


BMJ Open Clinical application of oral Chinese Patent Medicines in ophthalmology: a scoping review protocol

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ABSTRACT

Introduction The prevalence of eye diseases has been increasing worldwide. In China, in addition to conventional medicine, Traditional Chinese Medicine (TCM) plays an important role in maintaining people's vision health. Although less flexible and targeted than TCM decoction, Chinese Patent Medicines (CPMs) are stable and well used. In recent years, CPMs have been increasingly used in ophthalmology clinics by TCM practitioners and by Western doctors in general hospitals. However, comprehensive evidence for using CPMs in ophthalmology is lacking.

Aim We will apply the methodology of scoping review to systematically search and sort out the available evidence on oral CPMs for the treatment of eye diseases, identify the distribution of evidence in this field and provide a basis for clinical practice and medical decisions.

Methods The scoping review will be implemented in the following seven steps: (1) defining the research question; (2) searching *National Essential Medicines List (2018 edition)*, *National Basic Medical Insurance, Work Injury Insurance and Maternity Insurance Drug Catalog (2020 edition)* and *Chinese Pharmacopoeia (2020 edition)* for oral CPMs for the treatment of eye diseases; (3) searching Embase, Web of Science, PubMed, Cochrane Library, Chongqing VIP Chinese Scientific Journals Database, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database and Wanfang Database for relevant literature published from inception to December 2021; (4) developing eligibility criteria; (5) screening the studies based on inclusion criteria; (6) extracting relevant data and lastly, (7) collating, summarising and reporting the results.

Ethics and dissemination Since the scoping review aims at collecting data from publicly available publications, this study does not require ethical approval. The results will be published in a peer-reviewed journal and presented at scientific conferences.

INTRODUCTION

The eye is an essential sensory organ in the human body. About 90% of the information people obtain from the outside world through the sensory organs is done through the eyes.^{1 2} The fine structure of the eye, even a slight injury, may cause structural changes, resulting in decreased visual function or even complete loss, which will lead to

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The protocol is the first to systematically map out the evidence published in Chinese or English related to the clinical application of oral Chinese Patent Medicines (CPMs) in ophthalmology.
- ⇒ We will comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extensions for Scoping Reviews tools to ensure completeness and transparency of the scoping review.
- ⇒ The protocol only includes studies published in Chinese or English, which does not consider all oral CPMs to treat eye diseases.
- ⇒ We will not assess the quality of evidence that we searched as this is a scoping review.

immeasurable losses to individuals, families and society.^{2 3} Data from the World Report on Vision indicate that at least 2.2 billion people worldwide have visual impairment or blindness.⁴ Fricke *et al* found that 1.8 billion people worldwide have presbyopia, with 826 million of them suffering from near vision impairment due to unaddressed presbyopia.⁵ Flaxman *et al* Lancet Global Health have conducted an estimate of the number of people with distance vision impairment or causes of blindness was estimated globally.⁶ At least 237.1 million people worldwide were expected to have moderate or severe distance visual impairment in 2020, the number that includes unaddressed refractive error (127.7 million), cataract (57.1 million), age-related macular degeneration (8.8 million), glaucoma (4.5 million) and diabetic retinopathy (3.2 million).⁶ In 2020, 38.5 million people worldwide were expected to be blind, mainly due to cataract (13.4 million), unaddressed refractive error (8.0 million) and glaucoma (3.2 million).⁶ In addition, the ageing of the population, coupled with lifestyle changes, is still leading to an increase in the number of eye diseases and visual impairment.⁴ At the same time, the treatment of many diseases in ophthalmology suffers from undefined

pathogenesis, ineffective western medical treatment or local invasive drug injections as the main treatment, which can lead to treatment non-response or resistance, expensive treatment, limited maintenance of drug efficacy, injection-related complications and drug-related complications, which impose a heavy physical and psychological burden on patients. Therefore, health systems in various countries face considerable challenges⁴ and need to seek alternative drugs to treat eye diseases.

Traditional Chinese Medicine (TCM) ophthalmology has been an integral discipline of TCM for >2000 years. The unique theories and applications were developed on the basis of TCM and have gradually evolved.⁷ The earliest existing medical text in China, *the Yellow Emperor's Inner Classic (Huang Di Nei Jing, 黄帝内经)*, first proposed the anatomy and physiology of the eyes.^{7,8} Acupuncture treatments for >30 eye conditions and many systemic diseases were described in this book.^{7,8} In 1644, at the end of the Ming dynasty, Fu Ren-yu (傅仁宇) wrote *A Close Examination of the Precious Classic on Ophthalmology (Shen Shi Yao Han, 审视瑶函)* based on the former works on TCM ophthalmology.⁸ The book recorded 108 eye diseases and included >300 prescriptions.⁸ Among them, the listed *Shi Hu Ye Guang Wan* (Dendrobium and Night Light Pill, 石斛夜光丸) and *Zi Yin Di Huang Wan* (Yin-enriching Rehmannia Pill, 滋阴地黄丸) are famous ophthalmic medicines which are still in clinical use. Currently, ophthalmology education and research departments have been established in universities, and ophthalmology clinics and wards have been opened in hospitals in China.^{2,9,10} In addition, universities in some provinces have opened master's and doctoral programmes in TCM ophthalmology.⁸ Moreover, TCM Ophthalmology Association and the Integrated Ophthalmology Association have been established in various regions and cities to provide a platform for the development of TCM ophthalmology.⁷

With numerous eye prescriptions and treatments, we have formed a unique and complete treatment system, including TCM decoction, acupuncture, massage, topical applications and Chinese Patent Medicines (CPMs).¹¹ CPMs are the preparation that can be directly used to prevent and treat diseases under the guidance of TCM theory, using Chinese herbal slices as raw materials and made into a dosage form with certain specifications according to the prescribed prescriptions and standards.¹² The *Beneficial Formulas from the Taiping Imperial Pharmacy (Tai Ping Hui Min He Ji Ju Fang, 太平惠民和剂局方)*, which was issued in 1151, was compiled by the Northern Song Dynasty Tai Medical Bureau and was the first official standard for CPMs in the world.¹³ The book was divided into 10 volumes and 14 categories, with 788 prescriptions. It has a clear structure detailing the actions, indications, compositions, concoction requirements, production process, dosage, administration methods and contraindications of each prescription, which facilitates clinical use and passes it down to this day without fail. Many CPMs in the book, such as *Huo Xiang Zheng Qi San* (Agastache Qi-Correcting Powder, 藿香正气散), *Shen Ling Bai Zhu*

San (Ginseng, Poria and *Atractylodes macrocephala* Powder, 参苓白术散) and *Li Zhong Wan* (Center-Regulating Pill, 理中丸) are still in clinical use.¹⁴ Compared with TCM decoction, CPMs can be taken directly without being decocted, which is very convenient for patients with acute and critical illnesses and those who need long-term treatment. In addition, CPMs are widely used in China because of their small size and unique packaging, which makes them easy to store and carry.^{15,16} However, clinicians, patients and policymakers in China and other countries remain sceptical about the intervention due to the lack of comprehensive evidence on oral CPMs in ophthalmology. Therefore, in an era of evidence-based healthcare, it has become increasingly important to use appropriate methods to organise and summarise the evidence.

Peters *et al* pointed out that when the articles have not been thoroughly reviewed or have a considerable heterogeneity, it is impossible to conduct a more detailed systematic review of the evidence; the scoping review can be used.¹⁷ Contrary to other review methods, an attractive feature of the scoping review method is that it does not limit the parameters of the review to randomised controlled trials, nor does it require the articles included in the study to be methodologically consistent.¹⁸ By systematically searching, selecting and integrating existing knowledge, scoping review can be used to explore exploratory research questions, map types of evidence and gaps in research related to specific fields and guide future research priorities.¹⁹ Therefore, the scoping review will provide a systematic overview of the clinical use of oral CPMs in ophthalmology, mapping the distribution of relevant evidence. It will provide a basis for decision-making for ophthalmology clinicians and relevant researchers. Moreover, it can also promote the research and rational use of oral CPMs and provide a new option for global eye disease control.

METHODS

We will follow guidelines recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extensions for Scoping Reviews (PRISMA-ScR) checklist when reporting the scoping review.¹⁹ In addition, to increase their relevance for decision-making, further improve the completeness of reporting and facilitate appraisal of results, we will follow the PRISMA Protocol guidelines.²⁰ The methodology of the scoping review will be based on the framework proposed by Arksey and O'Malley²¹ and further refined by Levac *et al*¹⁸ and Daudt *et al*.^{18,22} As the prospective international register of systematic reviews (PROSPERO) does not accept the scoping review, so the protocol was not registered.

Identifying the research questions

Our objective is to answer the following research questions:

1. What are the oral CPMs recommended by the national government authorities in China for the treatment of eye diseases?

2. What are the actions and indications of the oral CPMs to be evaluated, and which eye diseases can be treated with oral CPMs?
3. What is the distribution of clinical evidence for oral CPMs in ophthalmology?

Identifying relevant medicines and studies

Identifying relevant medicines

First, we will search the *National Essential Medicines List (2018 edition)*, *National Basic Medical Insurance, Work Injury Insurance and Maternity Insurance Drug Catalog (2020 edition)* and *Chinese Pharmacopoeia (2020 edition)* promulgated by the Chinese government by computer. The search terms will be “eye”, “eyes”, “vision”, “eyesight” including oral drugs in the CPMs, excluding injections, topical medications. Then we will find and read the Instructions for Use (IFU) of oral CPMs through the official website of the National Medical Products Administration or www.yaozh.com and screen the CPMs based on whether the origins of the drugs described in the IFU were from China and whether eye diseases or eye symptoms were included.

Identifying relevant studies

The authors will search eight electronic databases, including Embase, Web of Science, PubMed, Cochrane Library, Chongqing VIP Chinese Scientific Journals Database (VIP), Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM) and Wanfang Database, for oral CPMs in the treatment of eye diseases that published from inception up to December 2021. The search terms will combine text words with the medical subject heading terms. There are two strategies available for searching. If the label of the CPM mentioned that the indications involve an eye disease, the search strategy would combine ‘generic name of the drug’ and ‘disease name’. If it only contained eye symptom of some relevant eye disease, the search words would use ‘generic name of the drug’ alone. We took Qiming granule for diabetic retinopathy as an example and listed the specific search details of the drug in eight databases in eight tables separately. The details are represented in online supplemental tables 1–8.

Eligibility criteria

Inclusion criteria

The scoping review will include clinical studies (randomised controlled trials, case-control studies, cohort studies and case series studies) and systematic reviews of CPMs for the treatment of eye diseases.

The experimental group intervention will be restricted to oral CPMs and the control group intervention to conventional medications (such as routine drugs, laser or surgery).

Exclusion criteria

Studies will be excluded if the following conditions are met:

1. The study’s experimental or control group interventions are combined with other TCM preparations or external treatments.
2. If there are duplicate publications, do not include the new publications and keep the old ones.

Medicine and study screening

Medicine screening

Oral CPMs will be retrieved and screened according to the requirements of ‘Identifying relevant medicines’. Finally, the CPMs will be entered into a predefined form and duplicate drugs will be removed to obtain the list of CPMs to be evaluated.

Study screening

We will conduct the study search based on the list of CPMs screened above. Two reviewers will participate in the study screening and select 50 studies for prescreening, and the formal screening will begin after unifying the criteria. First, we will export the data collected from the electric databases to EndNote (V.X9) reference management software and remove all duplicate studies. Next, two reviewers will independently screen all study abstracts and titles retrieved using the above literature search strategy to determine studies that meet the inclusion criteria. If there is a disagreement about the included studies, two reviewers will discuss and reach a consensus; those who cannot agree may consult a third reviewer. We will document this process and draw a flow chart to demonstrate the screening process.

Charting the data

Two reviewers will independently extract data using a predesigned form. They will first extract the information of five CPMs and five studies to ensure the conformity in the extraction process. Following this, two reviewers will independently complete the data extraction from CPMs and studies. Data extracted from the IFU of CPMs will include the following: generic names, dosage form, actions, indications, syndromes, duration of treatment, compositions and prices. Data extracted from studies will include the year of publication, financial support, study design, sample size, participant, intervention and outcome.

Collating, summarising and reporting the results

All extracted data will be presented as text combined with tables or charts, line graphs to depict trends, bubble charts to show the distribution of evidence and pie charts to portray the proportion of each component. The analysis will include the generic names, actions, indications, syndromes, duration of treatment, composition and prices of oral CPMs for the treatment of eye diseases; annual trends in publication, funding support, sample size, interventions and outcomes of clinical studies.

Patient and public involvement

The conception, design and planning of this study did not involve patients or the public.

The planned start and end dates

We drafted the protocol on 1 November 2021 and initiated the scoping review on 1 December 2021. We have completed drug screening and relevant literature screening. And now, we are extracting the data and charting the results. We anticipate that this review will be completed by the end of August in 2022.

ETHICS AND DISSEMINATION

This scoping review does not require ethical approval as it synthesises data from publicly available sources. The results of this review will be disseminated through a peer-reviewed journal or conference presentations.

DISCUSSION

We will use the protocol to conduct our scoping review. There are two reasons for the importance of the scoping review protocol: (1) it allows the reviewers to plan carefully to predict potential problems; (2) it strictly formulates the eligibility criteria to prevent arbitrary decisions in screening and data extraction.²³

Although systematic reviews related to oral CPMs for the treatment of eye diseases have been published previously, reviews have mostly focused on one CPM or one disease and have not provided comprehensive evidence on the clinical use of oral CPMs in ophthalmology. The purpose of this protocol is to identify and classify the evidence to review the research priorities for the use of oral CPMs in ophthalmology. The scoping review will help us to sort out the indications of CPMs, give more specific recommendations on the recipes and syndromes of CPMs for the treatment of eye diseases and make recommendations for future research. The target audience for the results will be researchers, institutional policymakers, pharmaceutical companies and patients.

In addition, this scoping review protocol provides a research framework, which can be used as a long-term goal to provide future research in the treatment of eye diseases with TCM. By pooling various sources of knowledge, it is helpful to determine the current lack of scientific evidence for the treatment of eye diseases in TCM and the areas that need to be studied. This kind of meaningful literature synthesis is the first step in developing new evidence-based practices, helping formulate interventions and programmes to improve patients' symptoms of eye diseases and helping global blindness prevention and treatment activities.

Contributors KX, XLiao and LL contributed to the design or conception of the scoping review. KX wrote the first draft of the manuscript. YL and ZH constructed the search. XLI, WZ and QZ performed a preliminary search. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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