PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Dietary supplements and herbal medicine for COVID-19: a systematic review of randomized control trials	1
ABSTRACT			
Structured summary	2	Background: The world is currently struggling with the Coronavirus disease 2019 (COVID-19) pandemic. Dietary supplements (DSs) and herbal medicine provide a potentially convenient and accessible method for its recovery, but direct evidence is limited. Objective: This study aims to investigate the effectiveness of DSs and herbs in patients with COVID-19. Methods: A systematic literature search was conducted in multiple electronic English and Chinese databases. Randomized controlled trials (RCTs) involving DSs or herbal medicine interventions on patients with COVID-19 from November 2019 to February 2021 were included. Data was extracted, summarized and critically examined. Results: Out of 9402 records identified in the initial search, twelve RCTs were included in this review. Risk of bias of these RCTs was deemed high. Most of the trials were of low methodologic quality. Nine studies showed herbal supplements were beneficial to the recovery of COVID-19 patients; zinc sulfate could shorten the duration of loss of smell but not total recovery from COVID-19. No severe adverse events were reported. Conclusion: Herbal supplements may help patients with COVID-19, zinc sulfate is likely to shorten the duration of olfactory dysfunction. DS therapy and herbal medicine appear to be safe and effective adjuvant therapies for patients with COVID-19. These results must be interpreted with caution due to the overall low quality of the included trials. More well-designed RCTs are needed in the future. Keywords: COVID-19; herbs; dietary supplement; diet; systematic review; virus	2
INTRODUCTION			
Rationale	3	This is a systematic review evaluated by the Cochrane Risk of Bias Tool, Review Manager (RevMan) and the Jadad scale.	3
Objectives	4	P: Participants with a diagnosis of COVID-19. I: Any type of DSs (dietary ingredients include vitamins, minerals, amino acids, and herbs or botanicals, as well as other substances that can be used to supplement the diet) and herbs medicine. C: Not DSs or herbal medicine O: Recovery S: RCT	/
METHODS			
Protocol and registration	5	The protocol is described in the Methods. Registration does not apply.	/
Eligibility criteria	6	Articles published in English or Chinese between November 2019 and February 2021 were included using the following inclusion criteria: human subjects relevant to COVID-19; RCTs; peer-reviewed journal articles; DSs or herbs	4

		involved in observational groups. Abstracts, surveys, editorials, commentaries, correspondence, case reports, literature reviews, and DSs or herbs vis extraoral administration or in the control group trials were excluded.	
		To observe the effect of DSs or herbs on COVID-19 patients, a comprehensive search strategies in Chinese and English data base before our submission date were designed and performed by experienced librarians, with a result of huge screening outcome. Since RCTs provide strong evidence for the efficacy of healthcare interventions, to best investigate the potential effect of DSs and herbs on patients with COVID-19, only RCT with human subjects were searched. Relevant trials and reviews for further eligible studies were searched synchronously for potentially eligible studies.	
Information sources	7	The English databases included Embase (1988 to 2021 Week 06), Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1996 to February 15, 2021), EBM Reviews - Cochrane Central Register of Controlled Trials (before January 2021), EBM Reviews - Cochrane Database of Systematic Reviews (2005 to February 10, 2021). The Chinese databases included China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), WanFang, and China Science and Technology Journal Database (VIP) (all before January 20, 2021).	3
Search	8	The electronic search strategies were shown in the attach files named "Systematic Review Search Strategies in English databases" and "Systematic Review Search Strategies in Chinese databases".	/
Study selection	9	The search strategy was designed and performed by experienced librarians with input from the study's principal investigators. Controlled vocabulary supplemented with keywords was used to search for studies describing DSs or herbs for COVID-19. Since RCTs provide strong evidence for the efficacy of healthcare interventions[23], to best investigate the potential effect of DSs and herbs on patients with COVID-19, only RCT with human subjects were searched. Relevant trials and reviews for further eligible studies were searched synchronously for potentially eligible studies. All the screenings were implemented by two authors independently, and any discrepancy was resolved by the discussion with the third author. Articles published in English or Chinese between November 2019 and February 2021 were included using the following inclusion criteria: human subjects relevant to COVID-19; RCTs; peer-reviewed journal articles; DSs or herbs involved in observational groups. Abstracts, surveys, editorials, commentaries, correspondence, case reports, literature reviews, and DSs or herbs vis extraoral administration or in the control group trials were excluded.	3
Data collection process	10	Data were extracted using a prepared excel table from each relevant trial by two reviewers independently: 1) RCT characteristics - first author, publication year, country, setting, design, registration, manufacture, and provider; 2) sample characteristics - population and sample size; 3) intervention characteristics - design, session, and follow up; 4) outcome characteristics - efficacy, main outcomes, follow up and safety monitoring. Safety was monitored by the reporting of adverse events (AEs). Data were extracted by two authors independently and revised by the third author.	4
Data items	11	A descriptive analysis of data items was completed for each study in Table1&2 in the manuscript.	8-9
Risk of bias in individual studies	12	The Cochrane Risk of Bias Tool for Randomized Controlled Trials was used to evaluate the potential risk of bias of the retrieved RCTs. The risk of bias tool covers six domains as the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Results were entered in the Revman software (Review Manager (RevMan) [Computer program]. Version 5.4.1, The Cochrane Collaboration, 2020) for the presentation of bias in a comprehensive manner. Additionally, the Jadad scale was used to evaluate the quality of each eligible study. The evaluation was determined in three domains: randomization, blinding and the fate of all participants. Studies with a total quality assessment score of 3–5 were categorized as high quality and 0–2 as low quality. All the assessments	4

PRISMA 2009 Checklist

		were conducted by two authors independently, and any discrepancy was settled through a discussion or consultation with the third review author.	
Summary measures	13	This is a systematic review without summary measures because meta-analysis was not conducted due to methodological and outcomes heterogeneity.	/
Synthesis of results	14	This is a systematic review without synthesis of results because meta-analysis was not conducted due to methodological and outcomes heterogeneity.	/

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	The risk of bias tool covers six domains as the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.	4
Additional analyses	16	This is a systematic review without additional analyses because meta-analysis was not conducted due to methodological and outcomes heterogeneity.	/
RESULTS			
Study selection	17	The study selection was included in the Figure 1 in the manuscript.	5
Study characteristics	18	The study characteristics were included in the Table1&2 in the manuscript.	8-9
Risk of bias within studies	19	The risk of bias of each study were shown in the Figure 2 and Table 1 in the manuscript.	7-8
Results of individual studies	20	A descriptive analysis of results of individual studies was completed for each study in Table1&2 in the manuscript.	8-9
Synthesis of results	21	This is a systematic review without synthesis of results because meta-analysis was not conducted due to methodological and outcomes heterogeneity.	/
Risk of bias across studies	22	The main reasons for downgrading the quality of included studies were the high risk of selection bias and performance bias. Detailed information on the evaluation of the methodological quality and risk of bias of original studies was summarized with Revman software in Figure 2.	6
Additional analysis	23	This is a systematic review without additional analysis because meta-analysis was not conducted due to methodological and outcomes heterogeneity.	/
DISCUSSION			
Summary of evidence	24	Herbal supplements seem to be an effective adjunctive therapy for patients with COVID-19, zinc sulfate is likely to shorten olfactory recovery. DS and herbal therapy appeared to be safe and effective adjuvant treatments for patients with COVID-19. Therefore, healthcare providers may be encouraged to provide herbal supplements for patients with COVID-19 and zinc sulfate may be used for patients with COVID-19 who suffered from anosmia and/or hyposmia with the support of relevant guideline makers.	13

Limitations	25	When interpreting findings regarding the impact of DSs and herbs on patients suffering from COVID-19, differences in study design should be considered. To reduce heterogeneity, we limited our analysis to RCTs only, excluding commentaries, cross-over trials, or case reports, which means that we could have missed some potentially important observational studies. It was difficult to compare these RCTs and generalize results because of the wide variation with the targeted population, modes of delivering the DS and herbal interventions, treatment sessions, outcomes, and follow-up periods. Based on evidence from this review, we found some promising effects of DSs and herbs on mitigating symptoms, improving inflammation markers, shortening recovery duration, and intensive care unit use of COVID-19 patients. However, most had a high or unclear risk of bias in many domains such as selection bias, detection bias, and reporting bias. Therefore, it is still premature to recommend those therapies in clinical practice. Further rigorous high-quality trials are required to confirm the efficacy of the DSs and herbs modalities for COVID-19.	13
Conclusions	26	Herbal supplements seem to be an effective adjunctive therapy for patients with COVID-19, zinc sulfate is likely to shorten olfactory recovery. DS and herbal therapy appeared to be safe and effective adjuvant treatments for patients with COVID-19. While this preliminary evidence showed a positive effect, the poor methodological quality of included studies makes it difficult to draw any firm conclusion. Caution is needed to translate these findings into clinical practice and standard care. More well-designed trials regarding interventions using DSs and herbs for COVID-19 are encouraged in the future.	13
FUNDING			
Funding	27	This study is supported by Shenzhen Special Fund for Introducing High-Level Medical Team Project (SZSM201502044).	13

For more information, visit: **www.prisma-statement.org**.