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Efficacy and safety of total glucosides of paeony in treating primary Sjögren's syndrome: a propensity-matched study

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Abstract. – OBJECTIVE: This study aimed to evaluate the efficacy and safety of total glucosides of paeony (TGP) in patients with primary Sjögren's syndrome (pSS).

PATIENTS AND METHODS: This study included 236 patients with pSS, including 118 TGP users and 118 non-users. Propensity score matching and Binary logistic regression analyses were used to minimize confounding factors and determine the association between TGP treatment and clinical variables.

RESULTS: The baseline indexes of TGP users and non-users were basically the same. The median time of follow-up in the two groups was also similar ($p < 0.05$). Compared with non-users, TGP users showed higher rates of improvement in dry mouth and eyes and musculoskeletal involvement, as well as more significant reductions in serum alanine aminotransferase (ALT) and direct bilirubin (DBIL) levels after treatment. Logistic regression confirmed that the use of TGP was negatively correlated with the increase of ALT and DBIL in pSS patients, and the reduction in these variables was more pronounced after 2 years of treatment. The incidence of adverse reactions in the TGP users was 11.9%, which was compatible with those in non-users.

CONCLUSIONS: TGP is often a safe option for treating pSS patients with musculoskeletal features and abnormal ALT levels. Besides, it can help improve dry mouth and dry eyes and decrease DBIL levels.

Key Words:
Primary Sjögren's syndrome, Total glucosides of paeony, Dry mouth, Direct bilirubin.

Introduction

Primary Sjögren's syndrome (pSS) is a heterogeneous autoimmune disease with the disease spectrum extending from sicca syndrome to systemic involvement[1]. The estimated prevalence of pSS is 0.60%, with a female prevalence of 20:1[2,3]. Patients with pSS may experience a wide range of symptoms, including glandular enlargement, sicca symptoms, disabling fatigue, arthritis, skin involvement, renal and lung involvement[4]. Among these, liver involvement is one of the first reported[5] extra glandular manifestations, and 7% of the patients had been reported[6] to have elevated liver enzymes. Although pSS has a significant impact on health-related quality of life and socioeconomic status, there is a relative shortage of treatments specifically for this condition[7,8]. Commonly used immunomodulatory agents, including hydroxyl-chloroquine, prednisone, methotrexate, mycophenolate sodium, and azathioprine, often fail to improve functional parameters of salivary and lacrimal glands in clinical trials[9-12] of SS.

The total glucosides of paeony (TGP) is a glycoside compound extracted from the root of peony, which has anti-inflammatory and immunomodulatory effects[13,14]. Studies[15-17] have shown that TGP can significantly improve the pathological damage of submandibular glands in NOD mice, and its therapeutic mechanisms include regulating the Programmed Cell Death 1 (PD-1)/Programmed Cell Death Ligand 1 (PD-L1) pathway, inhibiting the inflammatory response, and improving intestinal microecological structure[18-20]. In human pSS patients, two randomized trials[21,22] have confirmed the effectiveness of TGP, yet there is still controversy about which symptom could achieve the best therapeutic effect. In this study, we systematically analyzed the efficacy and safety of TGP in pSS patients by using propensity-matched samples, focusing on the variation in disease activity and improvement of specific variables.

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Patients and Methods

Research Design

This was a retrospective study to evaluate the clinical outcomes of TGP users *vs.* non-users in the treatment of pSS. The study protocol was approved by the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School (2023-209). This study was conducted in accordance with pertinent guidelines and regulations. As shown in Figure 1, totally the documents of 1,903 pSS patients admitted to the Department of Rheumatology and Immunology at Nanjing Drum Tower Hospital from January 1, 2016, to December 31, 2021, were reviewed. All patients met the 2016 American College of Rheumatology/European League Against Rheumatism primary classification criteria for Sjögren's syndrome[23]. Disease activity was assessed by the EULAR Sjögren's syndrome disease activity index (ESSDAI)[24]. Patients were followed up by the end of August 2022. Those with no follow-up information or incomplete variables, with a follow-up interval of less than 3 months, and patients over 80 years old have been excluded. To reduce the effect of confounding factors, a propensity score matching (PSM) method was performed, and a caliper equal to 0.05 was used to conduct the PSM with a 1:1 ratio[25]. The control group was obtained by considering age (continuous), gender (male = 1, female = 0), and ESSDAI score (continuous). Finally, 118 TGP users and 118 non-users were included.

Data Collection and Definition

Demographic data, diagnostic information, medical history, organ involvement, laboratory tests, concomitant medication, dosage of TGP, and adverse events related to TGP were collected from patients' medical records. Information after treatment was collected from the healthcare system or

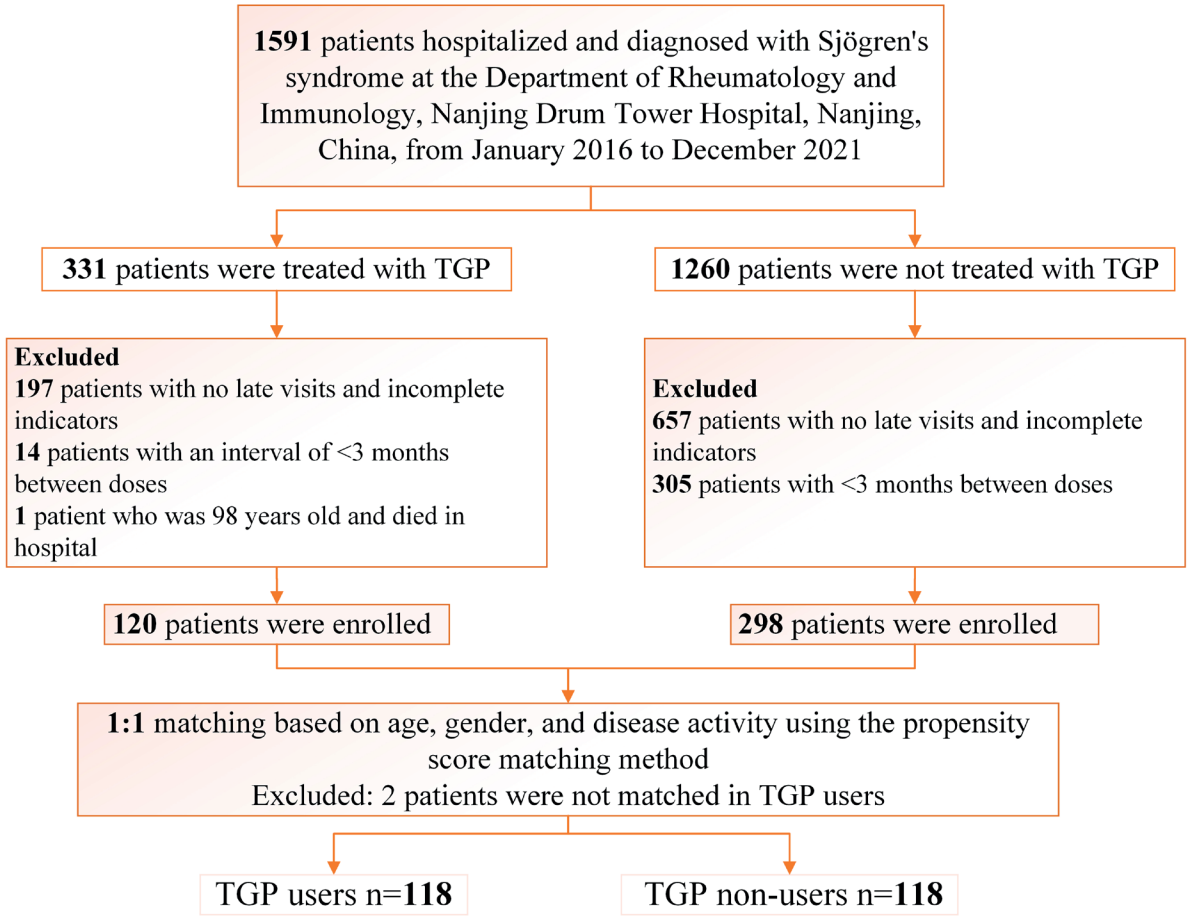

Figure 1. Flow chart of patient's recruitment.

by telephone follow-up. Detailed entries of organ involvement were listed in **Supplementary Table I**. Dry mouth and dry eyes are mainly judged on the basis of the patient's subjective feeling[26]. The range of normal values for routine laboratory results were as follows: white blood cells (WBC) 3.5-9.5×10^9/L, red blood cells (RBC) 3.8-5.1×10^{12}/L, platelet (PLT) 125-350×10^9/L, erythrocyte sedimentation rate (ESR) < 20 mm/h, C-reactive protein (CRP) 0-8 mg/L, alanine aminotransferase (ALT) 5-40 u/L, aspartate aminotransferase (AST) 8-40 u/L, albumin (ALB) 40-55 g/L, globulin (GLB) 20-40 g/L, direct bilirubin (DBIL) 1.7-6.8 umol/L, total bilirubin (TBIL) 5-20.5 umol/L, Serum creatinine 44-106 mmol, Uric acid 90-420 μmol/L, Complement C3 0.8-1.6 g/L, Complement C4 0.2-0.4 g/L, immunoglobulin (Ig) G 0-16 g/L, IgM 0.5-2.2 g/L, IgA 0.7-3.3 g/L, IgE 0-100 g/L.

Statistical Analysis

All calculations were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distributions were presented as mean ± standard deviation (SD), whereas non-normally distributed continuous variables were presented as median and interquartile range (IQR), and categorical variables were presented as frequency and percentage. To compare variables between two groups, the Student's *t*-test or the Wilcoxon rank sum test was used for continuous variables, and the Chi-square test or Fisher's exact test was used for categorical variables. A binary logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the association between TGP treatment and elevated ALT or DBIL, adjusted for potential confounders in the multivariate analysis model. $p < 0.05$ was considered statistically significant.

Results

Characteristics of the Patients

The baseline characteristics of our pSS patients are shown in Table I. The median age of TGP users was 54.0 (47.0, 62.0), the same as that of non-users ($p > 0.05$). Similarly, there was no significant difference in gender ratio and ESSDAI score between the two groups. After matching, almost all of the variables in the two groups were at the same level at baseline, except that TGP users had more musculoskeletal involvement ($p = 0.006$), fewer hematological involvement ($p = 0.001$) and higher ALT levels ($p = 0.02$). Importantly, there was no significant difference in the treatment medication between the two groups (including glucocorticoids, hydroxychloroquine, other immune-suppressants and liver protective drugs), except for TGP.

Improvement in Symptoms after TGP Treatment

Most of the patients were given a starting TGP dose of 1.2 g/day (101 patients), with the remainder at 0.6 g/day (6 patients) or 1.8 g/day (11 patients). By the time of follow-up, a total of 112 patients had achieved a maintenance dose of 1.2-1.8 g/day. The changes in variables after treatment compared to baseline were shown in Table II. There was no difference between the two groups in the follow-up interval (17 months *vs.* 20 months, $p > 0.05$), and the changes in ESSDAI scores between the two groups were similar after respective treatments. However, compared to non-users, TGP treatment more effectively relieved dryness-related symptoms, including rate of change in dry mouth (38.1% *vs.* 17.8%, $p < 0.05$) and dry eye (33.9% *vs.* 20.3%, $p < 0.05$), and musculoskeletal involvement (28.0% *vs.* 12.7%, $p < 0.05$). It was noteworthy that two patients in the TGP group resumed medication after shortly stopping it on their own during the follow-up period because both felt significantly worse in terms of dry mouth after the interruption of medication.

TGP Contributed to the Reduction of ALT in pSS Patients

As shown in Table II, the decrease in ALT and DBIL levels was more pronounced in the TGP group. For ALT, the median change was -3.0 for TGP users and -1.0 for non-users ($p = 0.017$), while for DBIL, the median change was -1.0 for TGP users and 0.0 for non-users ($p < 0.001$). To further clarify the relationship between TGP use and ALT decrease in patients with pSS, baseline key factors and those with significant changes after treatment were adjusted through logistic regression. The results showed that TGP application was inversely associated with ALT elevation compared with non-users, with an adjusted OR (95% CI) of 0.42 (0.21, 0.84) (Table III). In addition, the duration of TGP use also had an implication on its efficacy, as those who used TGP over two years had lower chances of ALT elevation, with an adjusted OR (95% CI) of 0.33 (0.14, 0.75).

Table I. Baseline characteristics of patients with pSS.

Variable	TGP users (n = 118)	Non-users (n = 118)	p
Age, years	54.0 (47.0, 62.0)	54.0 (46.8, 62.3)	0.896
Gender (female)	113.0 (95.8%)	112.0 (94.9%)	0.757
ESSDAI score	2.0 (1.0, 4.0)	2.5 (2.0, 4.0)	0.668
Follow-up interval, months	17.0 (7.0, 37.5)	20.0 (8.8, 39.3)	0.391
Time since diagnosis, years	3.0 (1.0, 9.0)	3.0 (0.0, 9.0)	0.552
Comorbidities			
Diabetes	6.0 (5.1%)	8.0 (6.8%)	0.582
Hypertension	25.0 (21.2%)	26.0 (22.0%)	0.874
Dryness-related symptoms			
Fatigue	36.0 (30.5%)	27.0 (22.8%)	0.185
Dry mouth	98.0 (83.1%)	88.0 (74.6%)	0.111
Dry eyes	76.0 (54.2%)	63.0 (53.4%)	0.085
Dental caries	16.0 (13.6%)	14.0 (11.9%)	0.696
Parotid swelling	3.0 (2.5%)	4.0 (3.4%)	1.000
Organ involvement			
Musculoskeletal	64.0 (54.2%)	43.0 (36.4%)	**0.006**
Mucocutaneous	25.0 (21.2%)	18.0 (15.3%)	0.238
Hepatobiliary	48.0 (40.7%)	46.0 (39.0%)	0.790
Gastrointestinal	33.0 (28.0%)	31.0 (26.3%)	0.770
Respiratory	42.0 (36.6%)	51.0 (43.2%)	0.231
Cardiovascular	17.0 (14.4%)	22.0 (18.6%)	0.381
Neuropsychiatric	16.0 (13.6%)	9.0 (7.63%)	0.139
Renal	22.0 (18.6%)	23.0 (19.5%)	0.868
Hematological	15.0 (12.7%)	36.0 (30.5%)	**0.001**
Routine laboratory results			
WBC (10^9/L)	5.0 (3.9, 6.4)	4.7 (3.6, 6.4)	0.539
RBC (10^{12}/L)	4.1 (3.8, 4.3)	4.03 (3.6, 4.4)	0.723
PLT (10^9/L)	199.0 (148.8, 236.3)	177.0 (136.0, 234.0)	0.109
ESR (mm/h)	21.0 (10.0, 45.0)	23.0 (11.0, 45.0)	0.712
CRP (mg/L)	3.7 (2.5, 5.2)	4.2 (2.6, 10)	0.161
ALT, u/L	22.0 (16.1, 34.6)	18.4 (12.3, 30.0)	**0.019**
AST, u/L	25.2 (17.4, 34.0)	23.0 (17.5, 33.0)	0.250
ALB, g/L	39.7 (37.0, 41.5)	38.5 (35.9, 41.3)	0.245
GLB, g/L	29.8 (24.8, 35.9)	29.8 (24.7, 39.3)	0.557
DBIL, umol/L	2.2 (1.6, 3.6)	2.3 (1.7, 3.6)	0.326
TBIL, umol/L	9.1 (6.8, 12.4)	8.3 (6.1, 11.2)	0.277
Serum creatinine, mmol	50.0 (44.0, 57.0)	53.0 (44.8, 59.3)	0.212
Uric acid, μmol/L	272.0 (229.0, 318.0)	284.5 (213.8, 343.5)	0.526
Immunological factors			
Positive-SSA	42.0 (35.6%)	47.0 (39.7%)	0.502
Positive-SSB	18.0 (15.3%)	24.0 (20.3%)	0.307
Positive-Ro-52	46.0 (40.0%)	58.0 (49.2%)	0.116
Complement C3, g/L	1.0 (0.9 ,1.2)	1.0 (0.9, 1.2)	0.416
Complement C4, g/L	0.2 (0.2, 0.3)	0.2 (0.1, 0.3)	0.598
IgG, g/L	14.2 (11.9, 18.8)	14.8 (12.1, 18.5)	0.712
IgM, g/L	1.2 (0.8, 1.7)	1.2 (0.7, 1.7)	0.867
IgA, g/L	2.4 (1.8, 3.2)	2.5 (1.8, 3.6)	0.744
IgE, g/L	81.0 (37.0, 167.5)	90.0 (48.8, 181.0)	0.388
Concomitant medication			
Glucocorticoids	73.0 (61.9%)	76.0 (64.4%)	0.686
Hydroxychloroquine	80.0 (67.8%)	73.0 (61.9%)	0.340
Other immunosuppressants[+]	64.0 (54.2%)	71 (60.2%)	0.357
Liver protective drugs	30.0 (25.4%)	20 (17.0%)	0.111

Data were shown as number (percentages) or median (IQR). $p < 0.05$ was represented in bold. ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index, WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, DBIL: direct bilirubin, TBIL: total bilirubin, TP: total protein, ALB: albumin, GLB: globulin, Ig: immunoglobulin.

[+]including cyclophosphamide, leflunomide, azathioprine, methotrexate, mycophenolate mofetil, *tripterygium wilfordii* and tacrolimus.

Table II. Changes in variables between TGP users and non-users.

Variable	TGP users (n = 118)	Non-users (n = 118)	p
TGP dose, g/day	1.2 (1.2, 1.2)	——	——
ESSDAI score	0.0 (-1.0, 1.0)	0.0 (-1.0, 1.0)	0.923
Dryness-related symptoms			
Dry mouth	45.0 (38.1%)	21.0 (17.8%)	**0.001**
Dry eye	40.0 (33.9%)	24.0 (20.3%)	**0.019**
Parotid swelling	3.0 (2.5%)	2.0 (1.7%)	1.000
Organ involvement			
Musculoskeletal	33.0 (28.0%)	15.0 (12.7%)	**0.004**
Mucocutaneous	9.0 (7.6%)	9.0 (7.6%)	1.000
Gastrointestinal	13.0 (11.02%)	16.0 (13.6%)	0.552
Respiratory	10.0 (8.5%)	13.0 (11.0%)	0.510
Cardiovascular	4.0 (3.4%)	2.0 (1.7%)	0.683
Renal	10.0 (8.5%)	9.0 (7.6%)	0.811
Hematological	9.0 (7.6%)	16 (13.6%)	0.204
Routine laboratory results			
WBC (10^9/L)	-0.1 (-0.9, 1)	0.2 (-0.8, 1.6)	0.155
RBC (10^{12}/L)	-0.1 (-0.9, 1.0)	0.2 (-0.8, 1.6)	0.155
PLT (10^9/L)	-7.0 (-47.8, 20.0)	-0.5 (-37.8, 31.5)	0.204
ESR, (mm/h)	-4.5 (-20.0, 4.0)	-1.0 (-16.0, 8.0)	0.212
CRP, (mg/L)	-0.7 (-2.8, 1.3)	-0.3 (-3.8, 2.5)	0.570
ALT, u/L	-3.0 (-14.1, 3.5)	-1.0 (-9.1, 8.7)	**0.017**
AST, u/L	0.1 (-8.1, 7.6)	1.7 (-7.1, 8.1)	0.346
ALB, g/L	1.6 (-0.7, 4.2)	1.9 (-1.3, 5.4)	0.879
GLB, g/L	-0.3 (-4, 4.5)	0.0 (-3.3, 4.2)	0.866
DBIL, umol/L	-1.0 (-1.8, 0)	0.0 (-0.9, 0.48)	**< 0.001**
TBIL, umol/L	0.0 (-2.3, 3.0)	1.6 (-1.1, 4.2)	**0.021**
Serum creatinine, mmol	4.0 (-1.6, 11.0)	4.0 (-2.0,10.0)	0.627
Uric acid, μmol/L	4.5 (-57.5, 39.5)	8.0 (-29.0,47.0)	0.639
Immunological factors			
Complemen C3, g/L	0.0 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0.419
Complemen C4, g/L	0.0 (-0.0, 0.0)	0.0 (-0.0, 0.1)	0.663
IgG, g/L	-0.4 (-2.6, 1.2)	-0.6 (-4.4, 1.0)	0.482
IgM, g/L	-0.1 (-0.3, 0.1)	-0.1 (-0.4, 0.1)	0.745
IgA, g/L	-0.1 (-0.4, 0.1)	-0.2 (-0.7, 0.2)	0.457
IgE, g/L	-23.0 (-65.8, 2.8)	-40.0 (-87.4, 1.5)	0.317

Data were shown as number (percentages) or median (IQR). $p < 0.05$ was represented in bold. The change in variables was equal to the value after treatment minus the value at baseline. ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index, WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, DBIL: direct bilirubin, TBIL: total bilirubin, TP: total protein, ALB: albumin, GLB: globulin, Ig: immunoglobulin.

Table III. Adjustment for the changes of ALT after TGP use in patients with pSS.

Variable	Change > 0 N = 93	Change < 0 N = 143	OR (95% CI)	Adjusted OR (95% CI)+	Adjusted OR (95% CI)++
TGP use					
No	55.0 (59.1%)	63.0 (44.1%)	1.00	1.00	1.00
Yes	38.0 (40.9%)	80.0 (55.9%)	0.54 (0.32, 0.92)	0.51 (0.29, 0.91)	0.42 (0.21, 0.84)
p			0.024	0.021	0.014
Duration with TGP/years					
No	55.0 (59.1%)	63.0 (44.1%)	1.00	1.00	1.00
< 2	19.0 (20.4%)	31.0 (21.7%)	0.70 (0.36, 1.38)	0.73 (0.36, 1.50)	0.57 (0.23, 1.39)
≥ 2	19.0 (20.4%)	49.0 (34.3%)	0.44 (0.23, 0.84)	0.37(0.18, 0.76)	0.33 (0.14, 0.75)
p			0.044	0.024	0.029

+Adjusted for baseline key factors including disease duration (continuous), history of the hepatobiliary disease (yes = 1, no = 0), use of liver protective drugs (yes = 1, no = 0), glucocorticoids (yes = 1, no = 0), other immunosuppressants (yes = 1, no = 0), hydroxychloroquine (yes = 1, no = 0), musculoskeletal (yes = 1, no = 0) and hematological involvement (yes = 1, no = 0).
++Adjusted for both baseline key factors (see above) and those with significant changes after treatment, including improved dry mouth (yes = 1, no = 0), improved dry eye (yes = 1, no = 0), improved musculoskeletal (yes = 1, no = 0) and change of DBIL (continuous).

TGP Contributed to the Reduction of DBIL in pSS Patients

59 patients had elevated DBIL levels after the treatment, and the proportion was quite higher in non-users (42.7%) than TGP users (20.2%, $p = 0.001$). Similarly, we performed logistic regression to adjust baseline key factors and those with significant changes after treatment. Consistently, TGP use was negatively associated with elevated DBIL in pSS patients, with an adjusted OR (95% CI) of 0.32 (0.15, 0.67). Those used for over two years had a low chance of DBIL elevation, with an adjusted OR (95% CI) of 0.15 (0.05, 0.41) (Table IV).

Adverse Reactions

History recorded adverse events between TGP and non-TGP groups during the observation period are shown in Table V. Diarrhea was the most common adverse event after TGP use and occurred in 8 TGP users and 2 non-users, but there was no significant difference between the two groups. For the 8 TGP users, only 2 discontinued the drug, 3 received no special treatment, and 3 improved after reducing the dose. Other adverse events, such as upset stomach, were relatively rare and often mild. Both groups had no deaths or serious adverse events related to treatment.

Discussion

It is now increasingly recognized that the efficacy of drugs in well-designed randomized controlled studies is often different from that in the real world, and this may be particularly true for TGP, derived from the dried root of *paeonia lactiflora* pall and used as a moderately acting drug for the treatment of rheumatic diseases. In this study, we evaluated the efficacy and safety of TGP in pSS patients by using a propensity-matched cohort, and the results showed that TGP had a good safety profile. This drug not only helped to relieve musculoskeletal symptoms but was also effective for dryness-related symptoms, including dry mouth and dry eyes. Meanwhile, among the liver function-related indexes, both ALT and DBIL significantly improved in the TGP treatment group.

Currently, there is still a lack of therapies specifically approved for pSS. TGP, a Chinese patent medicine used to improve joint pain, has been used to treat pSS in China after being proven effective in several randomized controlled studies in the literature. Our data indicated that TGP improved dry mouth and dry eyes in patients with pSS. Consistently, an increase in salivary flow after TGP treatment has been reported[22], especially in patients with mild glandular damage, while mouth and skin dryness symptoms also had a tendency of improvement[21]. A meta-analysis[27] suggested that the combination of TGP and hydroxychloroquine may be more beneficial in improving lacrimal secretion, whereas the combination with methotrexate may not be beneficial or may have antagonistic effects. Supportively, animal experiments[19] showed that TGP administration reduced the degree of lymphocyte infiltration and acinar structure destruction in NOD mice, and also had an early and direct effect on secretion-related molecules such as aquaporins in the salivary glands[17].

Table IV. Adjustment for the changes of DBIL after TGP use in patients with pSS.

Variable	Change > 0 N = 59	Change < 0 N = 126	OR (95% CI)	Adjusted OR (95% CI)+	Adjusted OR (95% CI)++
TGP use					
No	41.0 (69.5%)	55.0 (43.7%)	1.00	1.00	1.00
Yes	18.0 (30.5%)	71.0 (56.3%)	0.34 (0.18, 0.66)	0.36 (0.18, 0.73)	0.32 (0.15, 0.67)
p			0.001	0.004	0.003
Duration with TGP/years					
No	41.0 (69.5%)	55.0 (43.7%)	1.00	1.00	1.00
< 2	12.0 (20.3%)	23.0 (18.3%)	0.70 (0.31, 1.57)	0.80 (0.33, 1.90)	0.75 (0.30, 1.89)
≥ 2	6.0 (10.2%)	48.0 (38.0%)	0.17 (0.07, 0.43)	0.17 (0.06, 0.45)	0.15 (0.05, 0.41)
p			0.001	0.002	0.001

+Adjusted for baseline key factors including disease duration (continuous), history of the hepatobiliary disease (yes = 1, no = 0), use of liver protective drugs (yes = 1, no = 0), glucocorticoids (yes = 1, no = 0), other immunosuppressants (yes = 1, no = 0), hydroxychloroquine (yes = 1, no = 0), musculoskeletal (yes = 1, no = 0) and hematological involvement (yes = 1, no = 0).
++Adjusted for both baseline key factors (see above) and those with significant changes after treatment, including improved dry mouth (yes = 1, no = 0), improved dry eye (yes = 1, no = 0), improved musculoskeletal (yes = 1, no = 0) and change of ALT (continuous).

Table V. Adverse events related to TGP use in patients with pSS.

Adverse reactions	TGP users	Non-users	p
Upset stomach	2.0 (1.7%)	2.0 (1.7%)	1.000
Diarrhea	8.0 (6.8%)	2.0 (1.7%)	0.106
Skin rash	2.0 (1.7%)+	1.0 (0.8%)	1.000
Joint pain	1.0 (0.8%)+	2.0 (1.7%)	1.000
Blurred vision	0.0 (0.0%)	2.0 (1.7%)	0.498
Back pain	1.0 (0.8%)+	1.0 (0.8%)	1.000
Total events	14.0 (11.9%)	10.0 (8.5%)	0.389

+Most likely caused by concurrently used drugs.

TGP has been used in different animal models[28-30] to explain its association with liver function in different diseases. In the concanavalin A-induced experimental autoimmune hepatitis mouse model[28], TGP can reduce serum liver enzyme levels, histopathological damage, and hepatocyte apoptosis in mice. In a diabetic rat model[29], TGP can potentially treat diabetic liver injury by reducing endoplasmic reticulum stress and inflammation in the liver. In a rat model[30] of nonalcoholic fatty liver disease, TGP improved lipid metabolism disorders, enhanced insulin sensitivity, and improved liver function. However, although some studies[31,32] suggested that TGP could reduce the liver toxicity induced by immunosuppressive drugs in human patients, the hepatoprotective effect of TGP has not been reported in pSS. Our results revealed that there was a statistical difference in liver function-related indexes, especially ALT and DBIL, compared to baseline values after TGP treatment. Logistic regression analysis revealed that even after correcting for confounding factors, TGP treatment therapy had a more beneficial effect on liver function-related indexes. Thus, despite the effect being quite weak, administration of TGP helped to reduce the risk of ALT and DBIL elevation in pSS patients, with a greater benefit for a longer duration of use.

In this study, we failed to observe the effect of TGP on ESR, GLB and IgG levels, which may be due to the inclusion of hospitalized patients, resulting in a less significant superimposed effect of TGP due to combined medications, and the exclusion of those patients lost in the follow-up, leading to some selection bias. Due to the lack of information on the dosage of concurrent medications, we did not compare the dose of those drugs between the two groups. In addition, although propensity score matching was performed to minimize confounding bias, lifestyle variables (e.g., alcohol consumption) and other unmeasured factors might have been associated with changes in variables. Consistently, there was one double-blinded, placebo-controlled clinical trial[21] reporting ESSDAI score after TGP treatment, which did not differ significantly between the TGP group and the placebo group at any follow-up point.

Conclusions

To conclude, TGP treatment is associated with improved dryness symptoms and musculoskeletal involvement, as well as decreased ALT and DBIL levels, without increased risk of adverse reactions in pSS patients.

Conflict of Interest

The authors have declared that no competing interests exist.

Authors' Contributions

Methodology, Y.-Y. Cui and Z.-Y. Jin; software, Y.-Y. Cui; writing – original draft preparation, Y.-Y. Cui; data curation, Y.-Y. Cui and M. Abdukiyum; validation, X.-F. Xu, N. Zhao, and Y.-Q. Zhang; investigation, Z.-Y. Jia; visualization, Y.-Y. Zheng; writing – review and editing, X.-B. Feng and S.-S. Huang; funding acquisition, X.-B. Feng. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

This study was reviewed and approved by the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School (No. 2023-209).

Informed Consent
Not applicable due to the retrospective nature of the study.

Data Availability
Data are available on request from the corresponding author.

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