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Evidence-Based Integrative Medicine

Benefits and Safety of Tripterygium Glycosides and Total Glucosides of Paeony for Rheumatoid Arthritis: An Overview of Systematic Reviews*

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ABSTRACT **Objective:** To summarize the evidence from systematic reviews (SRs) on the benefits and safety of Tripterygium glycosides (TG) and total glucosides of paeony (TGP), commonly used to treat rheumatoid arthritis (RA) in China, for patients with RA. **Methods:** SRs of randomized controlled trials (RCTs) on TG or TGP in treating RA were included, by searching 8 databases from their inception until December 2017. Two authors extracted data independently. We assessed the quality of SRs using AMSTAR and graded the quality of evidence according to the GRADE approach. **Results:** Eleven SRs containing an average of 7.6 RCTs, involving a total of 7,012 participants were included in this overview. On the basis of included SRs, TG and TGP could improve the following indexes for RA patients: American College of Rheumatology (ACR) 20 response rate, ACR50 response rate and ACR70 response rate, swollen joint count, tender joint count, erythrocyte sedimentation rate and C-reactive protein. Moreover, TGP could reduce incidence of hepatotoxicity. The most common adverse effects of TG were gastrointestinal discomfort and gonad toxicity, while for TGP was mild to moderate diarrhea. The overall quality of evidence for these findings ranged from "low" to "moderate". **Conclusions:** TG and TGP might be 2 potentially effective complementary and alternative drugs for patients with RA. Nevertheless, due to gonad toxicity, TG should only be considered in elderly patients or patients without reproductive needs. More evidence from high quality RCTs and SRs is warranted to support the use of TG and TGP for RA patients.

KEYWORDS rheumatoid arthritis, tripterygium glycosides, total glucosides of paeony, overview, systematic review

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis of unknown etiology that can result in joint damage, loss of function and premature death. It affects 0.5%–1.0% of adults in industrialized countries, with a global prevalence of 0.24%.[1,2] Meanwhile, as one of 291 conditions in the Global Burden of Disease 2010 study, it ranked as the 42nd highest contributor to global disability, with an overall burden (disability-adjusted life years) increasing from 3.3 million in 1990 to 4.8 million in 2010.[2] Currently, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), are recommended as the first-line treatment for RA, and biologic agents (e.g. tumor necrosis factor inhibitors) as the second-line drugs.[3] However, due to insufficient response, adverse effects (AEs) and high cost, new source of drugs with therapeutic potential for RA is still warranted.[4-6]

Tripterygium glycosides (TG) is a Chinese patent medicine and total glucosides of paeony (TGP) is an active compound extracted from the roots of a Chinese herb named *Paeonia lactiflora* Pall. These two medicines are proved effective and commonly used to treat RA in China. The efficacy and safety profile of TG and TGP have been increasingly investigated with randomized controlled trials (RCTs) over the past decades. A recent RCT published in *Annals of the Rheumatic Diseases* reported that TG monotherapy

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was not inferior to, and TG combined with MTX was better than, MTX monotherapy for patients with active RA.[6] Another RCT tested in the West showed that compared with sulfasalazine, patients with active RA receiving TG had higher response rates for American College of Rheumatology (ACR) 20, ACR 50 and ACR 70.[7] Moreover, a systematic review (SR) included 22 RCTs enrolling 5,255 participants suggested that TG was effective and safe in treating RA and had better clinical efficacy in terms of ACR 20 and ACR 50 than DMARD.[8] A recent meta-analysis including 8 RCTs also showed that patients with RA receiving TGP plus DMARD might have a better clinical efficacy and less AEs than DMARD monotherapy.[9] These RCTs and SRs provided reasonably strong evidence supporting the efficacy of TG and TGP in treating RA. A few studies, however, yielded controversial results. A SR including 2 RCTs containing 105 patients concluded that TG had beneficial effects on symptoms of RA but was associated with serious AEs.[10]

Although use of TG and TGP is popular for the treatment of RA and many relevant SRs are available, clinical practice has not been informed by evidence from SRs. This overview aims to summarize and evaluate evidence from SRs on the benefits and safety of TG and TGP for patients with RA, to inform both practice and further research.

METHODS

This overview was reported according to the Preferred Reporting Items for Overviews of SRs Including Harms Checklist (PRIO-harms).[11] The protocol of this overview was documented in PROSPERO International Prospective Register of SRs (ID: CRD42017074841).[12]

Source of Literature and Search Strategy

The following databases were searched from their inception to December 2017: The Cochrane Library, PubMed, EMBASE, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Database and Chinese Scientific Journal Database (VIP). Unpublished postgraduate theses in databases were also searched. MeSH terms and text words were used depending on the characteristics of databases. No language restriction was applied. We also hand searched reference lists of retrieved review articles but did not include ongoing SRs. Search strategies used in English electronic databases were available in Appendix 1, and were adapted for Chinese databases with appropriate terms.

Inclusion and Exclusion Criteria

SRs of RCTs reporting TG or TGP as intervention in treating RA with full texts were included irrespective of language and publishing status. We only considered SRs comparing TG or TGP with placebo, no treatment, DMARDs or biologic agents. Co-interventions were allowed if applied in all arms. In view of the misuse of the term "SR", only articles whose overall methods and implementation conformed to SRs were included.

The following articles were excluded: protocols, overviews, methodological studies, repeat publications and SRs with entire-overlapping primary trials. Those without description of recognized diagnostic criteria of RA, or if the interventions focused on a broad concept of Chinese medicine (CM) were also ineligible.

Study Selection

Two authors (Xu Y and Chen GY) independently screened the citations, and retrieved full texts of potentially eligible articles for further identification in keeping with the inclusion and exclusion criteria. Overlapping of primary trials within SRs was also considered during study selection (e.g. we only included the most updated SR). Disagreements were resolved by discussion.

Data Extraction

Two authors (Luo J and Song WJ) independently extracted data from included SRs in accordance with a pre-designed form. Data were validated by a third reviewer (Tao QW). Extracted information included number of RCTs and participants, interventions and controls, study methodology, quality of primary RCTs, outcomes, results, etc. Discrepancies were resolved by discussion.

Outcomes were categorized into the following 7 types: disease remission, disease improvement, health-related quality of life (QOL), symptoms, surrogate outcomes, AEs and economic evaluations. Of which, disease remission and disease improvement should be measured by validated criteria of RA. Surrogate outcomes referred to serum markers such as C reactive protein (CRP) and erythrocyte

sedimentation rate (ESR). Primary outcomes include disease remission and disease improvement. Secondary outcomes include health-related QOL, symptoms, surrogate outcomes, AEs and economic evaluations.

Quality Assessment

Quality of Included SRs

Two authors independently appraised the methodological quality of included SRs using the 'Assessment of Multiple SRs' (AMSTAR) instrument containing 11 items (details in protocol).[13] We judged each item as follows: (1) yes (when the criterion is explicitly met), (2) no (when the criterion is explicitly not met), (3) can not answer (when the item is relevant but not described completely or not reported at all), (4) not applicable (when the item is not relevant). For item 3 (literature search), we judged it as "Yes" when authors searched 2 English databases among PubMed, the Cochrane Library and EMBASE, and 2 Chinese databases among CBM, CNKI, VIP and Wanfang databases.

In keeping with previous studies which have used AMSTAR,[14,15] each SR scored 1 point for each criterion met, otherwise scored 0. Finally, we graded the methodology quality of each SR as "high" (AMSTAR scores of 9 to 11), "moderate" (AMSTAR scores of 5 to 8), or "low" (AMSTAR scores of 0 to 4), in accordance with the rating system of 'Canadian Agency for Drugs and Technologies in Health' (CADTH).[16]

Quality of Evidence in Included SRs

Two authors independently evaluated the quality of evidence for main findings in included SRs using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) approach.[17] The quality of evidence for each main finding in each main comparison was graded as "high" (no downgrade), "moderate" (downgraded by 1 level), "low" (downgraded by 2 levels), or "very low" (downgraded by 3 or more levels), based on judgments considering the following five factors: (1) limitation in study design and execution, (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision, and (5) publication bias.

Statistical Analysis

SPSS software (version 17.0) was used for data analyses. All analyses were descriptive. Continuous variables were presented as means with standard deviations (SDs) or medians with inter-quartile ranges (IQRs), while categorical variables were reported as frequencies with percentages.

RESULTS

Study Identification

Our search identified 524 records, of which 178 were excluded for duplicates. After screening titles and abstracts, 263 records were excluded. A total of 83 records were retrieved in full text for scrutiny, of which 72 were excluded because they did not fulfill the eligibility criteria. Finally, 11 SRs[8-10,18-25] were included in this overview (Figure 1).

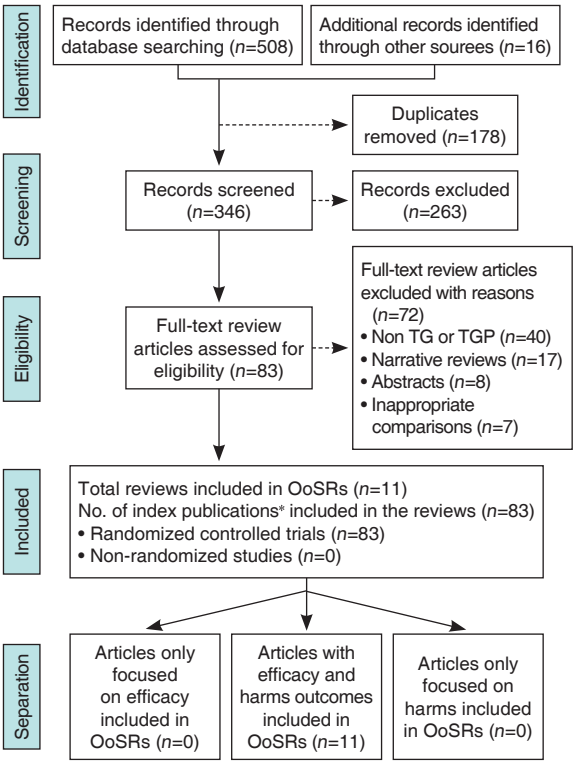

Figure 1. Flow Chart for Overview of Systematic Reviews on Benefits and Safety of TG and TGP for RA

Notes: *Index publication is the first occurrence of a primary publication in the included reviews. OoSRs: Overviews of systematic reviews

Characteristics of Included SRs

Characteristics and main results of the included 11 SRs were summarized in Table 1. Of the 11 SRs, 3 (27.3%)[18-20] were published in Chinese and the remaining were in English. No Cochrane review was included and none was reported as an update SR. Publication year of the 11 SRs ranged from 2006 to 2017.

TG (4/10, 40.0%) and TGP (6/10, 60.0%) were

Table 1. Characteristics of Included 11 SRs

Study ID	Included RCTs and participants (*n*)	Conditions	Comparisons	QT/QR*	Main results
Canter, et al 2006[10]	2 (105)	RA	TG *vs*. placebo	QT†: 3 and 5; QR: low	Compared with placebo, TG had beneficial effects on the symptoms of RA, but was associated with serious AEs.
Zhong, et al 2010[18]	9 (707)	RA	TGP plus basic therapy‡ *vs*. basic therapy	QT§: high risk of bias; QR: moderate	Compared with no treatment, TGP improved ACR 50 response rate (8 RCTs, *n*=538, RR=1.22, 95%CI 1.08 to 1.38), and reduced incidence of hepatotoxicity (5 RCTs, *n*=322, RR=0.66, 95%CI 0.48 to 0.92) at 12 weeks, on the basis of basic therapy.
Li, et al 2012[19]	10 (781)	RA	TGP plus MTX *vs*. MTX	QT§: unclear or high risk of bias; QR: moderate	Compared with MTX, TGP plus MTX further improved ACR50 response rate (7 RCTs, *n*=468, 12 weeks, OR=2.65, 95% CI 1.51 to 4.65; 3 RCTs, *n*=362, 24 weeks, OR=2.02, 95% CI 1.29 to 3.18), but had no difference in the incidence of AE.
Guo, et al 2013[20]	15 (1130)	RA	TGP plus basic therapy‡ *vs*. basic therapy	QT§: unclear or high risk of bias; QR: moderate	Compared with no treatment, TGP further improved ACR20 response rate (10 RCTs, *n*=672, RR=1.13, 95% CI 1.04 to 1.24) and reduced AE (14 RCTs, *n*=1060, RR=0.66, 95% CI 0.54 to 0.81), on the basis of basic therapy.
Liu, et al 2013[21]	10 (733)	RA	TG *vs*. placebo, TG *vs*. traditional DMARD(s), TG plus traditional DMARD(s) *vs*. traditional DMARD(s)	QT†: ≥4 (4 RCTs), <3 (6 RCTs); QR: high	Compared with placebo, TG had beneficial effects on the improvement of SJC (2 RCTs, *n*=92, MD=–4.13, 95%CI –5.69 to –2.58) and ESR (2 RCTs, *n*=90, MD=–28.63, 95%CI –42.12 to –15.14); TG showed no significant difference in therapeutic effect, compared with no treatment on the basis of traditional DMARD(s). The most common AE of TG were gastrointestinal discomfort, menstruation disorders and amenorrhea.
Wang, et al 2016[8]	3 (291)	RA	TG *vs* placebo, TG *vs*. MTX, TG *vs*. SSZ	QT§: low or unclear risk of bias; QR: high	By direct comparison, TG was superior to SSZ according to ACR 20, 50, 70, and was superior to placebo according to ACR 20, 50; by indirect comparisons, TG was superior to MTX, SSZ and placebo according to ACR 20; TG caused no more significant withdrawals than placebo.
Xu, et al 2016[23]	4 (248)	Late-onset RA	TG plus basic therapy‡ *vs*. basic therapy	QT§: high risk of bias; QR: high	Compared with no treatment, TG showed a favorable effect on SJC (MD=–1.58, 95% CI –1.64 to –1.51), TJC (MD=–1.71, 95% CI –2.26 to –1.15), CRP (MD=–9.96, 95% CI –10.96 to –8.96), ESR (MD=–10.74, 95% CI –12.47 to -9.00), and didn't increase AE, on the basis of basic therapy.
Feng, et al 2016[22]	8 (643)	RA	TGP plus LEF *vs*. LEF	QT§: high or unclear risk of bias; QR: moderate	Compared with LEF, TGP plus LEF further improved ESR (6 RCTs, *n*=456, MD=–6.67, 95% CI –9.88 to –3.47) and CRP (3 RCTs, *n*=259, MD=–5.85, 95% CI –8.66 to –3.05), and reduced incidence of hepatotoxicity (4 RCTs, *n*=380, OR=0.32, 95% CI 0.12 to 0.84).
Luo, et al 2017[9]	8 (1209)	RA	TGP plus traditional DMARD(s) *vs*. traditional DMARD(s)	QT§: high or unclear risk of bias; QR: high	Compared with no treatment, on the basis of traditional DMARD(s), TGP improved ACR 20, 50, 70 response rates at 3 months or 24 weeks, and reduced incidence of hepatotoxicity. The most common AE of TGP was mild to moderate loose stool or diarrhea.
Wang, et al 2017[25]	6 (643)	RA	TG plus MTX *vs*. MTX	QT†: range 3–5; QR: moderate	Compared with MTX, TG plus MTX further increased ACR20 (RR 1.16, 95% CI 1.09 to 1.25) and ACR50 (RR 1.34, 95% CI 1.19 to 1.51) response rate, reduced SJC and TJC, decreased ESR and CRP, but didn't increase AE.
Feng, et al 2018[24]	8 (522)	RA	TGP plus MTX *vs*. MTX	QT§: high or unclear risk of bias; QR: high	Compared with MTX, TGP plus MTX further improved therapeutic effects (6 RCTs, *n*=416, OR 3.70, 95% CI 1.51 to 9.04), reduced SJC (3 RCTs, *n*=180, MD=–5.85, 95% CI –8.67 to -3.02), and had fewer AE (4 RCTs, *n*=250, OR 0.34, 95% CI 0.18 to 0.64).

Notes: QT: quality of original trials; QR: quality of systematic reviews; RCT: randomized clinical trial; RA: rheumatoid arthritis; TG: Tripterygium glucosides; TGP: Total glucosides of paeony; ACR: American College of Rheumatology; RR: risk ratio; CI: confidence interval; AE: adverse effect; MTX: methotrexate; OR: odds ratio; DMARD(s): disease-modifying antirheumatic drugs; SJC: swollen joint count; MD: mean difference; ESR: erythrocyte sedimentation rate; SSZ: sulfasalazine; TJC: tender joint count; CRP: C-reactive protein; LEF: leflunomide. *Assessed by the 'Assessment of Multiple Systematic Reviews' (AMSTAR) instrument. ‡Basic therapy refers to traditional DMARD(s), TG or non-steroidal anti-inflammatory drugs. †Jadad scale: 0–5. §Cochrane risk of bias.

evaluated in 10 SRs[8-10,18-22,24,25] for treatment of RA in this overview. The included SRs contained an average of 7.6 RCTs (SD 3.7), involving a total of 7,012 participants, and each SR included a mean of 637.5 participants (SD 342.4). Overlapping existed in this overview. For TGP, 6 SRs[9,18-20,22,24] consisting of 58 primary trials were included, while 28 of the primary trials (48.3%) were overlapping, which were included in more than 1 SR. For TG, 5 SRs[8,10,21,23,25] comprising of 25 primary trials were included, and 4[8,10,21,25] of the primary trials (16.0%) were overlapping.

Four kinds of comparisons were included in this overview containing TGP plus basic therapy *vs*. basic therapy (6/11, 54.5%), TG *vs*. placebo (3/11, 27.3%), TG plus basic therapy *vs*. basic therapy (3/11, 27.3%), TG *vs*. traditional DMARD(s) (2/11, 18.2%). Basic therapy refers to traditional DMARD(s), TG or non-steroidal anti-inflammatory drugs. Almost all durations of treatment in primary trials in included SRs were 12 or 24 weeks.

For outcomes, all SRs assessed AEs (11/11,

100%), most SRs evaluated disease improvements such as ACR 20 (6/11, 54.5%) and surrogate outcomes (7/11, 63.6%). One SR considered disease remission and QOL.[9] None of the SRs reported economic evaluations.

For results (Table 1), most SRs suggested that: (1) both TG and TGP had potential therapeutic benefits for patients with RA; (2) TG caused no more AEs on the basis of traditional DMARD(s); (3) TGP might reduce incidence of hepatotoxicity. One SR reported that TG had no significant difference in therapeutic effect when compared with traditional DMARD(s) or no treatment on the basis of traditional DMARD(s).[21] Another SR reported that TG could improve symptoms of RA but cause serious AEs including gonad toxicity.[10] Meanwhile, 1 SR[21] described summarily that the most common AEs of TG were gastrointestinal discomfort, menstruation disorders and amenorrhea. In total, 10 SRs (10/11, 90.9%)[8,9,18-25] drew positive conclusions in favor of TG and TGP for treatment of RA. One SR drew opposed recommendation for use of TG due to serious AEs.[10]

Assessment of Methodological Quality of Included SRs

Quality of Included SRs

The overall scores on AMSTAR ranged from 3 to 10 (maximum score: 11) with a mean score of 7.6 (SD 2.5, Appendix 2). In accordance with the AMSTAR and the rating system used by the CADTH, 5 SRs[8,9,21,23,24] were of "high" quality (5/11, 45.5%), 5 SRs[18-20,22,25] were of "moderate" quality (5/11, 45.5%), only 1 SR[10] was of "low" quality (Table 1).

Of the included 11 SRs, only 3 (3/11, 27.3%)[8,9,23] registered protocols. Almost all SRs (10/11, 90.9%) data extraction was conducted independently by two authors, but 3 SRs (3/11, 27.3%)[10,18,19] did not provide flow charts for study selection. For literature search, although 8 SRs (8/11, 72.7%) of the SRs performed a comprehensive literature search, only 3 SRs (3/11, 27.3%) considered grey literature.[10.19.25] Ten out of 11 (90.9%) SRs[8-10,19-25] described characteristics of included primary trials adequately.

All SRs assessed methodological quality of primary trials by the Cochrane risk of bias stool (8/11, 72.7%) and Jadad score, respectively. The overall quality of primary trials was limited because most of them had unclear/high risk of bias or low Jadad scores (Table 1). Two SRs (2/11, 18.2%)[10,19] drew conclusions taking no consideration of methodological quality of primary trials. Ten SRs (10/11, 90.9%)[8,9,18-25] of the SRs appropriately synthesized data of primary trials, while 1 SR just described findings of primary trials summarily.[10] Only 4 SRs (4/11, 36.4%)[8,20,21,24] assessed potential publication bias, and 7 SRs (7/11, 63.6%)[8,9,21-25] stated the conflict of interest.

Quality of Evidence in Included SRs

According to the GRADE approach, the overall quality of evidence for main findings in included SRs was limited (range "low" to "moderate", Appendix 3). No "high" quality of evidence was found. Most of the quality of evidence was downgraded due to the serious or very serious limitations of primary trials in study design and execution.

For patients with RA, compared with placebo (3/11, 27.3%): (1) TG might be beneficial on the improvement of ACR 20 and ACR50 response rates, and caused no more AEs, while the corresponding quality of evidence was "moderate" (1/3, 33.3%); (2) TG could reduce swollen joint count (SJC) and ESR, with a "low" quality of evidence (1/3, 33.3%); (3) TG could improve symptoms of RA but had serious AEs, while the quality of evidence was "low" (1/3, 33.3%).

For patients with RA, compared with no intervention on the basis of basic therapy (2/11, 18.2%): (1) TG could improve ACR20 and ACR50 response rates, reduce SJC, tender joint count (TJC), ESR and CRP, but caused no more AEs, while the quality of evidence was "moderate" (1/2, 50.0%); (2) TG had no difference in therapeutic effect, with a "low" quality of evidence (1/2, 50.0%); (3) the most common AEs of TG were gastrointestinal discomfort, menstruation disorders and amenorrhea, with a "low" quality of evidence (1/2, 50.0%).

For patients with RA, compared with sulfasalazine alone (1/11, 9.1%), TG could increase ACR20 response rate, ACR50 response rate and ACR70 response rate, while the corresponding quality of evidence was "moderate". Compared with traditional DMARD(s) (1/11, 9.1%), TG had no difference in therapeutic effect, with a "low" quality of evidence.

For patients with RA, compared with no

intervention on the basis of basic therapy (6/11, 54.5%): (1) TGP might be beneficial on the improvement of ACR20 response rate, ACR50 response rate and ACR70 response rate, while the quality of evidence was "low" (1/6, 16.7%) to "moderate" (3/6, 50.0%); (2) TGP had effect on the reduction of SJC, ESR and CRP, but the quality of evidence was "low" (2/6, 33.3%); (3) TGP could reduce incidence of hepatotoxicity, and the quality of evidence was "low" (3/6, 50.0%) to "moderate" (1/6, 16.7%); (4) the most common AEs of TGP was mild to moderate loose stool or diarrhea, with a "moderate" quality of evidence (1/6, 16.7%).

For patients with late-onset RA, compared with no intervention on the basis of basic therapy (1/11, 9.1%), TG might benefit on the reduction of SJC, TJC, ESR and CRP, and caused no more AEs, while the quality of evidence was "low". Appendix 3 showed more detailed information about the quality of evidence for main findings in included SRs.

DISCUSSION

This PRIO-harms-compliant overview summarized and evaluated evidence from 11 SRs on the benefits and safety of TG and TGP for patients with RA. TG and TGP were assessed in included SRs. Based on most of the SRs: (1) TG and TGP could improve ACR20 response rate, ACR50 response rate and ACR70 response rate, and reduce SJC, TJC, ESR and CRP for patients with RA; (2) TGP could reduce incidence of hepatotoxicity and TG caused no more AEs on the basis of traditional DMARD(s); (3) the most common AEs of TG were gastrointestinal discomfort, menstruation disorders and amenorrhea, while for TGP was mild to moderate diarrhea. Only 1 SR drew negative recommendation on TG for patients with RA due to serious AEs. The overall quality of evidence for these findings was limited (range "low" to "moderate"), while the methodological quality of most included SRs was "moderate" or "high".

TG and TGP are widely used for patients with RA in China. Findings from this overview indicated that TG and TGP had potential therapeutic benefits for RA patients, which is consistent with some previous RCTs and SRs.[6-9,26] More importantly, the result from current overview showed that TGP could reduce incidence of hepatotoxicity and TG caused no more AEs on the basis of traditional DMARD(s), which is also consistent with previous RCTs and SR.[7,9,26] These findings suggested that TG and TGP might be two potentially effective alternative drugs for patients with RA. The most common AEs of TGP was mild to moderate loose stool or diarrhea,[9] which seems to be well tolerated. However, the gonad toxicity of TG such as menstruation disorders, amenorrhea and germ cell apoptosis should not be ignored.[21,27] For patients in childbearing age, TG should not be used. While for patients after menopause or without reproductive needs, TG might be an alternative choice.

The quality of evidence and the methodological quality of SRs are also important for stakeholders. Low quality of evidence should be cautiously interpreted since it might mislead readers. Our results found that most included SRs were of "moderate" or "high" methodological quality, but the overall quality of evidence was limited. Therefore, we considered all the benefits of TG and TGP for RA from included SRs were unclear. High quality of evidence from well designed and performed RCTs and SRs is warranted to support the use of TG and TGP for RA patients. In order to improve the quality of primary RCTs, we suggest future researchers to design and execute RCTs appropriately and report information transparently in accordance with CONSORT statement.[28,29] Meanwhile, future SRs of TG and TGP should be appropriately designed and conducted according to AMSTAR and reported in keeping with PRISMA standard.[30]

Even though appropriately designed, limitations might also exist in this overview. First, overlapping existed in included SRs. Primary trials included in more than one SR might result in a double counting of outcomes. Because none of included SRs had entire-overlapping primary trials and all analyses were descriptive, we finally summarized evidence from each included SR. Second, we assessed evidence on the basis of included SRs. The findings of current overview may be influenced by the methodological quality and reporting quality of included SRs. Third, despite the comprehensive research, no unpublished SR was retrieved in this overview. Moreover, potential publication bias could not be detected since the lack of relevant strategies. Publication bias might exist in our results.

Current overview suggested that TG and TGP might be 2 potentially effective complementary and

alternative drugs for patients with RA. However, the gonad toxicity of TG should not be ignored. Due to the limited quality of evidence, high quality of evidence from well designed and performed RCTs and SRs is warranted to support the application of TG and TGP in treating RA.

Conflict of Interest

None declared.

Author Contributions

Tao QW conceived and designed the study and revised the manuscript. Luo J developed the search strategy, extracted and analyzed data, drafted the manuscript. Song WJ developed the search strategy, extracted and analyzed data, revised the manuscript. Xu Y identified studies and revised the manuscript. Chen GY identified studies and revised the manuscript. Hu Q validated data and revised the manuscript.

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