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Articulo Original / Original Article

Effect of the Jiedu Tongluo Shengjin formulation on plasma immunoglobulin G (IgG) levels in patients with primary Sjögren's syndrome

[Efecto de la formulación Jiedu Tongluo Shengjin sobre los niveles de inmunoglobulina G (IgG) en plasma en pacientes con síndrome de Sjögren primario]

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Abstract: This study assessed the effect of Jiedu Tongluo Shengjin formulation on plasma IgG levels in pSS patients. 89 pSS patients were randomized into treatment (45 cases; 1 drop-out) and control (44 cases) groups using the random number table method. The control group received hydroxychloroquine sulfate and a placebo dose of Jiedu Tongluo Shengjin. The treatment group received hydroxychloroquine sulfate and the original Jiedu Tongluo Shengjin formulation. The treatment group showed significant decreases in SS disease activity index, TCM syndrome score, plasma IgG, and ESR, and significant increases in tear film break-up time, tear flow rate, salivary flow rate, C3, and C4 levels ($p<0.05$). No significant changes were observed in the control group ($p>0.05$). Jiedu Tongluo Shengjin effectively reduced eye and mouth dryness in pSS patients by improving inflammation and immune status.

Keywords: Hyperglobulinemia; Jiedu Tongluo Shengjin formulation; Primary Sjögren's syndrome; Salivary flow rate; Tear film break-up time

Resumen: Este estudio evaluó el efecto de la formulación Jiedu Tongluo Shengjin sobre los niveles de IgG en plasma en pacientes con Síndrome de Sjögren primario (pSS). Se asignaron 89 pacientes con pSS al grupo de tratamiento (45 casos; 1 paciente se retiró) y al grupo de control (44 casos) utilizando el método de tabla de números aleatorios. El grupo de control recibió sulfato de hidroxicloroquina y una dosis placebo de Jiedu Tongluo Shengjin. El grupo de tratamiento recibió sulfato de hidroxicloroquina y la formulación original de Jiedu Tongluo Shengjin. El grupo de tratamiento mostró descensos significativos en el índice de actividad del síndrome de Sjögren, el puntaje TCM de síndrome, los niveles de IgG en plasma, la velocidad de sedimentación eritrocitaria y los niveles de C3 y C4 ($p<0.05$). No se observaron cambios significativos en el grupo de control ($p>0.05$). Jiedu Tongluo Shengjin redujo efectivamente la sequedad ocular y bucal en pacientes con pSS al mejorar la inflamación y el estado inmunitario.

Palabras clave: Hiperglobulinemia; Formulación Jiedu Tongluo Shengjin; Síndrome de Sjögren primario; Flujo salival; Tiempo de ruptura del filme lacrimal

INTRODUCTION

Primary Sjögren's Syndrome (pSS) is a chronic inflammatory systemic autoimmune disease that mainly involves exocrine glands such as the salivary glands, the lacrimal glands, and the parotid glands. It has an estimated prevalence of 0.3% to 0.7% in China (Zhang *et al*., 2023). Its clinical manifestations include dryness of the mouth and eyes, which are accompanied by symptoms of blood, respiratory, renal, digestive, neurological, and immune involvement in about two-thirds of patients.

Notably, immune involvement typically manifests as hyperglobulinemia, predominantly resulting from elevated immunoglobulin G (IgG) levels, B-cell subpopulation imbalance, high lymphoma incidence, and inflammatory cell infiltration in the salivary glands. Importantly, the increased content of plasma IgG has emerged as an important reference index for evaluating the disease activity of pSS. Therefore, dynamic monitoring of plasma IgG levels in patients with pSS is essential for strengthening the clinical management of pSS. Complement deficiency, mainly composed of C4 and C3 components, is common in autoimmune diseases, especially pSS. Low C4 levels in 24% (n=81) of 355 pSS patients undergoing examination (Ramos-Casals *et al*., 2005), 8% of pSS patients were found to have hypocompletemia (García-Carrasco *et al*., 2002). At present, there is a lack of effective treatment for pSS with hyperglobulinemia in modern clinical medicine. With At present, traditional Chinese medicine (TCM) has been widely used in clinic (Bailly, 2022; Wan *et al*., 2022). In this study, we analyzed the effect of the *Jiedu Tongluo Shengjin* formulation on plasma IgG levels in pSS by treating 89 patients with the *Jiedu Tongluo Shengjin* formulation granules combined with hydroxychloroquine, thus providing a new approach for the clinical treatment of pSS with hyperglobulinemia.

CLINICAL INFORMATION

General information

In this trial, we selected 89 patients with pSS from the outpatient clinics and wards of the Department of Rheumatology and Immunology of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, China, between July 2017 and February 2019. We assigned the patients to the treatment (45 cases) and control (44 cases) groups using the random number table method. During the treatment, one patient in the treatment group withdrew from the study due to being out of town and, hence, unable to take the experimental medication. In the final analysis, each group had 44 patients.

Patients in the treatment group consisted of 35 females and 9 males, aged between 20 and 69 years, with a mean age of 49.00 (35.00, 61.75) years and a mean disease course of (4.27 ± 2.12) years (the disease course ranged from 1 to 10 years). Patients in the control group comprised 38 females and 6 males, aged between 27 and 68 years, with a mean age of 50.50 (44.25, 62.50) years and a mean disease course of 4.00 (2.00, 5.00) years (the disease course ranged from 6 months to 10 years). There was no significant difference between the two groups in terms of gender, age, and disease course (p>0.05), suggesting that the two groups were comparable.

The study was approved by the Ethics Committee of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, China (Ethics No. 201607502).

Diagnostic criteria

Diagnostic criteria in Western medicine

Patients in both groups fulfilled the American College of Rheumatology classification (diagnostic) criteria for SS, revised in 2012 (Table No. 1) (Shiboski *et al*., 2012).

Criteria for disease differentiation and syndrome differentiation in TCM

We developed the TCM criteria for disease differentiation and syndrome differentiation of pSS by referring to the diagnostic criteria of SS and the syndrome differentiation standard of *yin* deficiency and dryness-heat syndrome in the *Guidelines for the Diagnosis and Treatment of Common Internal Diseases in Chinese Medicine, Diseases of Modern Medicine* (NATCM, 2008).

As per these criteria and standards, the primary symptoms of SS are as follows: ① dry mouth or intake of fluid failing to resolve thirst; ② dry eyes; and ③ fatigue. The secondary symptoms are: ① low fever; ② parotid gland enlargement; ③ flushing of the face; ④ dysphoria in the chest, palms-soles, insomnia, and dizziness; ⑤ dry cough, or phlegm that is viscous and difficult to cough up;

⑥ red tongue, thin and dry coating, or little coating, or no coating; and ⑦ thready rapid pulse. Patients can be diagnosed with SS if they have two or more of the primary symptoms and must include any one of ① or ②. Meanwhile, patients could be differentiated as having *yin* deficiency and dryness-heat syndrome based on tongue and pulse conditions if they had two or more of the secondary symptoms.

Table No. 1
The American College of Rheumatology classification (diagnostic) criteria for Sjögren's syndrome (SS), revised in 2012

SS can be diagnosed if 2 or more of the following 3 criteria are met:
1. The Sjögren's International Collaborative Clinical Alliance (SICCA) Ocular Staining Score (lissamine green staining) ≥ grade 3 (or equivalent)
2. Lip biopsy grades suggestive of focal lymphocytic sialadenitis and focus score (FS) ≥ 1
3. Positive anti-Ro (SS-A) or anti-La (SS-B) antibodies or positive rheumatoid factor and anti-nuclear antibody (ANA) ≥ 1:320
The following conditions must be excluded: history of radiotherapy to the neck, head and face, hepatitis C virus infection, AIDS, amyloidosis, tuberculosis, graft-versus-host disease, and IgG4-related disease.

Inclusion criteria

The inclusion criteria for patients were as follows: ① patients aged 18 to 70 years; ② patients whose Western medicine diagnosis met the American College of Rheumatology classification (diagnostic) criteria for SS, revised in 2012; ③ patients whose TCM diagnosis and differentiation matched the criteria of SS and *yin* deficiency and dryness-heat syndrome in the *Guidelines for the Diagnosis and Treatment of Common Internal Diseases in Chinese Medicine, Diseases of Modern Medicine* (NATCM, 2008); ④ patients not receiving immunosuppressants or TCM treatment for 8 weeks or more (baseline); ⑤ patients who voluntarily signed an informed consent form and were able to strictly comply with the requirements of the study protocol.

Exclusion criteria

Patients who fulfilled any of the following criteria were excluded from our trial: ① patients with other connective tissue diseases, drug-induced lupus-like syndrome, various infectious or contagious diseases, and psychiatric illnesses; ② patients with severe or unmanaged primary diseases, including cardiovascular, cerebrovascular, hepatic, renal, and hematological diseases; ③ patients with alanine aminotransferase or aspartate aminotransferase higher than two times of the upper limit of normal value or total bilirubin higher than the upper limit of normal value; ④ patients with contraindications to the use of related drugs, such as retinitis pigmentosa, heart block (PR interval ≥ 0.20 seconds and QRS interval ≥ 0.08 seconds), or severe peptic ulcer; ⑤ patients with allergies; ⑥ women preparing for pregnancy or pregnant or lactating women; ⑦ patients who were unwilling to participate in our study or unable to strictly comply with the requirements of the study protocol; ⑧ patients who were participating in other drug trials.

Withdrawal criteria

Patients could withdraw from our trial as per the following criteria: ① patients with poor compliance that affected the judgment of the results during the trial; ② patients who used drugs during the trial that significantly impacted the trial and affected the determination of effectiveness and safety; ③ patients who experienced serious adverse events, complications, and unusual physiological changes during the trial; ④ patients who had to discontinue the trial due to various reasons (such as terminating treatment due to other diseases, choosing to withdraw from the trial, moving out of the country, and loss to follow-up).

METHODS

Treatment methods

Patients in both groups received basic treatment consisting of hydroxychloroquine sulfate tablets (trade name: Plaquenil; Shanghai Zhongxi Sunve Pharma Co., Ltd., Shanghai, China; H19990263; 100

mg/14 tablets), 200 mg given orally each time, twice a day.

Patients in the treatment group additionally took *Jiedu Tongluo Shengjin* formulation granules (drug batch number: JS20140328, Jiangyin Tianjiang Pharmaceutical Co., LTD, Jiangsu, China) consisting of 30 g of *Hedyotis diffusa*, 15 g of *Curcuma zedoaria*, 30 g of *Paenoiae alba*, 30 g of *Astragalus membranaceus*, 9 g of *Angelica sinensis*, and 6 g of *Glycyrrhizae radix*. Granules of the *Jiedu Tongluo Shengjin* formulation were mixed with water (each sachet of the granules was dissolved in 200 mL of warm water) and administered twice a day.

Patients in the control group were additionally given a placebo of *Jiedu Tongluo Shengjin* formulation granules (drug batch number: JS20140328, Jiangyin Tianjiang Pharmaceutical Co., LTD, Jiangsu, China). The placebo contained 3 g of *Hedyotis diffusa*, 1.5 g of *Curcuma zedoaria*, 3 g of *Paenoiae alba*, 3 g of *Astragalus membranaceus*, 0.9 g of *Angelica sinensis*, and 0.6 g of *Glycyrrhizae radix*. The method of taking the medicine was the same as that of the treatment group.

The course of treatment was 12 weeks in both groups.

Observation indicators and methods

The primary observation indicator was changes in plasma IgG levels.

The secondary observation indicators were as follows:

① changes in plasma complement component 3 (C3)and complement component 4 (C4) levels;

② the objective indicators for dryness of the mouth and eyes, including salivary flow rate, tear flow rate, tear film break-up time, and so on;

③ erythrocyte sedimentation rate (ESR);

④ SS disease activity index, which was objectively scored using the European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI) (Seror *et al*., 2016). The total score was the sum of the scores multiplied by the corresponding weight values, that is, ESSDAI score = [score of item ① × weight index] + [score of item ② × weight index] (score of item N × weight index).

⑤ the TCM syndrome score was obtained using the Quantitative Scale for Grading TCM Symptoms of SS (Zheng, 2002). TCM symptoms or signs included dryness of the mouth, eyes, skin, and nasal cavity; fatigue; constipation; salivary gland swelling; fever; joint pain; appearing preoccupied and having insomnia; dizziness; emaciation; and tongue conditions. For calculating the total score of TCM symptoms and signs, the two symptoms of dry eyes and dry mouth and throat were classified under four grades: no, mild, moderate, and severe, with scores of 0, 2, 4, and 6, respectively; and the remaining symptoms or signs were categorized under four grades: no, mild, moderate, and severe, with scores of0, 1, 2, and 3, respectively. The total score was the sum of the scores for each part. ⑥ Safety indicators such as hepatic and renal function alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (sCr)], routine urine, andfecal occult blood tests.

A fasting venous blood sample of patients in both groups was drawn in the morning before and after treatment and centrifuged at 3500 r/min for 10 minutes to obtain serum. Then, the serum was stored in the refrigerator at -80℃ for testing. Immunological examinations of plasma IgG, C3, and C4 levels were conducted using the rate nephelometry method on the Siemens BN II automatic specific protein analyzer (Siemens AG, Munich, Germany). Additionally, IgG, C3, and C4 kits (153086A, 153346D, and 153540D) were used. Hepatic and renal function (ALT, AST, and sCr) tests were performed using the dry chemical method with multilayer films. The instrument used was an automatic dry biochemistry analyzer (VITROS-4600; Ortho Clinical Diagnostics, Rochester, New York, USA), and the used reagents were dry chemical reagent tablets for detecting ALT (20152402856), AST (20152402831), and sCr (20152400564). ESR was measured with a Monitor- 100 automatic dynamic blood sedimentation analyzer (Vital Company, Forli, Italy).

The urine sample was 10 mL of midstream urine collected in the morning before and after treatment, and the sample was centrifuged at 3500 r/min for 10 minutes to obtain the supernatant, which was then stored in the refrigerator at -80℃ for testing. The test was performed using the dry reagent chemistry method on an AVE-752 urine dry chemistry analyzer (AVE Science & Technology Co. Ltd., Changsha, China). The used kit was the test strip (20162400338) that was provided with the AVE-752.

Fecal samples were collected within 24

hours before and after treatment. The fecal occult blood test was performed using the immune colloidal gold technique. The instrument (the KU-F20 automatic stool analyzer) and kit [the kit that was provided with the KU-F20 (20162400258)] were manufactured by Zhuhai Keyu Biological Engineering Co., Ltd. (Zhuhai, China).

The salivary flow rate, tear flow rate, and tear film break-up time were assessed once in both groups before and after treatment. The Schirmer test was conducted with the tear detection filter strips (Tianjin Jingming New Technology Development Co., Ltd., Tianjin, China, 20172200301). The top, unscaled notch of the filter strip was folded at a right angle and clamped inside the conjunctival sac in the outer one- third of the lower eyelid. The other end of the filter strip was hung on the outside of the lower eyelid. The eyes of patients were gently closed while they maintained a slight upward gaze, and no blinking was allowed. The strip of filter paper was removed after 5 minutes, and the wet length of the filter strip was observed and recorded.

The tear film break-up time was measured with fluorescein sodium ophthalmic strips (20172200300), manufactured by Tianjin Jingming New Technology Development Co., Ltd. The procedure was as follows: 1% fluorescein sodium eyedrops were used for each eye. After blinking 2 to 3 times, patients were asked to open their eyes. The eyes were examined under the cobalt blue light of a slit lamp microscope (KJ50D). The tear film break-up time was calculated as the time from the opening of the eye after the last eye closure to the appearance of the first dry spot on the cornea and was measured three times to calculate the average value.

The salivary flow rate was measured using the drop method. Before the test, the patients were asked to rinse their mouths and fast for 10 minutes. A test tube with a funnel was used to collect saliva for 15 minutes and then left to stand for 5 minutes, after which the value was noted. Each step was performed strictly in accordance with the relevant operating procedures.

Statistical analysis

The obtained data were entered into the computer and tabulated. The database was created and statistically analyzed using SPSS 22.0 software. Measurement data were expressed as mean ± standard deviation if conforming to a normal distribution and as M (P25, P75) if not in a normal distribution. Measurement data were compared with the t-test if complying with a normal distribution; if otherwise, we used the Wilcoxon rank sum test (two-group comparisons) and the Wilcoxon signed rank sum test (before-and-after comparisons). Count data were analyzed using the chi-squared test or Fisher's exact probability method. A p value of < 0.05 was considered a statistically significant difference.

RESULTS

Changes in objective indicators for the dryness of the mouth and eyes before and after treatment

Pre-treatment, there was no significant difference between the two groups in terms of the objective indicators for the dryness of the mouth and eyes ($p>0.05$), and these were comparable between the two groups. Intragroup comparisons revealed that post-treatment, the three objective indicators, namely, tear film break-up time, tear flow rate, and salivary flow rate, significantly changed in the treatment group ($p<0.05$), but the change was not statistically significant in the control group ($p>0.05$). The differences in the three objective indicators post-treatment were statistically significant between the two groups ($p<0.05$) (Table No. 2, Figure No. 1).

Changes in the SS disease activity index and TCM syndrome score before and after treatment

The pre-treatment differences in the SS disease activity index and TCM syndrome score were not statistically significant between the two groups ($p>0.05$) and were comparable. There were statistically significant differences between the SS disease activity index and TCM syndrome score of the treatment group pre- and post-treatment ($p<0.05$), while in the control group, the SS disease activity index and TCM syndrome score pre- and post-treatment did not show any statistically significant difference ($p>0.05$). Post-treatment, the SS disease activity index and TCM syndrome score were significantly different between the treatment and control groups ($p<0.05$) (Table No. 3, Figure No. 2).

Changes in plasma IgG, C3, and C4 contents in the two groups before and after treatment

Pre-treatment levels of plasma IgG, C3, and C4 were not significantly different between the two groups ($p>0.05$) and were comparable. Intragroup

comparisons showed statistically significant differences between the pre- and post-treatment levels of plasma IgG, C3, and C4 in the treatment group (p<0.05), but the differences in plasma IgG, C3, and C4 levels in the control group pre- and post-treatment were not statistically significant (p>0.05). Post-treatment, the plasma IgG, C3, and C4 levels in the treatment group were significantly different from those in the control group (p<0.05) (Table No. 4, Figure No. 3 and Figure No. 4).

Table No. 2
Comparisons of tear film break-up time, tear flow rate, and salivary flow rate pre- and post-treatment in thetwo groups [M (P25, P75), n = 44]

Groups	Time	Tear film break-up time/s	Tear flow rate /mm·5 min^{-1}	Salivary flow rate /mL·15 min^{-1}
Treatment group	Pre-treatment	5.00(4.00,6.75)	3.00(2.00,4.00)	0.30(0.20,0.56)
	Post-treatment	10.00(7.00,13.00)** ##	5.00(4.00,6.00)** ##	1.50(0.40,1.60)** ##
Control group	Pre-treatment	5.00(4.00,6.00)	3.00(3.00,4.00)	0.50(0.30,0.70)
	Post-treatment	5.00(4.00,6.00)	3.00(2.25,4.00)	0.50(0.30,0.70)

Note: Intragroup comparisons: $Z_{tear\ film\ break\text{-}up\ time}$ = 5.121, **p<0.01; $Z_{tear\ flow\ rate}$ = 5.117, *p<0.01; $Z_{salivary\ flow\ rate}$ = 5.236, **p<0.01. Comparisons between the two groups: $Z_{tear\ film\ break\text{-}up\ time}$ = -5.459, ##p<0.01; $Z_{tear\ flow\ rate}$ = -5.150, ##p<0.01; $Z_{salivary\ flow\ rate}$ = -4.202, ##p<0.01

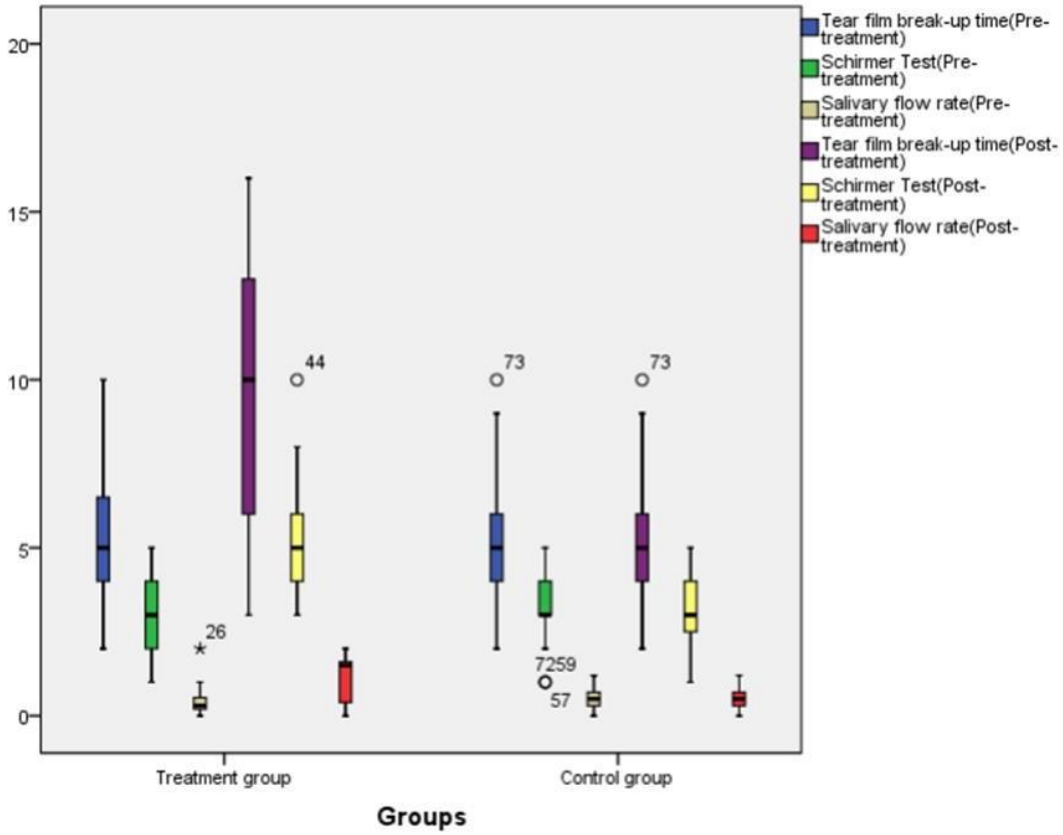

Figure No. 1
Comparisons of tear film break-up time, tear flow rate, and salivary flow rate pre- andpost-treatment in the two groups

Table No. 3
Comparisons of SS disease activity index and TCM syndrome score pre- and post-treatment in the two groups [M (P25, P75), n = 44]

Groups	Time	SS disease activity index	TCM syndrome score
Treatment group	Pre-treatment	5.00 (4.00,7.75)	18.00 (16.00,21.00)
	Post-treatment	1.50 (0.00,3.75)** ##	5.50 (4.00,14.00)** ##
Control group	Pre-treatment	5.00 (3.00,7.00)	17.00 (16.00,19.00)
	Post-treatment	5.00 (3.00,6.00)	17.00 (15.00,18.75)

Note: Intragroup comparisons: ZSS disease activity index = -5.301, **p<0.01; ZTCM syndrome score = -5.470, **p<0.01. Comparisons between the two groups: ZSS disease activity index = -4.788, ##p<0.01; Z TCM syndrome score = -6.450, ##p<0.01

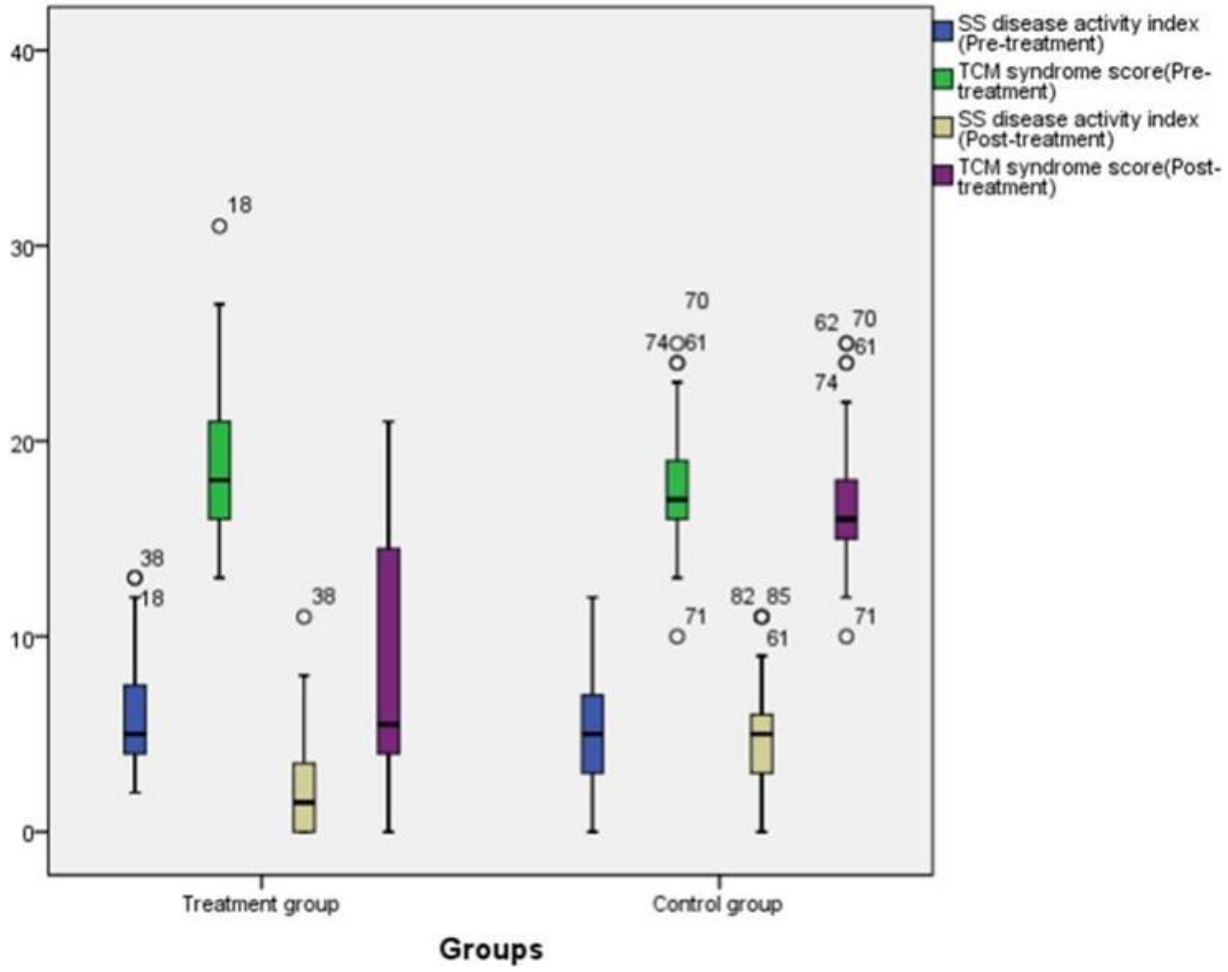

Figure No. 2
Comparisons of SS disease activity index and TCM syndrome score pre- andpost-treatment in the two groups

Table No. 4
Comparisons of plasma IgG, C3, and C4 levels pre- and post-treatmentin the two groups [M (P25, P75), n = 44, g·L^{-1}]

Groups	Time	IgG	C3	C4
Treatment group	Pre-treatment	16.25(12.60,19.13)	0.85(0.74,1.01)	0.18(0.16,0.25)
	Post-treatment	13.40(10.95,15.48)** ##	0.91(0.79,1.02)** ##	0.20(0.18,0.28)** ##
Control group	Pre-treatment	15.85(14.45,18.30)	0.85(0.76,0.98)	0.19(0.17,0.23)
	Post-treatment	15.70(13.90,18.03)	0.84(0.75,0.94)	0.19(0.17,0.22)

Note: Intragroup comparisons: Z_{IgG} = -3.606, **p<0.01; Z_{C3} = 2.567, **p<0.05; Z_{C4} = 2.420, **p<0.05 Comparisons between the two groups: Z_{IgG} = -3.351, ##p<0.01; Z_{C3} = -2.012, ##p<0.05; Z_{C4} = -2.091, ##p<0.05

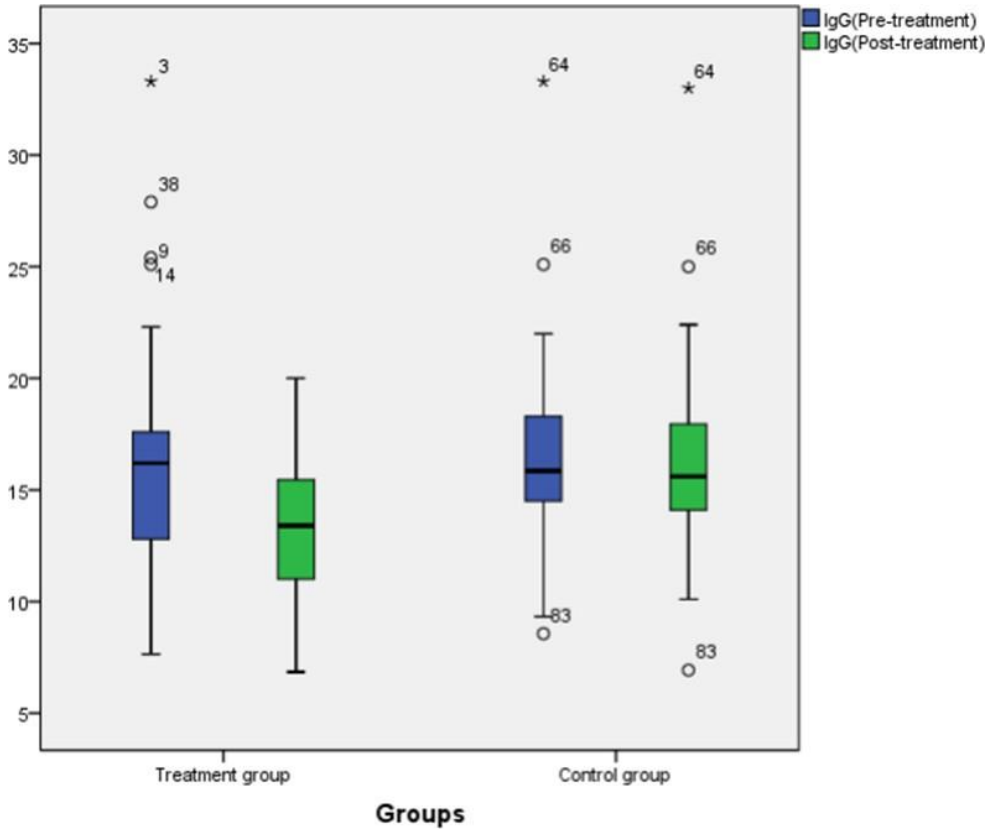

Figure No. 3
Comparisons of plasma IgG levels pre- and post-treatment in the two groups

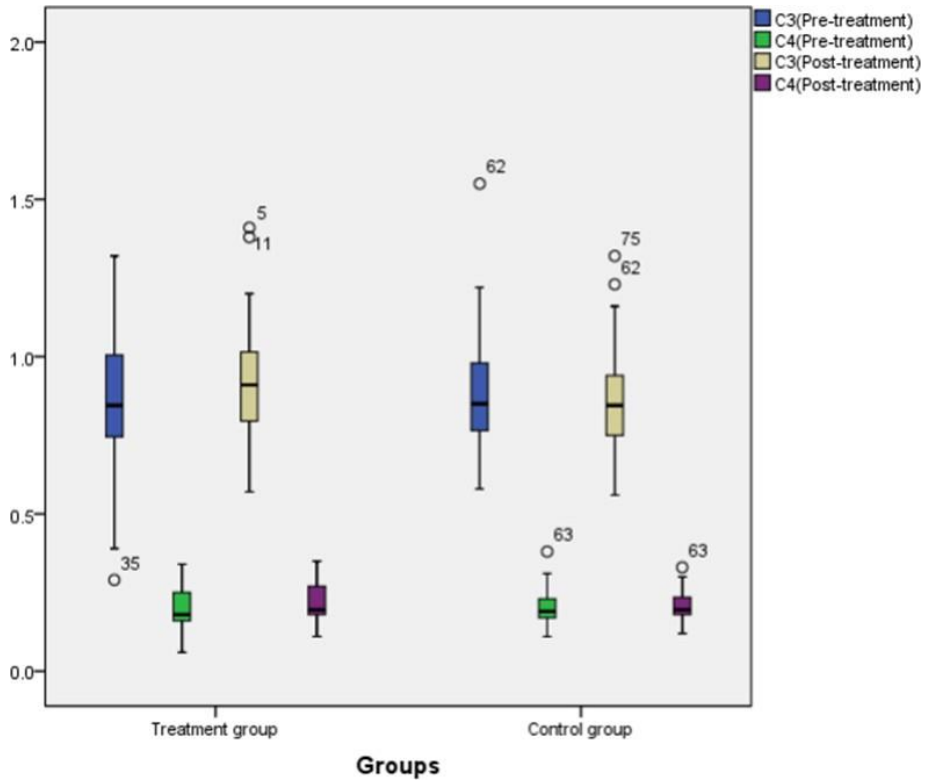

Figure No. 4
Comparisons of plasma C3 and C4 levels pre- and post-treatment in the two groups

Table No. 5
Comparison of plasma IgG levels pre- and post-treatment in the two groups of patients with high IgG [M(P25, P75), g·L^{-1}]

Groups	n	Pre-treatment	Post-treatment
Treatment group	24	17.60 (16.55,22.05)	14.50 (12.30,16.37)** ##
Control group	21	18.30 (16.90,20.45)	18.10 (16.30,19.80)

Note: Intragroup comparisons: Z_{IgG} = -3.743, **p<0.01. Comparisons between the two groups: Z_{IgG} = -3.471, ##p<0.01

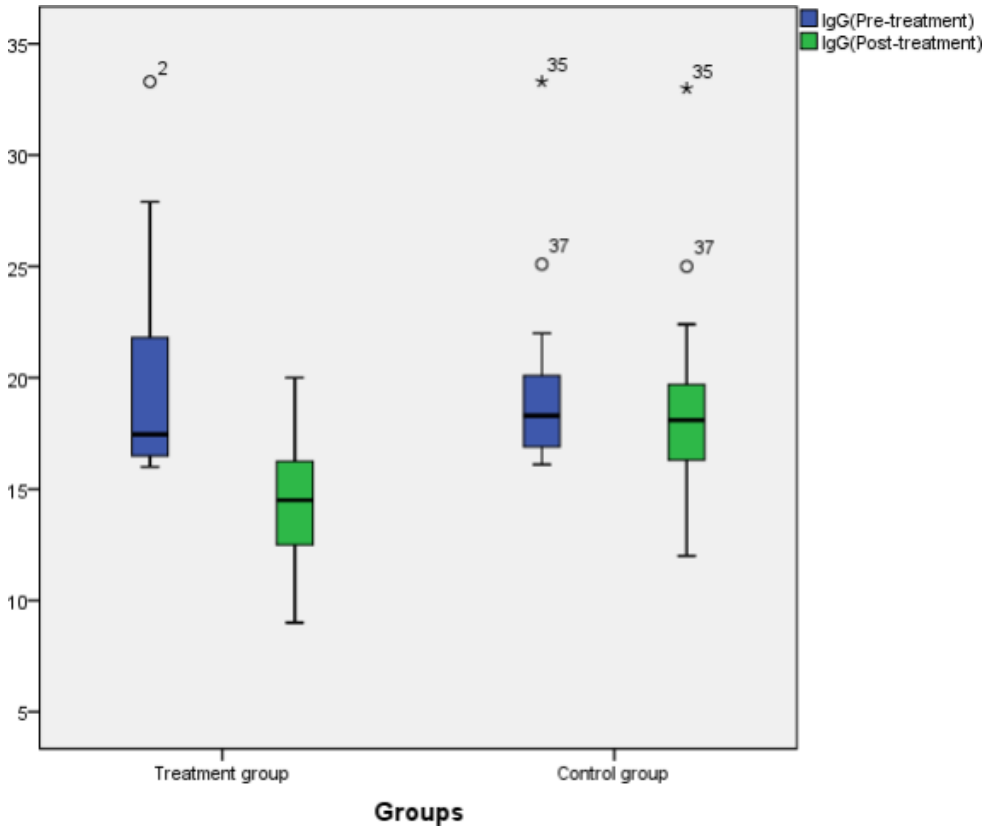

Figure No. 5
Comparison of plasma IgG levels pre- and post-treatment in the two groups of patients with high IgG

Changes in ESR before and after treatment

There was no statistically significant difference in terms of ESR before treatment between the two groups (p>0.05), and they were comparable. In the treatment group, post-treatment ESR was significantly different from the pre-treatment level (p<0.05), while in the control group, there was no significant difference in the pre- and post-treatment ESR levels (p>0.05). Compared to the control group, the post-treatment ESR was significantly different in the treatment group (p<0.05) (Table No. 6, Figure No. 6).

Table No. 6
Comparisons of ESR pre- and post-treatment in the two groups [M (P25, P75) n=44, mm·h^{-1}]

Groups	Pre-treatment	Post-treatment
Treatment group	36.00 (18.25,63.00)	25.50 (9.00,35.35)**$^{\#\#}$
Control group	36.00 (20.00,59.50)	33.00 (19.00,42.00)

Note: Intragroup comparisons: Z_{ESR} = -4.209, **p<0.01. Comparisons between the two groups: Z_{ESR} = -2.488, $^{\#\#}p$<0.05

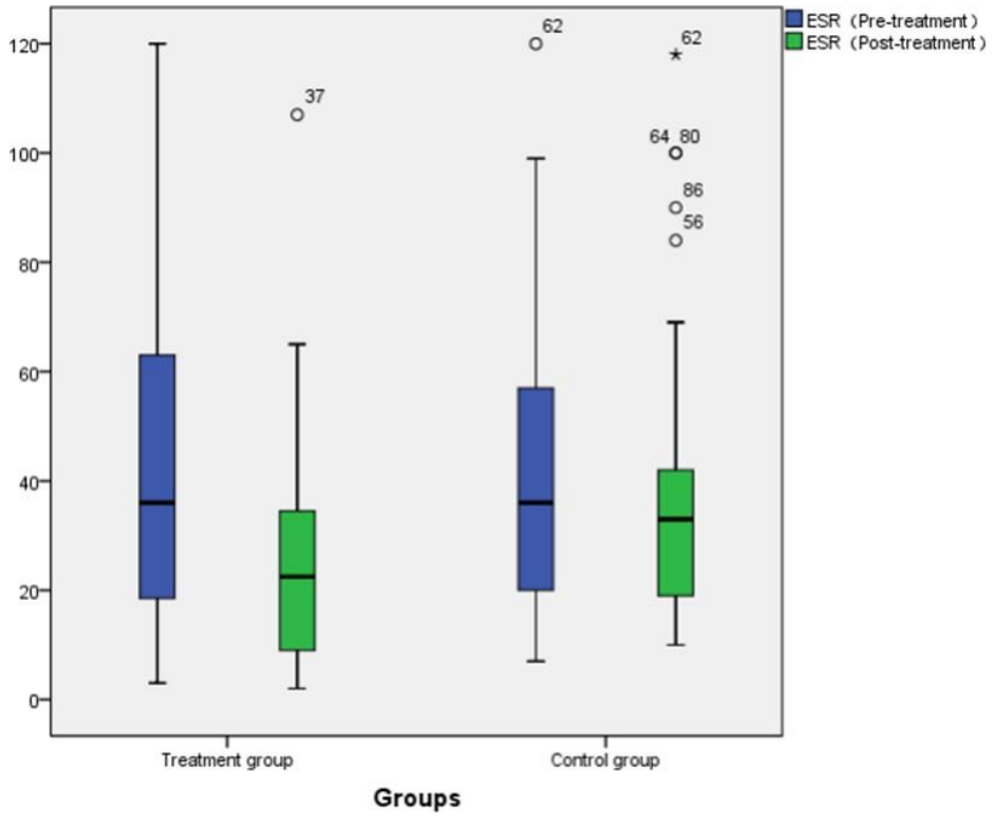

Figure No. 6
Comparisons of ESR pre- and post-treatment in the two groups

Safety indicators after treatment

There were no abnormalities in ALT, AST, sCr, routine urine test results, or fecal occult blood during treatment.

DISCUSSION

pSS is an autoimmune disease with an incidence rate second only to rheumatoid arthritis. Its pathogenesis is closely linked to B-cell overactivation induced by genetic inheritance (Peng *et al*., 2020), viral infection (Nakamura *et al*., 2020), hormone levels (Bruno *et al*., 2022), intrinsic immunity (Fasano *et al*., 2020; Nakamura *et al*., 2021; Zhu *et al*., 2021) and adaptive immunity (Pontarini *et al*., 2020; Thalayasingam *et al*., 2021; Manfre *et al*., 2022). Plasma IgG is one of the primary factors involved in humoral immunity and has been observed to be highly expressed in many diseases, particularly pSS. It is estimated that approximately 22% to 69% of patients with pSS show high IgG levels during the course of the disease (Sun, 2020). A retrospective study conducted by Sun et al. demonstrated that patients with pSS with hyper-IgG anemia showed more extensive extra-glandular involvement and immunologic abnormalities (Sun, 2020). In other words, the pathology of pSS was more complex (Baer *et al*., 2016; Ibrrahem, 2019; Szabo *et al*., 2021). Accordingly, dynamic monitoring of plasma IgG levels in patients with pSS is graduallybecoming an important component in improving the clinical management of pSS.

In TCM theory, pSS belongs to the category of "dry *bi*" (Lu & Jiao, 1996), with the basic pathogenesis of "*Yin* deficiency as the essential cause, dryness, stasis, toxicity, and depression as the symptoms" (Yueerlika *et al*., 2020). The key to its pathology lies in the internal invasion of dryness toxin, resulting in a simultaneous disorder of *qi* and blood, which manifests as unfavorable gasification of triple energizer, impaired body fluid generation or

dispersing in terms of *qi*, and as blood and essence deficiency and artery and vein stasis in terms of blood, inducing cementation of deficiency, stasis, and toxicity to cause diseases. Therefore, this condition is not comparable to a deficiency of *yin* fluid.

The *Jiedu Tongluo Shengjin* formulation is a special preparation for the treatment of SS created by Prof. Xue Luan of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. This is based on the therapeutic idea of the *Jiedu Tongluo Shengjin* method, which consists of six medicinal herbs, such as *Hedyotis diffusa*, *Curcuma zedoaria*, *Paenoiae alba*, *Astragalus membranaceus*, *Angelica sinensis*, and *Glycyrrhizae radix*. This formula integrates the three methods of "detoxifying, dredging collaterals, strengthening the body's resistance, and nourishing *yin*" and is mainly beneficial for patients with pSS with *yin* deficiency and dryness-heat syndrome.

In the formula, *Astragalus membranaceus* is used as the monarch drug to exert the effect of invigorating *qi* and strengthening the body resistance; *Angelica sinensis*, *Paeoniae radix*, and *Curcuma zedoaria* are the ministerial drugs, with *Hedyotis diffusa* as the adjuvant and *Glycyrrhizae radix* as the medicate. The synergy of *Glycyrrhizae radix* and *Astragalus membranaceus* in the formula assists healthy *qi* to expel pathogens from both the interior and exterior. *Glycyrrhizae radix* tonifies the *qi* of the spleen and stomach in the middle energizer, and *Astragalus membranaceus* solidifies defensive *qi*. Therefore, the combination of the two has the ability to maintain internal security and repel foreign invasions. *Glycyrrhizae radix* is combined with *Paeoniae radix* to nourish the *yin* with sour and sweet and with *Hedyotis diffusa* to eliminate pathogens and detoxify toxins.

This formula innovatively integrates the "Formation Theory of *Qi*, Blood, and Body Fluid", the "Theory of Toxin-Pathogen", and the "Collateral Disease Theory" to strengthen the body's resistance and eliminate pathogens simultaneously. Its capability of strengthening body resistance is better than its capability of eliminating pathogens. It specifically focuses on the spleen and stomach when strengthening body resistance, suggesting that a healthy spleen and stomach can lead to the orderly working of the body fluid chain. In addition to regulating immune status, *Astragalus membranaceus* in the prescription can improve the function of salivary gland secreting saliva and enhance the expression of Aquaporin5 (AQP5) by enhancing the release of water molecular channels in the submandibular gland, thereby expanding the filtration of water molecules in the submandibular gland and alleviating the symptoms of dry mouth. Total glucoside of Paeony, the main active ingredient in the prescription, is a dose-dependent bidirectional anti- inflammatory and immunomodulatory drug. By down-regulating TLR4/5, Fas/FasL, PD-1/PD-L1 signaling pathways, up-regulating the expression of AQP5 on glandular surface, inhibiting the proliferation of fibroblast-like synovial cells (FLS), increasing the level of cAMP, and decreasing the level of TNF-α, IL-6 and other inflammatory factors, it can play an anti-inflammatory role, improve glandular secretion, relieve joint and intestinal symptoms, etc The role of; Modern pharmacological studies have also confirmed that it has a wide range of immunomodulatory and anti-inflammatory effects.

We found that compared with the control group, the treatment group showed statistically significant improvement in the objective indicators for dryness of the mouth and eyes, SS disease activity index, TCM syndrome score, plasma C3 and C4 levels, and ESR after 12 weeks of treatment, and the plasma IgG level was significantly reduced and gradually reached the normal range (≥ 6 to ≤ 16 g/L) ($p<0.05$). The treatment method was also therapeutically effective in the treatment group for patients with comorbid hyperglobulinemia, with a statistically significant difference ($p<0.05$). There was no significant liver or kidney damage, positive fecal occult blood, or abnormal routine urine test results during the course of treatment.

Our study findings confirmed that the objective evaluation indexes for dryness of the mouth and eyes in pSS, namely, salivary flow rate, tear flow rate, and tear film break-up time, significantly improved in patients with pSS after treatment with the *Jiedu Tongluo Shengjin* formulation, indicating that the *Jiedu Tongluo Shengjin* formulation was effective in improving the subjective symptoms of dry mouth and dry eyes as well as the objective indexes for dryness of the mouth and eyes. This effect of this formula may be related to its role in inhibiting lymphocyte infiltration in the submaxillary glands, protecting the gland cells, upregulating AQP5 expression in salivary gland acinar, and ameliorating histopathological damage (Lu & Jiao, 1996).

The SS disease activity index is a comprehensive reference for assessing the disease activity of pSS. In our study, we found that the *Jiedu Tongluo Shengjin* formulation significantly reduced these index scores, illustrating that the *Jiedu Tongluo Shengjin* formulation was beneficial in controlling disease activity, slowing down disease progression, and improving prognosis.

The TCM syndrome score is one of the important quantitative indexes in TCM syndromes. Inthe present study, we found that the *Jiedu Tongluo Shengjin* formulation effectively decreased the TCM syndrome score of patients with pSS, highlighting that this formula could improve the subjective and objective symptoms of patients.

ESR is a typical indicator of the acute inflammatory phase and reflects the level of inflammatory activity within the body. In our study, we confirmed that the *Jiedu Tongluo Shengjin* formulation substantially lowered ESR in patients with pSS, indicating that the *Jiedu Tongluo Shengjin* formulation could decrease ESR by inhibiting inflammatory responses in patients with pSS. It is speculated that this effect may be related to the anti-inflammatory effect of alkaloids contained in Radix Paeoniae, Radix Hydnoglossa and glycyrrhiza, and may also be related to the up-regulation of Foxp3 + Treg expression and the decrease of p-PI3K, p-AKT, IL-2 and TNF-α secretion (Li *et al*., 2019). However, this specific mechanism requires further in-depth investigation.

C3, C4, and IgG are used as critical referenceindexes for evaluating the immune status of patients with pSS. Notably, a previous clinical trial found that the effect of lowering plasma IgG levels using a combination of the *Jiedu Tongluo Shengjin* formulation and hydroxychloroquine was comparable to a combination of hydroxychloroquine and prednisone (Hou *et al*., 2016). The present study demonstrated that the *Jiedu Tongluo Shengjin* formulation significantly elevated plasma C3 and C4 levels and decreased plasma IgG contents in patients with pSS. Significantly, patients with hyperglobulinemia also showed the obvious effect of the *Jiedu Tongluo Shengjin* formulation on decreasing plasma IgG levels. These results demonstrate that the *Jiedu Tongluo Shengjin* formulation could play an immunomodulatory role by elevating the levels of C3 and C4 and decreasing plasma IgG levels. It is speculated that this effect may be related to the many alkaloid components contained in medicines such as Astragalus membranaceus, Paeonia lactiflora, Hedyotis diffusa, and licorice in the formula, which have effects on immune regulation and anti- inflammatory effects. At the same time, it may also be related to a series of processes in our formula, such as upregulating Foxp3+Treg and downregulating IL-2 expression, which affect the proliferation and activation of T and B cells, as well as the transition from B cells to plasma cells (Li *et al*., 2019). However, the specific pathway of action needs to be further explored.

CONCLUSIONS

In conclusion, we found that the *Jiedu Tongluo Shengjin* formulation was effective in alleviating dryness of the mouth and eyes and reducing the disease activity index in patients with pSS with a high safety profile through the improvement of inflammation levels and immune status. However, the sample size of this study was small, and the follow- up period was limited. Accordingly, further studies with a large sample size and a prolonged follow-up period are warranted to further validate the therapeutic effect of the *Jiedu Tongluo Shengjin* formulation on patients with pSS. Our preliminary findings lay the foundation for further in-depth research on the specific pathways and mechanisms by which the *Jiedu Tongluo Shengjin* formulation is effective in lowering plasma IgG concentrations in patients with pSS.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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