacy and safety of TGs for the treatment of SS.

Conclusions

In conclusion, TGs can be considered potentially clinically effective agents for the treatment of SS. The administration of TGs alone reduced systemic inflammatory indices (CRP levels) and immunoglobulins (IgA and globulin levels) to an extent greater than HCQ. Furthermore, the combination of TGs with other therapies reduced dryness symptom scores and the levels of immunoglobulins (IgG, IgM, and IgA), in addition to enhancing the efficacy rate and secretion function of lacrimal (Schirmer's test) and salivary glands (saliva flow rate). However, the potential benefits and safety of TGs should be further investigated using high-quality, multi-center, and large-scale RCTs.

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Footnote

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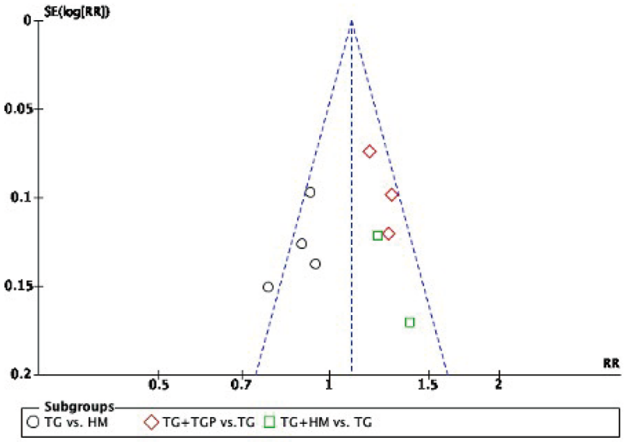

Figure S1 Funnel plot on the safety and efficacy of Tripterygium glycosides for Sjögren's syndrome. TG, Tripterygium glycosides; HM, herbal medicine; TGP, total glucosides of paeony.

	TG+HM	TG	TG+TGP	TG	TG+TGP	TG	TG+TGP	TG	TG	HCQ	TG	HCQ	
Gastrointestinal symptom	2	1	4	2	3	6	2	3	0	0	0	0	Intestinal toxicity
Menstrual disorder	1	3	0	0	0	0	0	0	1	0	1	0	Reproductive toxicity
Abnormal liver function	2	2	0	0	0	0	0	0	2	1	2	0	Hepatotoxicity
Cardiovascular	0	0	0	0	1	6	0	0	0	0	0	0	Circulatory toxicity
Abnormal blood function	0	0	0	0	0	0	0	0	2	1	0	0	Hematotoxicity
Ocular form	0	0	0	0	0	0	0	0	0	1	0	0	Other damage
Summary	5	6	4	2	4	12	2	3	5	3	3	0	
	Lan 2019		Wang 2017		Zhao 2019		Su 2019		Ma 2012		Guo 2012		

Figure S2 Mapping of specific adverse events between Tripterygium glycosides and control groups. TG, Tripterygium glycosides; HM, herbal medicine; TGP, total glucosides of paeony; HCQ, hydroxychloroquine.

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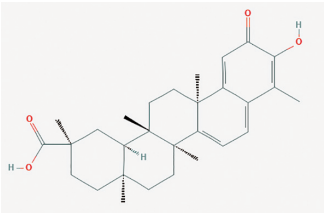
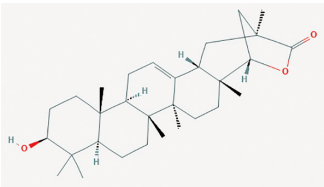
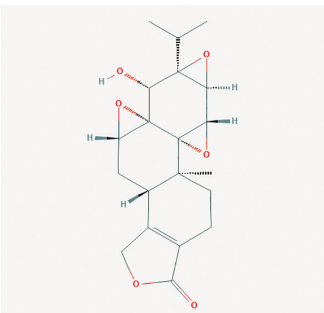
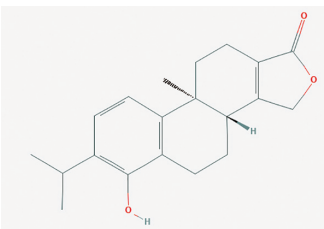
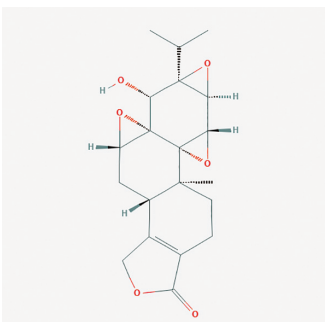
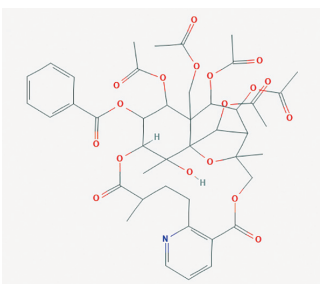
Table S1 Molecular structure of main chemical constituents of Tripterygium glycosides

Name	Molecular formula	Structure
Celastrol	$C_{29}H_{38}O_4$	
Wilforlide A	$C_{30}H_{46}O_3$	
Triptolide	$C_{20}H_{22}O_6$	
Triptophenolide	$C_{20}H_{24}O_3$	
Triptolide	$C_{20}H_{24}O_6$	
Wilforine	$C_{43}H_{49}NO_{18}$	

https://dx.doi.org/10.21037/apm-21-256

Table S2 Search strategy

Database	Search strategy of electronic database in sequence
PubMed	1. *Tripterygium* [Mesh]
	2. *Tripterygium* glycoside [Title/Abstract]
	3. Radix tripterygium [Title/Abstract]
	4 TG [Title/Abstract]
	5. 1 or 2 or 3 or 4
	6. Sjögren's Syndrome [Mesh]
	7. Sjogren's Syndrome [Title/Abstract]
	8. Sicca [Title/Abstract]
	9. SS [Title/Abstract]
	10. 6 or 7 or 8 or 9 or 10
	11. 5 and 10
Embase	1. *Tripterygium*'/exp
	2. *Tripterygium* glycoside'
	3. Radix tripterygium'
	4. TG'
	5. 1 or 2 or 3 or 4
	6. Sjögren's Syndrome'/exp
	7. Sjogren's Syndrome'
	8. Sicca'
	9. SS'
	10. 6 or 7 or 8 or 9 or 10
	11. 5 and 10
Cochrane Central Register of Controlled Trials	1. MeSH descriptor: [Tripterygium] explode all trees
	2. *Tripterygium* glycoside:ti,ab,kw
	3. Radix tripterygium:ti,ab,kw
	4. TG:ti,ab,kw
	5. 1 or 2 or 3 or 4 or 5
	6. MeSH descriptor: [Sjögren's Syndrome] explode all trees
	7. Sjogren's Syndrom:ti,ab,kw
	8. Sicca:ti,ab,kw
	9. SS:ti,ab,kw
	10. 6 or 7 or 8 or 9
	11. 5 and 10
CNKI & CQVIP & Wanfang & CBM	1. 雷公藤 :ti,ab,kw
	2. 雷公藤多甙 :ti,ab,kw
	3. 雷公藤多苷 :ti,ab,kw
	4. 1 or 2 or 3
	5. 干燥综合征 :ti,ab,kw
	6. 4 and 5

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Table S3 Participants, intervention, comparison, outcome, and study design criteria (PICOS) for inclusion and exclusion of studies

Items	Descriptions
Participants	Patients diagnosed with Sjögren's syndrome
Intervention	Tripterygium glycosides alone or combined therapies
Comparison	Control groups of conventional therapies
Outcomes	Efficacy rate, symptom scores, serum index, physical index, adverse events
Study design	Randomized controlled trials

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