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Total Glucosides of Paeony for Rheumatoid Arthritis: a Protocol for a Systematic Review

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Total Glucosides of Paeony for Rheumatoid Arthritis: a Protocol for a Systematic Review

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Strengths and limitations of this study

- This will be the first PRISMA-compliant systematic review to assess the effectiveness and safety of total glucosides of paeony for patients with rheumatoid arthritis. It will provide a high-quality synthesis of current evidence for patients and rheumatologists seeking alternative and beneficial treatments of RA.
- In addition to measurement of methodological quality of each included studies, this systematic review will evaluate the strength of evidence according to the GRADE approach, to inform clinical decision-makers.
- The results of this systematic review are on the basis of the randomized controlled trials only. Some relevant trials might be missed in spite of the robust search strategies, especially those unpublished trials with negative findings.

ABSTRACT

Introduction: Total glucosides of paeony (TGP) is a natural plant extract, which is widely used in China in treating rheumatoid arthritis. Many relevant randomized controlled trials (RCTs) about TGP for rheumatoid arthritis are available. However, these RCTs haven't been systematically reviewed. This systematic review aims to examine the effectiveness and safety of TGP in patients with rheumatoid arthritis.

Methods and analyses: We will search RCTs on TGP in treating rheumatoid arthritis until October 2015, by searching PubMed, Embase, Cochrane Central Register of Controlled Trials and four Chinese databases. Additional Searches will also be performed to identify potential missing articles. Data will be extracted according to a pre-designed form. The methodological quality of each included studies will be evaluated using the Cochrane risk of bias tool, and the strength of evidence on pre-specified outcomes will be assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation approach. Review Manager 5.3 software will be used for data analyses. Meta-analyses will be performed if the data are sufficiently homogeneous, both statistically and clinically. Possible publication bias will also be checked by funnel plots once the number of included studies is sufficient.

Ethics and dissemination: Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research.

Trial registration number: PROSPERO 2015:CRD42015026345

Key Words: Rheumatoid Arthritis; Total Glucosides of Paeony; Oral Medicine; Systematic reviews; Meta-analyses

INTRODUCTION

Description of the condition

Rheumatoid arthritis (RA) is the most common type of chronic autoimmune arthritis that causes pain, stiffness, joint swelling, deformity and loss of function. Recently, an estimated over 1.3 million Americans experience RA, with a global prevalence of 0.24%.[1, 2] Data from the Global Burden of Disease 2010 study showed that the disability adjusted life years (DALYs) for RA had been increased from 3.3 million in 1990 to 4.8 million in 2010.[2] Therefore, RA remains a serious disease imposing a considerable burden for patients, their families and society. In order to relieve pain, avoid irreversible joint destruction and disability, RA calls for early and systematic treatment with timely adjustment. Nowadays, disease modifying anti-rheumatic drugs (DMARDs) with effects of lowering disease activity and retarding joint erosion, remain the first-line treatment for RA. Meanwhile, the most common concern about DMARDs is safety. A clinical trial published in Annals of the Rheumatic Diseases has reported that methotrexate (MTX) and leflunomide (LEF) are associated with the increase incidence of hepatotoxicity.[3] Some patients may need to stop treatment with DMARDs because of adverse effects. In addition, not all patients with RA have sufficient response to DMARDs. Biologic agents, also known as biologic DMARDs, have been proven to be effective for RA, especially for patients with insufficient response to DMARDs.[4, 5] Nevertheless, the remarkably high costs limit the application of biologics. Meanwhile, biologics exposure appears to confer an increased risk of serious infections.[6] In these cases, natural products with therapeutic potential have drawn more and more attention.[7]

Description of the intervention

Total glucosides of paeony (TGP) is an active compound extracted from the roots of a Chinese herb named *Paeonia lactiflora Pall,* with paeoniflorin accounting for 90% of its active components.[8] In China, TGP has been approved as a disease-modifying oral drug for RA since 1998, by the China Food and Drug Administration. Now, TGP is widely used to treat RA in China. So far, plenty of experiment studies have shown the anti-inflammatory and immunoregulation actions

of TGP.[9, 10, 11] The beneficial effects of TGP have also been reported in some clinical trials including randomized controlled trials (RCTs).[12, 13] A recent RCT enrolled 268 patients with active RA suggested that TGP could significantly reduce the incidence of liver damage caused by MTX and LEF.[13]

Why it is important to perform this review

TGP is a natural plant extract and is popularly applied to treat RA in China. Some studies have reported the potential benefits of TGP alone in treating RA or combination with some other DMARDs.[12, 13] However, the effectiveness and safety of TGP for RA have not been reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[14] A comprehensive and PRISMA-compliant systematic review of RCTs to evaluate the effect of TGP for RA is important to inform both clinical practice and further research.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness and safety of TGP for patients with RA.

METHODS AND ANALYSIS

Study registration

The protocol of this systematic review has been documented in PROSPERO (ID= CRD42015026345).[15] We will report this review in accordance with the PRISMA statement.

Eligibility criteria

Types of studies

Only RCTs will be eligible for inclusion irrespective of language or publication status. The duration of RCTs should be more than 12 weeks. Quasi-randomized trials will be excluded.

Types of participants

Adult participants (18 years and older) of any gender or ethnicity, meeting with one recognized diagnostic criteria of RA (the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria) will be included.[16, 17] Studies without description of diagnostic criteria will

not be considered.

Types of interventions

Studies assessing TGP with or without co-intervention(s) for patients with RA regardless of dosage will be included. Control interventions could be placebo, no treatment, DMARDs (traditional or biologic). TGP compared with any of complementary and alternative medicine will be ineligible. Complex intervention involving TGP but no detailed description on TGP will be excluded.

Types of outcome measures

Primary outcomes

(1) Disease improvement (Measured by any validated improvement criteria of RA, such as the ACR20 response.[18])

(2) Disease remission (Measured by any validated remission criteria of RA, such as the Disease Activity Score (DAS28) less than 2.6.[19, 20])

Secondary outcomes

(1) Adverse effects

(2) Pain (Measured by a visual analog scale (VAS))

(3) Health-related quality of life (Measured by a validated tool)

(4) C reactive protein (CRP)

(5) Erythrocyte sedimentation rate (ESR)

Search methods

Electronic searches

The following databases will be searched from their inception to October 2015: Pubmed, Embase, Cochrane Central Register of Controlled Trials, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Database and Chinese Scientific Journal Database (VIP).

Searching other resources

Clinical trials registry platforms will be searched, including the International Clinical Trials Registry platform (http://www.who.int/ictrp/network/primary/en/), the U.S. National Institutes of Health Ongoing Trials Register (http://clinicaltrials.gov/), and

the ISRCTN registry (http://www.controlled-trials.com/). We will also screen the reference lists of retrieved reviews to identify missing eligible studies.

Search strategies

Search strategies in English electronic databases will be listed in Appendix 1, and will be adapted for other resources with appropriate terms. No language restriction will be applied.

Study selection

Two reviewers will independently screen all titles and abstracts of the records. Full texts of potentially eligible studies will be retrieved for further identification according to the eligibility criteria. Any uncertainty or discrepancy will be resolved by consensus. Details of the study screening process will be shown in Figure 1.

Data extraction

Two reviewers will independently extract data in accordance with a pre-designed data form using Excel (version Microsoft Excel 2007). Data will be checked by additional two reviewers. Disagreements will be resolved by consensus.

Extracted information will comprise the following sections:

(1) General information (publication years, number of authors, the first author, study design, sample size, demographics, etc.)

(2) Participants (diagnostic criteria, condition of RA, baseline comparison, etc.)

(3) Interventions (dosage, administration, duration, comparisons, etc.)

(4) Outcomes measures, results and adverse effects.

We will seek missing information by contacting the original authors whenever possible and resolve discrepancies by discussion or consulting a third reviewer.

Quality assessment

Assessment of Risk of Bias

Two reviewers will independently evaluate the risk of bias for each included studies using the Cochrane Collaboration's risk of bias tool,[21] consisting of the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. We will judge each item as low, high, or unclear risk of bias.

Any uncertainty or discrepancy will be resolved by consulting a third reviewer.

Quality of Evidence

We will judge the quality of evidence for the main comparison according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[22] The following five factors will be judged for each outcome in the main comparison: limitations in study design and execution, inconsistency of results, indirectness of evidence, imprecision and publication bias. Accordingly, the quality of the evidence for each outcome will be graded as high, moderate, low or very low.

Data analysis

RevMan 5.3 software will be used for data analysis. Studies included will be stratified by different types of comparisons. Dichotomous data will be reported as risk ratios (RR) and continuous data as mean difference (MD) or weighted mean difference (WMD), both with their 95% confidence intervals (CI). We will perform intention-to-treat analysis (ITT) where possible. For missing or incomplete data, we will attempt to obtain by contacting with the original authors.

Meta-analyses will be performed if the data are sufficiently homogeneous, both statistically and clinically. Otherwise, analyses will be descriptive. Before pooling data, heterogeneity will be tested using I-squared (I^2). If heterogeneity is low ($I^2 \leqslant 50\%$), fixed effect model will be applied to analyze data, and random effects model will be used when heterogeneity is moderate ($50\% < I^2 < 75\%$). Data will not be pooled when heterogeneity is high ($I^2 \geqslant 75\%$).

We will perform subgroup analyses according to different clinical characteristics (e.g., different durations) and sensitivity analyses on the basis of study quality where possible. Funnel plots will be created to detect possible publication bias when sufficient studies (more than 8) are identified.

In addition, we will generate a "Summary of finding table" using GRADE profiler (version 3.6) to calculate the relative effect and the number of patients needed to treat in order to present important outcomes and the strength of evidence supporting these outcomes under the main comparison.

Ethics and dissemination

Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research.

DISCUSSION

RA can cause pain, joint destruction and disability, placing a considerable burden on patients and society. Nowadays, DMARDs remain the first-line treatment for RA. However, some patients may need to stop treatment with DMARDs due to adverse effects, and some patients may have insufficient response to DMARDs. Biologic agents have been proven to be effective for RA, but the remarkably high costs limit its use. TGP, a natural plant extract, has been approved as a disease-modifying drug for RA in China since 1998. Nowadays, TGP is widely used for the treatment of RA in China. So far, some studies have reported the beneficial effects of TGP in treating RA alone or in combination with some other DMARDs. However, the effectiveness and safety of TGP for RA have not been systematically reviewed according to the PRISMA statement. This systematic review will provide a high-quality synthesis of current evidence for patients and rheumatologists seeking alternative and beneficial treatments of RA.

The strengths of this systematic review may be twofold. Firstly, this will be the first PRISMA-compliant systematic review to assess the effectiveness and safety of TGP for patients with RA. The study selection, data extraction and quality assessment will be conducted independently by two reviewers. Secondly, in addition to measurement of methodological quality of each included studies, this systematic review will evaluate the strength of evidence according to the GRADE approach. Nevertheless, limitations may also exist in this systematic review. The results of this systematic review are on the basis of the RCTs only. Some relevant trials might be missed in spite of the robust search strategies, especially those unpublished trials with negative findings.

Figures

Figure 1 Flow Diagram of Study Search and Identification.

Appendixes

Appendix 1 Search strategies for English electronic databases.

Contributors

QWT and JL conceived and designed the study. JL and DEJ developed the search strategy. GYY and QWT provided methodological perspectives. JL drafted and refined the study protocol with contributions from all coauthors (GYY, DEJ, YZZ, JMW, WPK, QWT). YZZ and WPK will search articles and conduct study selection. JL and JMW will perform data extraction and assessment of quality. DEJ will conduct data analyses. YZZ and QWT will verify data extraction and data analyses. All authors read and approved the final manuscript.

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Competing interests

None declared.

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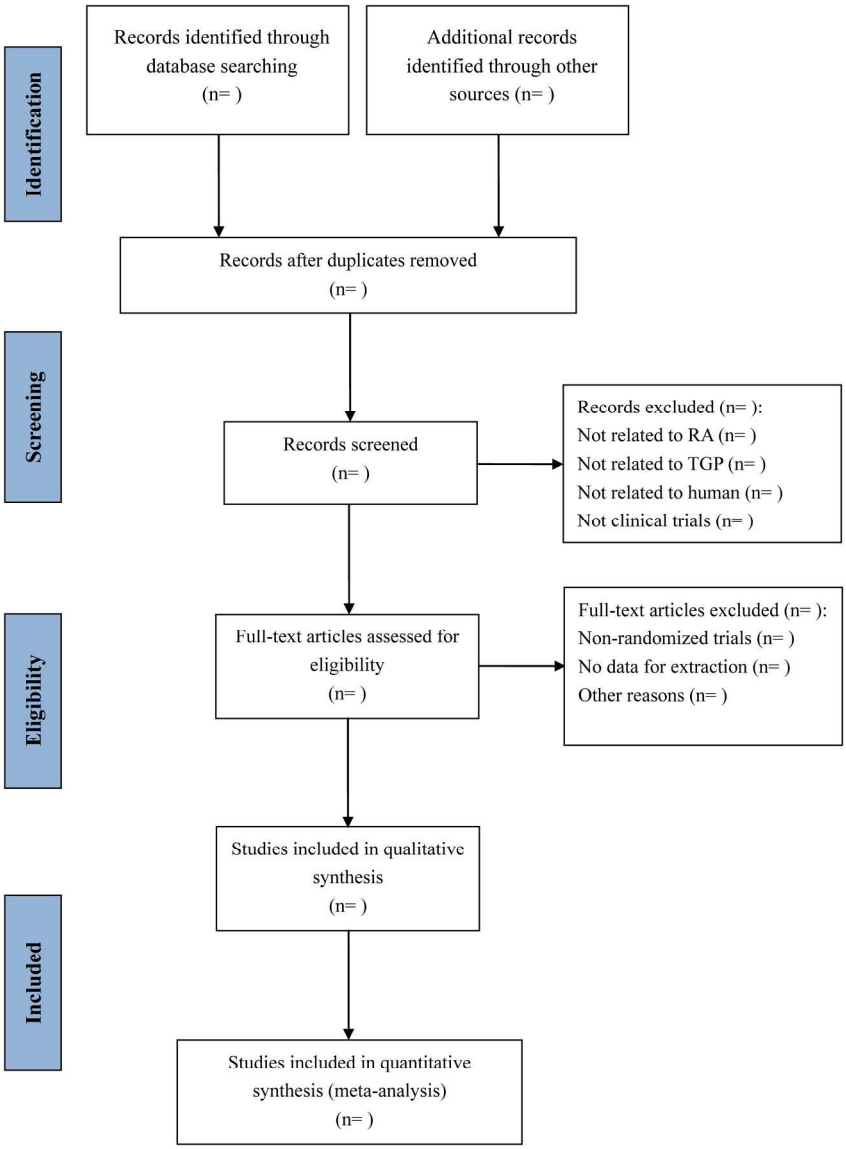

Figure 1 Flow Diagram of Study Search and Identification.
175x231mm (300 x 300 DPI)

Appendix 1. Search strategies for English electronic databases.

Databases	Strategies
Pubmed	#1 paeon*[Title/Abstract] #2 TGP[Title/Abstract] #3 "Arthritis, Rheumatoid"[Mesh] #4 rheumatoid arthritis[Title/Abstract] #5 (#1 OR #2) #6 (#3 OR #4) #7 (#5 AND #6)
Cochrane	#1 paeon*:ti,ab,kw (Word variations have been searched) #2 TGP:ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees #4 rheumatoid arthritis:ti,ab,kw (Word variations have been searched) #5 (#1 OR #2) #6 (#3 OR #4) #7 (#5 AND #6)
Embase	#1 paeon* #2 TGP #3 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis' #4 #1 OR #2 #5 #3 AND #4

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3, 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4, 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5, 6, 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	Appendix 1

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, Figure 1
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7, 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8, 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8, 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

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Words count: 1985

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- In addition to measurement of methodological quality of each included studies, this systematic review will evaluate the strength of evidence according to the GRADE approach, to inform clinical decision-makers.
- Some unpublished randomized controlled trials with negative findings might be missed, so funnel plots will be conduct to detect possible publication bias in order to get an objective conclusion.

ABSTRACT

Introduction: Total glucosides of paeony (TGP) is a natural plant extract, which is widely used in China in treating rheumatoid arthritis. Many relevant randomized controlled trials (RCTs) about TGP for rheumatoid arthritis are available. However, these RCTs haven't been systematically reviewed. This systematic review aims to examine the effectiveness and safety of TGP in patients with rheumatoid arthritis.

Methods and analyses: We will search RCTs on TGP in treating rheumatoid arthritis until February 2016, by searching PubMed, Embase, Cochrane Central Register of Controlled Trials and four Chinese databases (Chinese Biomedical Database, China National Knowledge Infrastructure, Wanfang Database and Chinese Scientific Journal Database). Trial registers and reference lists of retrieved reviews will also be performed to identify potential missing articles. RCTs comparing TGP with placebo, no treatment, or disease modifying anti-rheumatic drugs for patients with RA will be retrieved. Disease improvement and disease remission will be measured as primary outcomes. Surrogate outcomes, symptoms, adverse effects and quality of life will be measured as secondary outcomes. Two reviewers will independently extract data containing participants, interventions, comparisons, outcomes, etc. The methodological quality of each included studies will be evaluated using the Cochrane risk of bias tool, and the strength of evidence on pre-specified outcomes will be assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation approach. Review Manager 5.3 software will be used for data analyses. Meta-analyses will be performed if the data are sufficiently homogeneous, both statistically and clinically. Possible publication bias will also be checked by funnel plots once the number of included studies is sufficient.

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INTRODUCTION

Description of the condition

Rheumatoid arthritis (RA) is the most common type of chronic autoimmune arthritis that causes pain, stiffness, joint swelling, deformity and loss of function. Recently, an estimated over 1.3 million Americans experience RA, with a global prevalence of 0.24%.[1, 2] Data from the Global Burden of Disease 2010 study showed that the disability adjusted life years (DALYs) for RA had been increased from 3.3 million in 1990 to 4.8 million in 2010.[2] Therefore, RA remains a serious disease imposing a considerable burden for patients, their families and society. In order to relieve pain, avoid irreversible joint destruction and disability, RA calls for early and systematic treatment with timely adjustment.

Nowadays, disease modifying anti-rheumatic drugs (DMARDs) with effects of lowering disease activity and retarding joint erosion, remain the first-line treatment for RA. Meanwhile, the most common concern about DMARDs is safety. A clinical trial published in Annals of the Rheumatic Diseases has reported that methotrexate (MTX) and leflunomide (LEF) are associated with the increase incidence of hepatotoxicity.[3] Some patients may need to stop treatment with DMARDs because of adverse effects. In addition, not all patients with RA have sufficient response to DMARDs. Biologic agents, also known as biologic DMARDs, have been proven to be effective for RA, especially for patients with insufficient response to DMARDs.[4, 5] Nevertheless, the remarkably high costs limit the application of biologics. Meanwhile, biologics exposure appears to confer an increased risk of serious infections.[6] In these cases, natural products with therapeutic potential have drawn more and more attention.[7]

Description of the intervention

Total glucosides of paeony (TGP) is an active compound extracted from the roots of a Chinese herb named *Paeonia lactiflora Pall,* with paeoniflorin accounting for 90% of its active components.[8] In China, TGP has been approved as a disease-modifying oral drug for RA since 1998, by the China Food and Drug Administration. Now, TGP is widely used to treat RA in China. So far, many

experiment studies have shown the anti-inflammatory and immunoregulation actions of TGP.[9, 10, 11] For example, a study[9] investigating the effects of TGP on the activities of synoviocytes in rats with collagen-induced arthritis, found that TGP could significantly decrease the production of TNF-alpha and interleukin-1, and inhibit the proliferation of synoviocytes. Another study[10] published in *clinical immunology* revealed that TGP treatment could significantly increase the number and percentage of Treg cells in lupus CD4(+) T cells. A review[11] published in 2011 reported that paeoniflorin had immunosuppressive effects in adjuvant arthritis rats. In addition, the beneficial effects of TGP have also been reported in some clinical trials including randomized controlled trials (RCTs).[12, 13] A multicenter RCT included 370 patients with RA found that TGP might be effective on the improvement of joint function without severe adverse effects.[12] A recent RCT published in English enrolled 268 patients with active RA suggested that TGP could significantly reduce the incidence of liver damage caused by MTX and LEF.[13]

Why it is important to perform this review

TGP is a natural plant extract and is popularly applied to treat RA in China. Although four systematic reviews on TGP in treating RA are available,[14,15,16,17] none of them are adequate in systematic reviewing according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[18] Two reviews [14,15] respectively included seven studies (published in 2005-2007) and 10 studies (published in 2002-2010) with different methodological quality. However, no subgroup or sensitivity analysis was performed in them. A review including nine studies between 2005 and 2009 pooled different outcomes using fixed-effect model.[16] The latest review published in Chinese included 15 studies between 2005 and 2011.[17] The main outcome measure evaluated in this review was a composite outcome measure named overall effects. As such, the effect of TGP for RA could not be properly assessed. Therefore, a comprehensive, updated and PRISMA-compliant systematic review of RCTs is necessary to evaluate the effect of TGP for RA, to inform both clinical practice and further research.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness and safety of TGP for patients with RA.

METHODS AND ANALYSIS

Study registration

The original protocol of this systematic review has been documented in PROSPERO(ID= CRD42015026345).[19] This is a revised version which will also be uploaded in PROSPERO.[19] This systematic review will be conducted according to the revised protocol and be reported in accordance with the PRISMA statement.

Eligibility criteria

Types of studies

Only RCTs will be eligible for inclusion irrespective of language or publication status. Quasi-randomized trials will be excluded.

Types of participants

Adult participants (18 years and older) of any gender or ethnicity, meeting with one recognized diagnostic criteria of RA (the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria) will be included.[20, 21] Studies without description of diagnostic criteria will not be considered.

Types of interventions

Studies assessing TGP with or without co-intervention(s) for patients with RA regardless of dosage will be included. Control interventions should be placebo, no treatment, DMARDs (traditional or biologic). TGP compared with any of Chinese patent medicines or herbal formulations will be ineligible. Complex intervention involving TGP but without separate report on outcomes of TGP will be excluded. The duration of therapy should be more than 12 weeks.

Types of outcome measures

Primary outcomes

(1) Disease improvement (Measured by any validated improvement criteria of RA, such as the ACR20 response.[22])

(2) Disease remission (Measured by any validated remission criteria of RA, such as

the Disease Activity Score (DAS28) less than 2.6.[23, 24])

Secondary outcomes

(1) Adverse effects

(2) Pain (Measured by a visual analog scale (VAS))

(3) Health-related quality of life (Measured by a validated tool)

(4) C reactive protein (CRP)

(5) Erythrocyte sedimentation rate (ESR)

Search methods

Electronic searches

The following databases will be searched from their inception to February 2016: Pubmed, Embase, Cochrane Central Register of Controlled Trials, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Database and Chinese Scientific Journal Database (VIP).

Searching other resources

Clinical trials registry platforms will be searched, including the International Clinical Trials Registry platform (http://www.who.int/ictrp/network/primary/en/), the U.S. National Institutes of Health Ongoing Trials Register (http://clinicaltrials.gov/), and the ISRCTN registry (http://www.controlled-trials.com/). We will also screen the reference lists of retrieved reviews to identify missing eligible studies.

Search strategies

Search strategies in English electronic databases will be listed in Appendix 1, and will be adapted for other resources with appropriate terms. No language restriction will be applied.

Study selection

Two reviewers will independently screen all titles and abstracts of the records. Full texts of potentially eligible studies will be retrieved for further identification according to the eligibility criteria. Any uncertainty or discrepancy will be resolved by discussion. Details of the study screening process will be shown in Figure 1.

Data extraction

Two reviewers will independently extract data in accordance with a pre-designed data

form using Excel (version Microsoft Excel 2007). Data will be checked by additional two reviewers. Disagreements will be resolved by discussion.

Extracted information will comprise the following sections:

(1) General information (publication years, number of authors, the first author, study design, sample size, demographics, setting.)

(2) Participants (diagnostic criteria, condition of RA, baseline comparison, withdrawals, loss to follow-up.)

(3) Interventions (dosage, administration, duration, follow-up, comparisons.)

(4) Outcome measures, results and adverse effects.

We will seek missing information by contacting the original authors whenever possible and resolve discrepancies by discussion or consulting a third reviewer.

Quality assessment

Assessment of Risk of Bias

Two reviewers will independently evaluate the risk of bias for each included studies using the Cochrane Collaboration's risk of bias tool,[25] consisting of the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. We will judge each item as low, high, or unclear risk of bias. Any uncertainty or discrepancy will be resolved by consulting a third reviewer.

Quality of Evidence

We will judge the quality of evidence for the main comparison according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[26] The following five factors will be judged for each outcome in the main comparison: limitations in study design and execution, inconsistency of results, indirectness of evidence, imprecision and publication bias. Accordingly, the quality of the evidence for each outcome will be graded as high, moderate, low or very low.

Data analysis

RevMan 5.3 software will be used for data analysis. Studies included will be stratified by different types of comparisons. Dichotomous data will be reported as risk ratios (RR) and continuous data as mean difference (MD) or weighted mean

difference (WMD), both with their 95% confidence intervals (CI). We will perform intention-to-treat analysis (ITT) where possible. For missing or incomplete data, we will attempt to obtain by contacting with the original authors.

Meta-analyses will be performed if the data are sufficiently homogeneous, both statistically and clinically. Otherwise, analyses will be descriptive. Before pooling data, heterogeneity will be tested using I-squared (I^2). If heterogeneity is low ($I^2 \leqslant 50\%$), fixed effect model will be applied to analyze data, and random effects model will be used when heterogeneity is moderate ($50\% < I^2 < 75\%$). Data will not be pooled when heterogeneity is high ($I^2 \geqslant 75\%$).

We will perform subgroup analyses according to different clinical characteristics (e.g., different durations) and sensitivity analyses on the basis of study quality where possible. Funnel plots will be created to detect possible publication bias when sufficient studies (more than 8) are identified.

In addition, we will generate a "Summary of finding table" using GRADE profiler (version 3.6) to calculate the relative effect and the number of patients needed to treat in order to present important outcomes and the strength of evidence supporting these outcomes under the main comparison.

Ethics and dissemination

Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research.

DISCUSSION

RA can cause pain, joint destruction and disability, placing a considerable burden on patients and society. Nowadays, DMARDs remain the first-line treatment for RA. However, some patients may need to stop treatment with DMARDs due to adverse effects, and some patients may have insufficient response to DMARDs. Biologic agents have been proven to be effective for RA, but the remarkably high costs limit its use. TGP, a natural plant extract, has been approved as a disease-modifying drug for RA in China since 1998. Nowadays, TGP is widely used for the treatment of RA in China. So far, some RCTs have reported the beneficial effects of TGP in treating RA

alone or in combination with some other DMARDs. However, the effectiveness and safety of TGP for RA have not been systematically reviewed according to the PRISMA statement. This systematic review will provide a high-quality synthesis of current evidence for patients and rheumatologists seeking alternative and beneficial treatments of RA.

The strengths of this systematic review may be twofold. Firstly, this will be the first PRISMA-compliant systematic review to assess the effectiveness and safety of TGP for patients with RA. The study selection, data extraction and quality assessment will be conducted independently by two reviewers. Secondly, in addition to measurement of methodological quality of each included studies, this systematic review will evaluate the strength of evidence according to the GRADE approach. Nevertheless, limitations may also exist in this systematic review.. Although we will conduct an extensive and unbiased search, some unpublished RCTs with negative findings might be missed. This is a possible cause of bias. We will detect possible publication bias through funnel plots in order to get an objective conclusion. Additionally, it might be difficulty to retrieve raw date from some published papers. We will try to contact the original authors. However, we believe the results of this study could provide objective evidence on the effect of TGP in treating RA, which will be beneficial for patients and practitioners.

Figures

Figure 1 Flow Diagram of Study Search and Identification.

Appendixes

Appendix 1 Search strategies for English electronic databases.

Contributors

QWT and JL conceived and designed the study. JL and DEJ developed the search

strategy. GYY and QWT provided methodological perspectives. JL drafted and refined the study protocol with contributions from all coauthors (GYY, DEJ, YZZ, JMW, WPK, QWT). YZZ and WPK will search articles and conduct study selection. JL and JMW will perform data extraction and assessment of quality. DEJ will conduct data analyses. YZZ and QWT will verify data extraction and data analyses. All authors read and approved the final manuscript.

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Competing interests

None declared.

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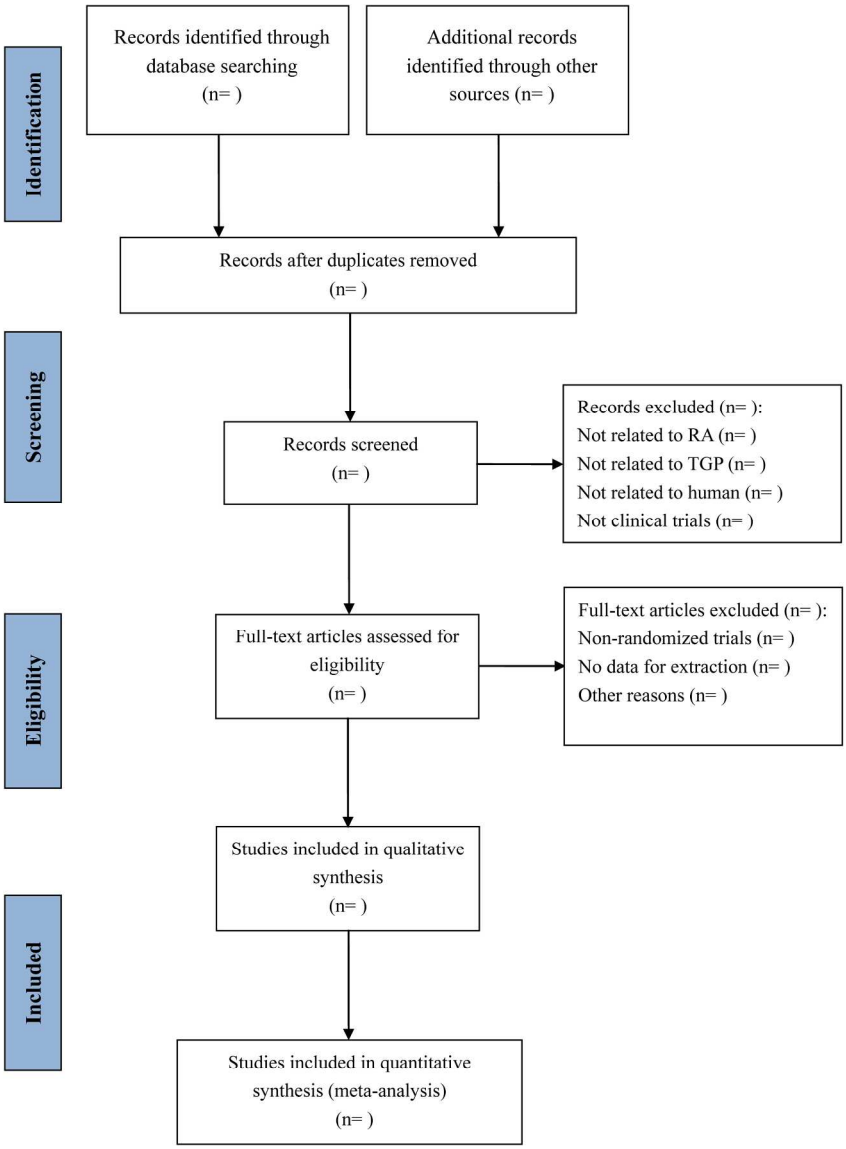

Figure 1 Flow Diagram of Study Search and Identification.
175x231mm (300 x 300 DPI)

Appendix 1. Search strategies for English electronic databases.

Databases	Strategies
Pubmed	#1 paeon*[Title/Abstract] #2 TGP[Title/Abstract] #3 "Arthritis, Rheumatoid"[Mesh] #4 rheumatoid arthritis[Title/Abstract] #5 (#1 OR #2) #6 (#3 OR #4) #7 (#5 AND #6)
Cochrane	#1 paeon*:ti,ab,kw (Word variations have been searched) #2 TGP:ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees #4 rheumatoid arthritis:ti,ab,kw (Word variations have been searched) #5 (#1 OR #2) #6 (#3 OR #4) #7 (#5 AND #6)
Embase	#1 paeon* #2 TGP #3 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis' #4 #1 OR #2 #5 #3 AND #4

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3, 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4, 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5, 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6, 7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6, 7, 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	Appendix 1

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, Figure 1
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7, 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6, 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8, 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8, 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

BMJ Open

Total Glucosides of Paeony for Rheumatoid Arthritis: a Protocol for a Systematic Review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010116.R2
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Complete List of Authors:	Luo, Jing; China-Japan Friendship Hospital, Traditional Chinese Medicine Department of Rheumatism Jin, Di-Er; China-Japan Friendship Hospital, Traditional Chinese Medicine Department of Rheumatism Yang, Guo-Yan; Western Sydney University, National Institute of Complementary Medicine Zhang, Ying-Ze; China-Japan Friendship Hospital, Traditional Chinese Medicine Department of Rheumatism Wang, Jian-Ming; China-Japan Friendship Hospital, Traditional Chinese Medicine Department of Rheumatism Kong, Wei-Ping; China-Japan Friendship Hospital, Traditional Chinese Medicine Department of Rheumatism Tao, Qing-Wen; China-Japan Friendship Hospital, Traditional Chinese Medicine Department of Rheumatism
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Complementary medicine
Keywords:	ORAL MEDICINE, RHEUMATOLOGY, COMPLEMENTARY MEDICINE

Total Glucosides of Paeony for Rheumatoid Arthritis: a Protocol for a Systematic Review

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JL: luojinggg@sina.com

DEJ: kingdafu@sina.com

GYY: yangguoyanbeijing@126.com

YZZ:zyzzhri@163.com

JMW: wendall1972@163.com

WPK: kongweiping75@126.com

QWT: taoqg1@sina.com

Words count: 2084

Strengths and limitations of this study

- This will be the first PRISMA-compliant systematic review to assess the effectiveness and safety of total glucosides of paeony for patients with rheumatoid arthritis. It will provide a high-quality synthesis of current evidence for patients and rheumatologists seeking alternative and beneficial treatments for rheumatoid arthritis.
- In addition to measurement of methodological quality of included studies by Cochrane risk of bias tool, this systematic review will evaluate the strength of evidence according to the GRADE approach, to inform clinical decision-makers.
- Some unpublished randomized controlled trials with negative findings might be missed, so funnel plots will be conducted to detect possible publication bias in order to get an objective conclusion.

ABSTRACT

Introduction: Total glucosides of paeony (TGP) is a natural plant extract, which is widely used in China in treating rheumatoid arthritis. Many relevant randomized controlled trials (RCTs) about TGP for rheumatoid arthritis are available. However, these RCTs haven't been systematically reviewed. This systematic review aims to examine the effectiveness and safety of TGP in patients with rheumatoid arthritis.

Methods and analyses: We will search RCTs on TGP in treating rheumatoid arthritis until February 2016, by searching PubMed, Embase, Cochrane Central Register of Controlled Trials and four Chinese databases (Chinese Biomedical Database, China National Knowledge Infrastructure, Wanfang Database and Chinese Scientific Journal Database). Trial registers and reference lists of retrieved articles will also be searched to identify potential articles. RCTs comparing TGP with placebo, no treatment, or disease modifying anti-rheumatic drugs for patients with RA will be retrieved. The primary outcomes will be disease improvement and disease remission. The secondary outcomes will be surrogate outcomes, symptoms, adverse effects and quality of life. Two reviewers will independently extract data containing participants, interventions, comparisons, outcomes, etc. The methodological quality of each included studies will be evaluated using the Cochrane risk of bias tool, and the strength of evidence on pre-specified outcomes will be assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation approach. Review Manager 5.3 software will be used for data analyses. Meta-analyses will be performed if the data are sufficiently homogeneous, both statistically and clinically. Possible publication bias will also be checked by funnel plots once the number of included studies is sufficient.

Ethics and dissemination: Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research.

Trial registration number: PROSPERO 2015:CRD42015026345

Key Words: Rheumatoid Arthritis; Total Glucosides of Paeony; Herbal Medicine; Systematic Reviews; Meta-analyses

INTRODUCTION

Description of the condition

Rheumatoid arthritis (RA) is the most common type of chronic autoimmune arthritis that causes pain, stiffness, joint swelling, deformity and loss of function. Recently, an estimated over 1.3 million Americans suffer RA, with a global prevalence of 0.24%.[1, 2] Data from the Global Burden of Disease 2010 study showed that the disability adjusted life years (DALYs) for RA had been increased from 3.3 million in 1990 to 4.8 million in 2010.[2] Therefore, RA remains a serious disease imposing a considerable burden for patients, their families and society. In order to relieve pain, avoid irreversible joint destruction and disability, RA calls for early and systematic treatment with timely adjustment.

Nowadays, disease modifying anti-rheumatic drugs (DMARDs) with effects of lowering disease activity and retarding joint erosion, remain the first-line treatment for RA. Meanwhile, the most common concern about DMARDs is safety. A clinical trial published in Annals of the Rheumatic Diseases has reported that methotrexate (MTX) and leflunomide (LEF) are associated with the increased incidence of hepatotoxicity.[3] Some patients may need to stop treatment with DMARDs because of adverse effects. In addition, some patients with RA do not respond to DMARDs. Biologic agents, also known as biologic DMARDs, have been proven to be effective for RA, especially for patients who fail to respond to DMARDs.[4, 5] Nevertheless, the remarkably high costs limit the application of biologics. Meanwhile, biologics exposure appears to confer an increased risk of serious infections.[6] In these cases, natural products with therapeutic potential have drawn more and more attention.[7]

Description of the intervention

Total glucosides of paeony (TGP) is an active compound extracted from the roots of a Chinese herb named *Paeonia lactiflora Pall,* with paeoniflorin accounting for 90% of its active components.[8] In China, TGP has been approved as a disease-modifying oral drug for RA since 1998, by the China Food and Drug Administration. Now, TGP is widely used to treat RA in China. So far, many experimental studies have shown the anti-inflammatory and immunoregulation actions of TGP.[9, 10, 11] For example, a study

investigating the effects of TGP on the activities of synoviocytes in rats with collagen-induced arthritis, found that TGP could significantly decrease the production of TNF-alpha and interleukin-1, and inhibit the proliferation of synoviocytes.[9] Another study revealed that TGP treatment could significantly increase the number and percentage of Treg cells in lupus CD4(+) T cells.[10] A review published in 2011 reported that paeoniflorin had immunosuppressive effects in adjuvant arthritis rats.[11] In addition, the beneficial effects of TGP have also been reported in some clinical trials including randomized controlled trials (RCTs).[12, 13] A multicenter RCT included 370 patients with RA found that TGP might be effective in the improvement of joint function without severe adverse effects.[12] A recent RCT published in English enrolled 268 patients with active RA suggested that TGP could significantly reduce the incidence of liver damage caused by MTX and LEF.[13]

Why it is important to perform this review

TGP is a natural plant extract and is popularly applied to treat RA in China. Although four systematic reviews on TGP in treating RA are available,[14,15,16,17] all of them are in Chinese and none of them are adequate in systematic reviewing according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[18] Two reviews [14,15] respectively included seven studies (published in 2005-2007) and 10 studies (published in 2002-2010) with different methodological quality. However, no subgroup analysis or sensitivity analysis was performed in them. A review including nine studies between 2005 and 2009 pooled different outcomes using fixed-effect model.[16] The latest review including 15 studies between 2005 and 2011 evaluating a composite outcome measure named overall effect as the main outcome measure.[17] Due to these shortcomings, the effect of TGP for RA has not be been adequately assessed. Therefore, a comprehensive, updated and PRISMA-compliant systematic review of RCTs is necessary to evaluate the effect of TGP for RA, to inform both clinical practice and further research.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness and safety of TGP for patients with RA.

METHODS AND ANALYSIS

Study registration

The original protocol of this systematic review has been documented in PROSPERO(ID= CRD42015026345).[19] This is a revised version which will also be uploaded in PROSPERO.[19] The systematic review will be conducted according to the revised protocol and be reported in accordance with the PRISMA statement.

Eligibility criteria

Types of studies

Only RCTs will be eligible for inclusion irrespective of language or publication status. Quasi-randomized trials will be excluded.

Types of participants

Adult participants (18 years and older) of any gender or ethnicity, meeting with one recognized diagnostic criteria of RA (the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria) will be included.[20, 21] Studies without description of diagnostic criteria will not be considered.

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Studies assessing TGP with or without co-intervention(s) for patients with RA regardless of dosage will be included. Control interventions should be placebo, no treatment, DMARDs (traditional or biologic). TGP compared with any of Chinese patent medicines or herbal formulations will be ineligible. Complex intervention involving TGP but no separate report on outcomes of TGP will be excluded. The duration of therapy should be more than 12 weeks.

Types of outcome measures

Primary outcomes

(1) Disease improvement (Measured by any validated improvement criteria of RA, such as the ACR20 response.[22])

(2) Disease remission (Measured by any validated remission criteria of RA, such as the Disease Activity Score (DAS28) less than 2.6.[23, 24])

Secondary outcomes

(1) Adverse effects

(2) Pain (Measured by a visual analog scale (VAS))

(3) Health-related quality of life (Measured by a validated tool)

(4) C reactive protein (CRP)

(5) Erythrocyte sedimentation rate (ESR)

Search methods

Electronic searches

The following databases will be searched from their inception to February 2016: Pubmed, Embase, Cochrane Central Register of Controlled Trials, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Database and Chinese Scientific Journal Database (VIP).

Searching other resources

Clinical trials registry platforms will be searched, including the International Clinical Trials Registry platform (http://www.who.int/ictrp/network/primary/en/), the U.S. National Institutes of Health Ongoing Trials Register (http://clinicaltrials.gov/), and the ISRCTN registry (http://www.controlled-trials.com/). We will also screen the reference lists of retrieved articles to identify missing eligible studies.

Search strategies

Search strategies in English electronic databases will be listed in Appendix 1, and will be adapted for other resources with appropriate terms. No language restriction will be applied.

Study selection

Two reviewers will independently screen all titles and abstracts of the records. Full texts of potentially eligible studies will be retrieved for further identification according to the eligibility criteria. Any uncertainty or discrepancy will be resolved by discussion. Details of the study screening process will be shown in Figure 1.

Data extraction

Two reviewers will independently extract data in accordance with a pre-designed data form using Excel (version Microsoft Excel 2007). Data will be checked by additional two reviewers. Disagreements will be resolved by discussion.

Extracted information will comprise the following sections:

(1) General information (publication years, number of authors, the first author, study design, sample size, demographics, setting.)

(2) Participants (diagnostic criteria, condition of RA, baseline comparison, withdrawals, loss to follow-up.)

(3) Interventions (dosage, administration, duration, follow-up, comparisons.)

(4) Outcome measures, results and adverse effects.

We will seek missing information by contacting the original authors whenever possible. Any discrepancies will be resolved by discussion or consulting a third reviewer.

Quality assessment

Assessment of Risk of Bias

Two reviewers will independently evaluate the risk of bias for each included studies using the Cochrane Collaboration's risk of bias tool, consisting of the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.[25] We will judge each item as low, high, or unclear risk of bias. Any uncertainty or discrepancy will be resolved by consulting a third reviewer.

Quality of Evidence

We will judge the quality of evidence for the main comparison according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[26] The following five factors will be judged for each outcome in the main comparison: limitations in study design and execution, inconsistency of results, indirectness of evidence, imprecision and publication bias. Accordingly, the quality of the evidence for each outcome will be graded as high, moderate, low or very low.

Data analysis

RevMan 5.3 software will be used for data analysis. Studies included will be stratified by different types of comparisons. Dichotomous data will be reported as risk ratios (RR) and continuous data as mean difference (MD) or weighted mean difference (WMD), both with their 95% confidence intervals (CI). We will perform

intention-to-treat analysis (ITT) where possible. For missing or incomplete data, we will attempt to obtain by contacting the original authors.

Meta-analyses will be performed if the data are sufficiently homogeneous, both statistically and clinically. Otherwise, analyses will be descriptive. Before pooling data, heterogeneity will be tested using I-squared (I^2). If heterogeneity is low ($I^2 \leqslant 50\%$), fixed effect model will be applied to analyze data, and random effects model will be used when heterogeneity is moderate ($50\% < I^2 < 75\%$). Data will not be pooled when heterogeneity is high ($I^2 \geqslant 75\%$).

We will perform subgroup analyses according to different clinical characteristics (e.g., different durations) and sensitivity analyses on the basis of study quality where possible. Funnel plots will be created to detect possible publication bias when sufficient studies (more than 8) are identified.

In addition, we will generate a "Summary of finding table" using GRADE profiler (version 3.6) to calculate the relative effect and the number of patients needed to treat in order to present important outcomes and the strength of evidence supporting these outcomes under the main comparison.

Ethics and dissemination

Ethics approval is not required as this study will not involve patients. The results of this study will be submitted to a peer-reviewed journal for publication, to inform both clinical practice and further research.

DISCUSSION

RA can cause pain, joint destruction and disability, placing a considerable burden on patients and society. Nowadays, DMARDs remain the first-line treatment for RA. However, some patients may need to stop treatment with DMARDs due to adverse effects, and some patients do not respond to DMARDs. Biologic agents have been proven to be effective for RA, but the remarkably high costs limit its use. TGP, a natural plant extract, has been approved as a disease-modifying drug for RA in China since 1998. Nowadays, TGP is widely used for the treatment of RA in China. So far, some RCTs have reported the beneficial effects of TGP in treating RA alone or in combination with some other DMARDs. However, the effectiveness and safety of

TGP for RA have not been systematically reviewed according to the PRISMA statement. This systematic review will provide a high-quality synthesis of current evidence for patients and rheumatologists seeking alternative and beneficial treatments of RA.

The strengths of this systematic review are twofold. Firstly, this will be the first PRISMA-compliant systematic review to assess the effectiveness and safety of TGP for patients with RA. The study selection, data extraction and quality assessment will be conducted independently by two reviewers. Secondly, in addition to measurement of methodological quality of each included studies, this systematic review will evaluate the strength of evidence according to the GRADE approach. Nevertheless, limitations may also exist in this systematic review. Although we will conduct an extensive and unbiased search, some unpublished RCTs with negative findings might be missed. We will detect possible publication bias through funnel plots in order to get an objective conclusion. Additionally, it might be difficult to retrieve raw date from some published papers. We will try to contact the original authors to seek information. However, we believe the results of this study could provide objective evidence on the effect of TGP in treating RA, which will be beneficial for patients and practitioners.

Figures

Figure 1 Flow Diagram of Study Search and Identification.

Appendixes

Appendix 1 Search strategies for English electronic databases.

Contributors

QWT and JL conceived and designed the study. JL and DEJ developed the search strategy. GYY and QWT provided methodological perspectives. JL drafted and refined the study protocol with contributions from all coauthors (GYY, DEJ, YZZ,

JMW, WPK, QWT). YZZ and WPK will search articles and conduct study selection. JL and JMW will perform data extraction and assessment of quality. DEJ will conduct data analyses. YZZ and QWT will verify data extraction and data analyses. All authors read and approved the final manuscript.

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Competing interests

None declared.

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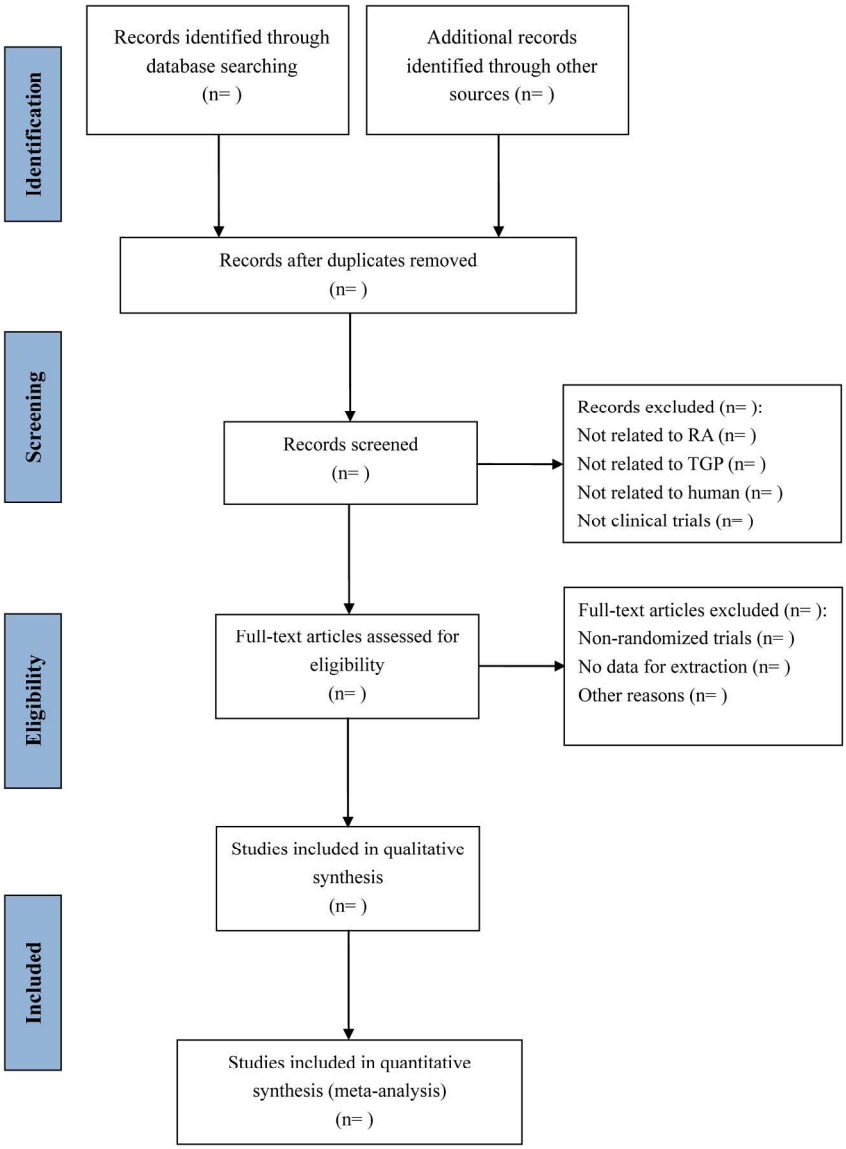

Figure 1 Flow Diagram of Study Search and Identification.
175x231mm (300 x 300 DPI)

Appendix 1. Search strategies for English electronic databases.

Databases	Strategies
Pubmed	#1 paeon*[Title/Abstract] #2 TGP[Title/Abstract] #3 "Arthritis, Rheumatoid"[Mesh] #4 rheumatoid arthritis[Title/Abstract] #5 (#1 OR #2) #6 (#3 OR #4) #7 (#5 AND #6)
Cochrane	#1 paeon*:ti,ab,kw (Word variations have been searched) #2 TGP:ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees #4 rheumatoid arthritis:ti,ab,kw (Word variations have been searched) #5 (#1 OR #2) #6 (#3 OR #4) #7 (#5 AND #6)
Embase	#1 paeon* #2 TGP #3 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis' #4 #1 OR #2 #5 #3 AND #4

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3, 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4, 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5, 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6, 7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6, 7, 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	Appendix 1

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, Figure 1
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7, 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6, 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8, 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8, 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8