INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Toujie Quwen Granule Used With Conventional Western Therapy for COVID-19: a protocol for systematic review and meta-analysis

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Review question / Objective: **The purpose of this study is to explore the efficacy and safety of Toujie Quwen granules(TJQW) in the treatment for COVID-19 by pooling the current randomized controlled trials, in order to provide high-quality clinical evidence.**
Eligibility criteria: **Inclusion criteria: Type of study In this study only RCTs will be eligible for inclusion. Types of participants The eligible patients with confirmed COVID-19 according to the "New Coronavirus Pneumonia Diagnosis and Treatment Program" (trial seventh edition). Types of interventions . Experimental interventions The experimental interventions was treated with Toujie Quwen granules combined basic treatment. Control interventions The control group include antiviral, oxygen therapy and nutritional support.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 May 2021 and was last updated on 11 May 2021 (registration number INPLASY202150038).

INTRODUCTION

Review question / Objective: **The purpose of this study is to explore the efficacy and safety of Toujie Quwen granules(TJQW) in the treatment for COVID-19 by pooling the current randomized controlled trials, in order to provide high-quality clinical evidence.**

Condition being studied: **Coronavirus Disease 2019 (COVID-19) is epidemic infectious disease result from 2019 novel coronavirus (2019-nCoV). COVID-19 has**

unique characteristics, for example strong infectivity, long incubation period, various clinical manifestations and wide susceptible range. Up to now, COVID-19 have swept the globe. According to the disease severity, COVID-19 include mild, ordinary, severe and critical types. The clinical manifestations of patient include Fever, cough, nasal congestion, runny nose, diarrhea, dyspnea, muscle or joint pain, pneumonia, and the severe cases even dead. Currently, the therapy recommended in western clinical practice guidelines for COVID-19 include antiviral, oxygen therapy and nutritional support, however, no specific and effective drug is available for COVID-19. In China, Chinese traditional medicine are recommended by the Chinese Clinical Guidance of COVID-19 Pneumonia Diagnosis and Treatment (7th edition) published by China National Health Commission on March 4, 2020, for example Xuebijing injection, lianhua qingwen granules, jinhua qinggan granules. Moreover, since the spread of COVID-19, Chinese medicine hospital of every province recommended unique TCM formulations for COVID-19 treatment, for exampe Toujie Quwen granules(TJQW). TJQW includes 16 TCM components, including Forsythiae Fructus (lian-qiao), edible tulip (shan-ci-gu), Lonicera japonica (Japanese honeysuckle flower, jin-yin-hua), Radix Scutellariae baicalensis (huang-qin), Folium Isatidis (da-qing-ye), Bupleurum root (chai-hu), Artemisia apiacea (qing-hao), Periostracum Cicadae (chan-tui), Radix Peucedani (qian-hu), Fritillaria cirrhosa (chuan-bei-mu), Fritillaria thunbergii (zhe-bei-mu), Poria cocos (fu-ling), Fructus Mume (wu-mei), radix Scrophulariae (xuan-shen), Astragalus propinquus (huang-qi), and radix Pseudostellariae (tai-zi-shen). In addition, network pharmacology studies have demonstrated that therapeutic mechanism of Toujie Quwen granules in COVID-19, and TJQW treatment for COVID-19 was associated with elevation of immunity and suppression of inflammatory stress, including regulation of inflammatory response, viral process, neutrophil mediated immunity, PI3K-Akt signaling pathway, MAPK signaling pathway, Jak-STAT signaling pathway, Complement and coagulation cascades, and HIF-1 signaling pathway.

METHODS

Search strategy: Relevant randomized controlled trials(RCTs) were systematically searched from four English medical databases (PubMed, Embase, Web of Science, the Cochrane Library) and four Chinese medical databases (CNKI, VIP, CBM, WF database), and the search time is January 2020 to May 2021. The search strategy will be based on the guidance of the Cochrane handbook.

Participant or population: Patients with confirmed COVID-19.

Intervention: Toujiequwen granules and basic treatment(antiviral, oxygen therapy and nutritional support).

Comparator: Basic treatment(antiviral, oxygen therapy and nutritional support).

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Inclusion criteria: Type of study In this study only RCTs will be eligible for inclusion. Types of participants The eligible patients with confirmed COVID-19 according to the "New Coronavirus Pneumonia Diagnosis and Treatment Program" (trial seventh edition). Types of interventions . Experimental interventions The experimental interventions was treated with Toujie Quwen granules combined basic treatment. Control interventions The control group include antiviral, oxygen therapy and nutritional support.

Information sources: Four English medical databases (PubMed, Embase, Web of Science, the Cochrane Library) and four Chinese medical databases (CNKI, VIP, CBM, WF database).

Main outcome(s): The cure, aggravation and mortality rate.

Additional outcome(s): The recovery rate of fever; the recovery rate of cough; the recovery rate of fatigue; the duration of fever; the duration of cough; the duration of fatigue; negative conversion rate of nucleic acid test; improvement or recovery of chest CT manifestations; Length of hospitalization; adverse events.

Data management: Two researchers will independently and repeatedly screen the literature, extract the data, and cross check the results. The researchers first screened out the irrelevant articles by reading the title and abstract, then read the full text and re screened strictly according to the inclusion / exclusion criteria to determine the final included RCTs. When different opinions arise, differences will be decided by three investigators through consultation. The following information from selected studies will be summarized in a unified table: 1) basic characteristics: author name, time of publication, country, diagnostic criteria, inclusion criteria, exclusion criteria, sample size; 2) baseline characteristics of the patients: mean baseline age, the level of severity of COVID-19, basic therapies; 3)treatment and control measurements: dose of TJQW, type of control, frequency and course of treatment; 4)outcomes; 5)Adverse events.

Quality assessment / Risk of bias analysis: Two researchers will independently and repeatedly evaluate risk of bias in included studies, and cross check the results. When different opinions arise, differences will be decided by three investigators through consultation. Risk of bias for the included RCTs will be assessed by Review Manager 5.3. Evaluation items are as follows: 1)whether random sequences are generated; 2)whether distribution is hidden; 3)whether participator and researchers are blinded; 4)whether study outcomes are blinded; 5)whether outcome data exist missing; 6)whether reporting is selective; 7) other sources of bias.

Strategy of data synthesis: 1) Meta-analysis for continuous outcomes: Mean difference (MD) or Std Mean difference (SMD), 95% Confidence interval (CI) and P values 2) Meta-analysis for dichotomous outcomes: Odds ratio (OR) or relative risk (RR), 95% Confidence interval (CI) and P values 3) the statistical heterogeneity: The Q value test and I2 index.

Subgroup analysis: 1) the level of severity of COVID-19: mild, ordinary, and severe types.

Sensitivity analysis: Sensitivity analysis will be performed by excluding studies with high risk of bias and change the statistical model.

Country(ies) involved: China.

Keywords: Toujie Quwen granule; Coronavirus Disease 2019; protocol; systematic review.

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