Herbal Medicine and COVID-19: An Umbrella Review

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ABSTRACT

Background: Most systems of traditional medicine have been using herbal medicines to prevent and treat acute respiratory conditions and various other conditions for centuries. The aim of this project is to identify and examine the systematic and narrative reviews reporting on the therapeutic use of herbal medicines as it relates to the prevention and treatment of COVID-19 and long COVID.

Methods: This paper is part of an umbrella review of studies related to natural health products and natural therapies for the prevention or treatment of COVID-19. It is a follow-up to a live review that was conducted by the World Naturopathic Federation between May 2022 and May 2023. PubMed and Google Scholar were searched for systematic and narrative reviews that met defined quality criteria.

Results: Over half of the initial systematic reviews were excluded as they did not meet the inclusion and AMSTAR criteria. The final paper included 25 narrative reviews and 41 systematic reviews (SR), with half of the SRs reporting on the safety of herbal interventions. Various therapeutic properties of over 60 herbal medicines were outlined, some individually and most of them as part of herbal formula (combinations).

Conclusion/Summary: Herbal interventions demonstrated statistically significant improved recovery in patients with COVID-19. The most common therapeutic properties identified were immunological properties, anti-inflammatory, anti-microbial, and antioxidant while the most frequently investigated herbs were *Glycyrrhiza glabra/uralensis, Tinospora cordifolia,* and *Curcuma longa*. More attention is needed on the regulation of herbal medicines, the quality of research, and the safety of herbal medicines.

Key Words Traditional medicine, effectiveness, complementary medicine, immune health, Chinese medicine, coronavirus

INTRODUCTION

Herbal medicine is a core component of traditional and complementary medicine worldwide.[1,2] Traditional systems of medicine, including Ayurveda, Caribbean, First Nations and Indigenous, Kampo, Traditional Chinese (TCM; see Appendix 1 for a glossary of terms and acronyms used in this manuscript), Tibetan, and Unani systems, among others, all employ herbal products or extracts in the treatment and prevention of disease. More than half of visits to naturopathic practitioners result in a form of herbal prescription.[2] Herbal medicines include materials, preparations, and products that contain all or parts of plants, fungi, lichen, and/or algae to prevent and treat disease.[2,3] Herbs can be prescribed internally as part of diet, as teas, tinctures, essential oils, or tablets/capsules, and can also be used topically in creams, oils, poultices, and compresses[2].

Herbal medicine has historically been used for upper respiratory tract infections and immune health. Identification of treatments and preventive strategies for COVID-19 (severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2) became a focus for international research following its emergence in early 2020[4] and traditional and complementary medicine (T&CM) researchers have contributed to the body of research that outlines the role of herbal medicine for the prevention and treatment of COVID-19 and the management of post-COVID syndrome.[4]

Research conducted prior to, and early in, the emergence of COVID-19 suggested that commonly used herbal medicines may contribute to the prevention and treatment of COVID-19 and management of post-COVID syndrome. For example, Aucoin et al.,[5] noted that the role of *Echinacea* with respect to the treatment and prevention of respiratory diseases has been researched for over a century and that it is a major component of commercially

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available herbal medicine products. Its immuno-modulatory properties contribute to its popularity for immune support.[5] Similarly, *Hedera helix* preparations have been commonly used for the treatment of early symptoms of acute inflammatory respiratory conditions, particularly coughing, in both adults and children.[1] Clinical studies of preparations of *sambucus nigra*, conducted prior to the pandemic, indicated that it may reduce the duration and severity of influenza and the common cold, particularly when taken within 48 hours of symptom onset.[6]

Interest in the role of natural health products (NHPs) generally, and herbal medicine specifically, in the prevention and treatment of COVID-19 grew during the global pandemic as evidenced by the growth in research attention throughout the period of the live review.[4] A range of herbal interventions have been studied, both individually and as patent formulae.[4]

Evidence collected early in the emergence of COVID-19 suggested that herbal medicine had a valuable role in the prevention, treatment, and management of COVID-19 and post-COVID syndrome. However, much of this evidence for the benefit of herbal medicine was extrapolated based on its use in broad respiratory/immunological conditions in the absence of COVID-19–specific knowledge. The objective of this paper is to review and synthesize the published peer-reviewed narrative and systematic reviews on the use of herbal medicine to prevent or treat COVID and identify key considerations for future research and clinical application of herbal medicine.

METHODS

Design

This report follows from the live review conducted by the World Naturopathic Federation (WNF) and the Canadian College of Naturopathic Medicine (CCNM) from May 2022 to May 2023. It is part of an umbrella review instigated by the WNF to examine and report on the NHPs and therapies that were being researched with respect to the prevention and/or treatment of COVID-19 and post-COVID.

Search Strategy

Throughout the live review, monthly literature searches were undertaken following the Cochrane Guidelines for a Living Systematic Review. Both PubMed and Google Scholar databases were included, with search terms including "natur*," "herb*," "nutraceutical," "botanical," "medicinal plant," "Ayurvedic," "Chinese medicine," "herbal patent formula," combined with "prevention," "prophylaxis," "deficiency," "treatment," "management," and "*COVID*," "Coronavirus," "SARS-CoV-2." Individual plant names and compounds cited in the literature were also searched. Articles were grouped based on the type of review—systematic, narrative, meta-analysis, and others.

Inclusion and Exclusion Criteria

Both systematic reviews and narrative reviews were included in this study. Systematic reviews were reviewed by 2 blinded reviewers based on the A Measurement Tool to Assess Systematic Reviews (AMSTAR) guidelines.[7] Reviews were included where a satisfactory Risk of Bias (RoB) technique for assessing risk in individual studies was used and if the study accounted for the RoB of individual studies in interpreting or discussing the review results.[7] Narrative reviews were reviewed based on the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines.[8] Reviews were included if a scientific reasoning score of 1 or 2 was noted AND an overall total sum was >5. A separate reviewer verified inclusion/exclusion where there was a discrepancy for the inclusion questions. A reference overlap analysis was also conducted to ensure that the results of any single study were not overstated. Included articles were published in English. Inclusion criteria are outlined in Table 1.

Data Extraction

Data was extracted only for those studies that were statistically significant, and only for those outcomes relevant to NHPs/therapies. As with the living review, online spreadsheets were used to collate included studies and collate extracted data.

For narrative reviews, the recorded data included study number, study identification, author(s), date of publication, journal, country/WHO region, review objective, details of any search conducted, area of focus (prevention, treatment, or post-COVID management), dosages, therapeutic considerations, including herbal properties (anti-inflammatory, antiviral, etc., as per https://www.ndhealthfacts.org/wiki/Action_of_Herbs), associations (relationship to other NHPs), therapeutic considerations, and additional clinical notes.

For systematic reviews, the data recorded included study number, study identification, author(s), date of publication, journal, area of focus (prevention, treatment, post-COVID), review objective, review type (systematic or meta-analysis), search date, search databases, study designs, country of included studies, WHO region, publication date range of studies included within the systematic review, tools for assessment of risk of bias, and methods of synthesis/analysis. Study results recorded included interventions relevant to herbal medicine, measured outcomes (rate of recovery (ROR) for key symptoms such as fever, cough, dyspnea; rate of conversion (ROC), such as duration of hospital stay, mortality, etc., imaging, laboratory testing measures, and adverse reaction reporting (ARR)), the number of studies, participant characteristics such as the number, age average or range, and gender percentages, results, and heterogeneity (where meta-analysis was conducted).

TABLE 1 PICO Inclusion Criteria

Population	Clinical or observational (humans of any age or gender, and in any setting), *in vivo* (including animal studies), *in vitro,* or *in silico* (including molecular docking)
Intervention	Any natural health product or approach
Comparison	No limitation for comparator studies
Outcome	Any symptom, biological marker, diagnostic criteria, or viral traits related to severe acute respiratory syndrome or viral respiratory tract infections of the coronavirus or COVID-19.

RESULTS

A total of 123 papers (24 narrative reviews and 99 systematic reviews) were retrieved for inclusion/exclusion screening. One additional narrative review was retrieved and included following initial screening.

Narrative Reviews

Although umbrella reviews do not typically include narrative reviews, these potentially provide broader information useful for considering potential clinical implications, such as for diagnosis and treatment.[9] Twenty-five narrative reviews[10-34] were included in this project (Table 2). Most (n = 16)[10,11,13-17,20,21,25-28,32,33,34] focussed on treatment of COVID-19 while a further six (6)[12,18,19,22-24] papers examined both prevention and treatment and one (1)[29] examined prevention, treatment, and post-COVID syndrome. Additionally, two (2)[30,31] papers examined the use of herbal medicine as an adjunct for COVID vaccination. WHO world regions represented included the Americas (n = 9), South-East Asia (n = 5), Western Pacific (n = 5), Eastern Mediterranean (n = 3) and European region (n = 3). A broad range of herbs, used in Ayurvedic, Traditional Chinese, Thai, Tibetan, and Western naturopathic systems of medicine used in the prevention and treatment of COVID-19 and post-COVID syndrome were examined.

TABLE 2 (Part 1 of 2) Overview of Studies: Narrative Reviews

First Author, Year	WHO Region	Focus	Herbal Medicines Investigated	Review Objective
Apiwansri et al., 2022[10]	AMR	Treatment	Various herbs	The potential use of herbal and medicinal plants as a form of treatment in mitigating mild to moderate COVID-19 symptoms.
Marmitt et al., 2022[11]	AMR	Treatment	South American herbs	Investigate the anti-inflammatory properties of South American plants and their potential for inhibiting/decreasing inflammatory markers of SARS-CoV-2.
Pergolizzi et al., 2021[12]	AMR	Prevention, Treatment	TCM, Ayurvedic herbs	Examine use of TCM and Ayurvedic herbal formulations in prevention and treatment of COVID-19.
Wang et al., 2020[13]	EUR	Treatment	TCM herbs	Examine the broad-spectrum antiviral, antibacterial, anti-inflammatory, and immunomodulatory effects of TCM herbs.
Nimesh et al., 2021[14]	SEA	Treatment	Various herbs	Review of immunity-boosting herbs to combat COVID-19.
López-Alcalde et al., 2020[15]	EUR	Treatment	Various herbs	Examine use of various herbs in treatment and symptomatic management of COVID-19.
Kwon et al., 2020[16]	SEA	Treatment	Soshihotang (SSHT)	Examine use of Soshihotang (SSHT, Xiao Chai Hu Tang in Chinese) to treat viral diseases.
DiPietro et al., 2021[17]	AMR	Treatment, Toxicity	Oleandrin (*Nerium oleander*), Datura, *Aconitum carmichaelii* (Fuzi), Semen armeniacae amarum (Xing Ren), Ephedra, Glycyrrhizin	Examine toxicities of herbal preparations used in treatment of COVID-19.
Bibi et al., 2021[18]	WPR	Prevention, Treatment	Various herbs	Explore potential of herbs with antiviral potential for development of novel, safe drugs for prevention and cure of coronavirus infection.
BASE Medicine Task Force, 2020[19]	AMR	Prevention, Treatment	*Radix isatidis,* Ban-lan-gen*, Bupleurum, Coptis,* Chinese herbal compounds	Review use of Chinese herbal compounds in occurrence, development, and treatment of COVID-19.
Malabadi et al., 2021[20]	SEA	Treatment	Ayurvedic herbs	Highlight potential immunity-boosting herbal medicines, antiviral plant extracts and herbs with viral growth inhibition properties used in treatment of COVID-19
Trivedi et al., 2022[21]	AMR	Treatment	Phytochemicals, alkaloids, polyphenols, polysaccharides, cannabinoids, plant lipids	Explore the antiviral and anti-inflammatory properties in plant foods.
Pisoschi et al., 2022[22]	EMR	Prevention, Treatment	Various plant constituents (including glycyrrhizin)	Explore the role of plant constituents in preventing and treating COVID-19.
Chakraborty et al., 2022[23]	SEA	Prevention, Treatment	*Withania somnifera*	Explore the potential of *Withania somnifera* in preventive and therapeutic interventions for COVID-19.
Lu et al., 2022[24]	WPR	Prevention, Treatment	*Crocus sativus*, saffron, *Gardenia jasminoides*	Explore the benefits of various herbal constituents to propose possible mechanisms of action which may protect against the effects of COVID-19.
de Oliveira et al., 2022[25]	AMR	Treatment	*Andrographis paniculata*, *Artemisia annua*, *Artemisia afra, Cannabis sativa, Curcuma longa, Echinacea purpurea, Olea europaea, Piper nigrum, and Punica granatum* and phytocompounds derived from medicinal plants (artemisinins, glycyrrhizin, and phenolic compounds)	Examine antiviral activity of herbs and plant extracts against SARS-CoV-2.
Jamshidi et al., 2022[26]	EMR	Treatment	Boswellia	Provide an overview of the antiviral properties of Boswellia species and their potential therapeutic effects against COVID-19.

TABLE 2 (Part 2 of 2) Overview of Studies: Narrative Reviews

First Author, Year	WHO Region	Focus	Herbal Medicines Investigated	Review Objective
Wu et al., 2022[27]	WPR	Treatment	*Curcumae* rhizoma	Provide an overview of the active constituents of *Curcumae* rhizoma, their applications and mechanisms in infectious diseases.
Pérez et al., 2022[28]	AMR	Treatment	*Cannabis sativa*	Summarize the latest knowledge regarding the advantages of using cannabinoids in the treatment of COVID-19.
Suresh et al., 2023[29]	AMR	Treatment, Prevention, Long COVID-19	Curcumin	Consider the role of curcumin in modulating the pathogenesis of bacterial/viral induced ARDS and COVID-19.
Nazeam & Singab, 2022[30]	EMR	Vaccine	Lectins, Neospora lysate, *Trypanosoma cruzi*, leishmania, and *Paracoccidioides brasiliensi*	Examine preclinical studies of immunoadjuvant plant proteins in use with antiparasitic, antifungal, and antiviral vaccines and outline potential immunostimulant plant proteins that could be used to develop new generations of vaccine-adjuvants.
Kumar et al., 2022[31]	SEA	Vaccine	Polysaccharides, glycosides, glycoprotein, lectins, inulin, saponins	Discuss the immunological adjuvant properties and potential application of plant compounds as an anti-COVID-19 therapy.
Ji et al., 2022[32]	WPR	Treatment	TCM herbs	Identify the mechanisms of action, advantages and disadvantages of select TCM herbs in treatment of COVID-19 and SARS-CoV-2
Fan et al., 2023[33]	WPR	Treatment	Tibetan herbs	Outline the basic theory and treatment strategies of Tibetan herbs for the treatment of COVID-19.
Heleno et al., 2023[34]	EUR	Treatment	Various herbs, plant extracts	Outline the relationship between herbal extracts for the treatment of SARS-CoV.

AMR=Region of the Americas; ARDS=Acute Respiratory Distress Syndrome; EMR=Eastern Mediterranean region; EUR=European region; SEA=South-East Asian region; TCM=Traditional Chinese medicine; WPR=Western Pacific region.

Systematic Reviews

After the inclusion/exclusion screening phase, 51 systematic reviews were included for data extraction. During data extraction, a further 10 systematic reviews were excluded. In total, 41 systematic reviews[35-75] examining the contribution of herbal medicine were included in this umbrella review (Tables 3 and 4). The focus of the systematic reviews was treatment of COVID-19 (n = 40). Most of the research originated from the Western Pacific (n = 30). As with the narrative reviews, a variety of herbal interventions were considered in the systematic reviews. Most (n = 32) examined patent herbal formulas either alone or in conjunction with other interventions. All systematic reviews identified specific tools for assessing risk of bias (RoB). Eleven studies[35,45,46-48,55,61-63,67,75] reported that studies had moderate to high reported RoB. Factors reported as contributing to high RoB included lack of information regarding blinding or randomization, problems with measurement of outcomes and selective reporting, selection bias, and small sample size.

The degree of citation overlap across the 41 systematic reviews included in this paper is 3.8% (268 individual references, in 687 unique instances across 41 total systematic reviews). Overall, this would be considered a slight overlap. Twenty-seven[35,37-55,60,61,64,65,68-70] out of the 41 systematic reviews included in this paper (67.5%) contained 5 or more articles cited more than once across all included reviews (see Table S1 in the supplemental material). All these reviews studied TCM, including patent TCM herbal formulas. This represents 27 out of the 32 total reviews that studied TCM herbal formulas. One review[38] also examined herbs used in the Ayurvedic system of medicine. We determined that the impact any occurrence of overlap would have on our review findings was high. This means that findings related to TCM should be interpreted cautiously to consider the possible duplication of findings reported across the reviews citing the same papers.

Improvement in Rate of Recovery (ROR) and Rate of Conversion (ROC)

Twenty-five[35,37-39,41-45,47,48,51-55,57,60,65,66,68,69,70,72,74] of the systematic reviews found significant improvement in ROR, based on one or more of the symptoms associated with COVID-19, primarily fever, cough, fatigue. Other ROR that improved included chest pain, sore throat, and expectoration. Reduction in ROC, especially as it related to duration of stay in the hospital, was reported as significant in 19 of the systematic reviews[37,38,40,41,43-45,48-50,51,53,54,56,57,59,68,69,70] and indicated as insignificant in four reviews.[38,43,61,67]

Improvement in Imaging Laboratory Measurements

Most systematic reviews indicated significant improvements in lung computed tomography (CT) scan readings. Fifteen reviews[37,39,42,43,46,47,51,52,54,58,60,65,68,70,73] indicated significant improvements in other laboratory measures, such as viral nucleic acid levels, inflammatory markers, and reverse transcription polymerase chain reaction (RT-PCR) negativity. Some studies[50,51,54,63,67,73] reported that there were no significant improvements in measures of viral clearance,[63] nucleic acid test,[50,51] or pro-inflammatory markers.[54,63]

TABLE 3 (Part 1 of 3) Overview of Studies: Systematic Reviews

Study Information	WHO Region	Area of Focus	Review Type / Search Databases	Herbal Focus	Review Objective
Feng et al., 2021[35]	WPR	Treatment	SR (RCTs) / Embase, Cochrane Database of Systematic Reviews, MEDLINE® Cochrane Central Register of Controlled Trials, Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Scopus, Web of Science, CNKI, CBM, Wanfang data, VIP	Patent herbal formula, curcumin	Investigate the effectiveness of herbs in patients with COVID-19.
Jeon et al., 2022[36]	SEA	Treatment	SR / PubMed, Embase, Cochrane Library	Patent herbal formula	Summarize the evidence for herbal interventions in the treatment of COVID-19 patients.
Du et al., 2021[37]	WPR	Treatment	SR and MA (RCTs) / PubMed, Embase, Cochrane Library, CNKI, VIP, Wanfang, CBM	*Lonicera*	Investigate honeysuckle combined with conventional therapy.
Kumar et al., 2022[38]	SEA	Treatment	SR and MA (RCTs and quasi RCTs) / PubMed, Cochrane Central Register of Controlled Trials, Embase, AMED, National Institute of Health and Clinical Trials Database International Clinical Trials Registry Platform, Clinical Trials Registry – India, Science Direct, AYUSH Research Portal, Google Scholar	Patent herbal formula, Ayurveda, *Withania*	Evaluate the effectiveness and safety of herbal intervention in COVID-19 management.
Ang et al., 2020[39]	SEA	Treatment	SR (RCTs, quasi RCTs) / PubMed, Embase, AMED, Cochrane Register of Controlled Trials, CNKI, VIP, CBM, Wanfang, KoreaMed, KMBase, RISS, OASIS, National Institute of Health and Clinical Trials database, international Clinical Trials Registry Platform, Chinese Clinical Trial Registry (ChiCTR)	Patent herbal formula, herbal decoctions, combined interventions using herbal medicine and Western medicine.	Evaluate the effectiveness and adverse events of herbal medicines for the treatment of COVID-19.
Kang et al., 2022[40]	WPR	Treatment	SR and MA (RCTs, cohort studies, case control studies) / PubMed, Embase, Cochrane Library, CNKI, CBM, VIP, Wanfang	Patent herbal formula	Evaluate the efficacy and explore the mechanisms of TCM herbs for COVID-19.
Zhang et al., 2022[41]	WPR	Treatment	SR and MA (RCTs, retrospective studies) / Medline, Embase, Cochrane Library, PubMed, Web of Science, SpringerLink, CNKI, CBM, ClinicalTrials.gov, Wanfang data, Weipu Database	Patent herbal formula	Evaluate the efficacy, safety, and precision of 3 CHM patents and 3 TCM herbal prescriptions for COVID-19.
Fan et al., 2020[42]	AMR	Treatment	SR and MA (RCTs) / PubMed, Medline, Cochrane Library, CNKI, ScienceDirect, Google Scholar, Wanfang data	Patent herbal formula	Summarize contemporary studies that report the use of CHMs to treat COVID-19
Luo et al., 2021[43]	WPR	Treatment	SR and MA (RCTs, cohort studies, and case-control studies) / CNKI, CBM, Wanfang, PubMed, Cochrane Library, Embase, Chinese Journal Medical Network databases, Google Scholar, Journal preprint services (including ChemRxiv, MedRxiv, BioRxiv, and SSRN).	Patent herbal formula	Investigate the efficacy and safety of CHMs for COVID-19.
Xiong et al., 2019[44]	WPR	Treatment	SR and MA (RCTs) / Cochrane, Central Register of Controlled Trials, Embase, PubMed, CNKI, VIP, CBM, Wanfang	Patent herbal formula	Evaluate the current clinical evidence on CHMs for the treatment of COVID-19.
Fei et al., 2021[45]	WPR	Treatment	SR and MA (RCTs, CCTs, retrospective cohort studies) / PubMed, Cochrane Central Register of Controlled Trials, CBM, CNKI, VIP, Wanfang data	Patent herbal formula	Provide current evidence for the efficacy and safety of treating COVID-19 with combined TCM and conventional medicine.
Sun et al., 2020[46]	WPR	Treatment	SR and MA (RCTs) / Cochrane Central Register of Controlled Trials, PubMed, Embase, CNKI, CBM, VIP, Wanfang data	Patent herbal formula	Evaluate the clinical efficacy and safety of herbal formulae in the treatment of COVID-19 pneumonia.
Yin et al., 2021[47]	WPR	Treatment	SR and MA (RCTs) / PubMed, Embase, Web of Science, SinoMed, CNKI, Chongqing VIP, Wanfang data	Patent herbal formula	Evaluate the efficacy of integrated medicine therapy for patients with COVID-19.
Zhou et al., 2021[48]	WPR	Treatment	SR and MA (RCTs) / Web of Science, PubMed, Embase, Cochrane Central Register of Controlled Trials, CNKI, Wanfang data, SinoMed, ClinicalTrials.gov, Chinese Clinical Trial Register, International Clinical Trials Registry and Platform	Patent herbal formula	Assess the effects of Traditional CHM as an auxiliary treatment for COVID-19.

TABLE 3 (Part 2 of 3) Overview of Studies: Systematic Reviews

Study Information	WHO Region	Area of Focus	Review Type / Search Databases	Herbal Focus	Review Objective
Liang et al., 2021[49]	WPR	Treatment	SR and MA (RCTs) / CNKI, Wanfang data, VIP, Web of Science, SinoMed, PubMed, Embase, BioRxiv, MedRxiv, arXiv	Patent herbal formula	Evaluate the therapeutic effects and safety of oral Chinese Proprietary Medicine for COVID-19.
Wang et al., 2021[50]	WPR	Treatment	SR and MA (RCTs) / PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, CBM, CNKI, Wanfang data, VIP, Chinese Clinical Trial Registry (ChiCTR), ClinicalTrials.gov	Patent herbal formula	Evaluate the efficacy and safety of TCM for COVID-19.
Yu et al., 2022[51]	WPR	Treatment	SR and MA (RCTs, NRCs) / PubMed, Embase, Cochrane Central Register of Controlled Trials, China Clinical Trial Registry, CBM, CNKI, Wanfang data	Patent herbal formula	Compare the outcomes of COVID-19 patients treated with Western medicine in combination with TCM versus Western medicine alone.
Wu et al., 2022[52]	WPR	Treatment	SR and MA / (RCTs) / PubMed, Cochrane Library, Embase, CNKI, Chongqing VIP, Wanfang data, Chinese Clinical Trial Registry (ChiCTR)	Patent herbal formula	Evaluate the efficacy and safety of TCM for COVID-19 treatment with a focus on the benefits of symptomatic relief and time-related indexes.
Pang et al., 2020[53]	WPR	Treatment	SR and MA (RCTs, quasi RCTs) / SinoMed, CNKI, Wanfang data, PubMed, Embase, Cochrane Library	Patent herbal formula	Evaluate the efficacy and safety of Chinese medical drugs for COVID-19.
Shi et al., 2021[54]	WPR	Treatment	SR and MA (RCTs + observational studies) / PubMed, Cochrane Library, Web of Science, ScienceDirect, Scopus, Google Scholar, Embase, ProQuest, VIP, CNKI, Wanfang data, WHO Covid-19 website, Centers for Disease Control and Prevention COVID-19	Patent herbal formula	Assess the effect of oral CHM on immunogenicity and whether oral CHM improves clinical parameters through the immunity profile during COVID-19.
Fan et al., 2021[55]	WPR	Treatment	MA (RCTs and RTs) / Medline (OVID), Embase, Cochrane Library, CNKI, Wanfang data, CBM, VIP	Patent herbal formula	Assess the efficacy and safety of Lianhua Qingwen (LQ) combined with usual treatment vs usual treatment alone in treating mild or moderate COVID-19.
Liu et al., 2021[56]	WPR	Treatment	SR and MA (RCTs, case control studies, case series) / CNKI, CBM, Wanfang data, PubMed, Embase, Web of Science	Patent herbal formula	Assess the efficacy and safety of Lianhua Qingwen (LQ) in treating patients with COVID-19.
Zhuang et al., 2021[57]	WPR	Treatment	SR and MA / (RCTs, Retrospective case-control studies), Cochrane Central Register of Controlled Trials, Embase, PubMed, CNKI, VIP, CBM, Wanfang data	Patent herbal formula	Clinical efficacy of Lianhua Qingwen (LQ) Granules on the treatment of COVID-19.
Abdelazeem et al., 2022[58]	AMR	Treatment	SR (RCTs) / PubMed, Embase, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, Google Scholar.	Curcumin	Evaluate the effects of curcumin on patients with COVID-19.
Kow et al., 2022[59]	WPR	Treatment	SR and MA (RCTs) / PubMed, Cochrane Central Register of Controlled Trials, Google Scholar, Scopus, Pre-print servers (medRxiv, Research Square, SSRN).	Curcumin	Validate the mortality benefits of curcumin in patients with COVID-19.
Li et al., 2022[60]	WPR	Treatment	SR and MA (RCTs) / CNKI, PubMed, Wanfang data, ClinicalTrials.gov, Chinese Clinical Trial Registry (ChiCTR), Embase, International Clinical Trials Registry Platform (ICTRP)	Patent herbal formula	Systematically review the clinical efficacy and safety of CHM with and without Western medicine for different severity of COVID-19.
Zhang et al., 2022[61]	WPR	Treatment	SR and MA (RCTs and NRCs) / PubMed, Embase, Cochrane Library, CNKI, CSTJ, CBM, Wanfang data	Patent herbal formula	Systematically assemble the evidence on the efficacy and safety of QFPD combined with Western medicine treatments for COVID-19.
Yang et al., 2022[62]	WPR	Treatment	SR and MA (RCTs and retrospective trials) / Cochrane Library, Embase, Medline, PubMed, Springer link, Web of Science, Clinicaltrials.gov, CBM, CNKI, Wanfang data, VIP Database	Patent herbal formula	Systematically evaluate the efficacy and safety of QFPD for COVID-19.
Rai et al., 2022[63]	SEA	Treatment	SR and MA (RCTs) / AYUSH Research Portal, PubMed, Cochrane Central Register of Controlled Trials, DHARA, COVID-19 Evidence Alerts from McMaster PLUS, Epistemonikos, TRIP database, National Collaborating Centre for Methods and Tools database of COVID-19 studies, Google Scholar, Clinical Trial Registry of India, WHO dashboard for clinical trials related to COVID-19	Ayurveda herbal formulation AYUSH-64	Critically appraise the evidence from randomized controlled trials on the efficacy and safety of AYUSH-64 in the management of COVID-19.

TABLE 3 (Part 3 of 3) Overview of Studies: Systematic Reviews

Study Information	WHO Region	Area of Focus	Review Type / Search Databases	Herbal Focus	Review Objective
Ang et al., 2022[64]	WPR	Treatment	SR and MA (RCTs) / PubMed, Cochrane Register of Controlled Trials, Embase, AMED, CNKI, Wanfang data, VIP, RISS, KMBase, KoreaMed, OASIS database, COVID-19 Study Registry, WHO's COVID-19 Database, The Institute of Medical Information (IMI) and Library, Chinese Academy of Medical Sciences and Peking Union Medical College	Patent herbal formula, *Ephedra*, *Scutellaria*, *Zingiber*, Ginseng, Glycyrrhiza, Curcuma	Compile up-to-date evidence of the benefits and risks of herbal medicine for the treatment of COVID-19 symptoms.
Chien et al., 2022[65]	WPR	Treatment	SR and MA (RCTs) / Embase (Elsevier), Medline (Ovid, including epub ahead of print, in-process, and other nonindexed citations), Cochrane Library (including clinical registers from WHO ICTRP and US ClinicalTrials.gov), CINAHL Complete (EBSCOhost), Scopus, CNKI, Wanfang data	Patent herbal formula	Evaluate the effects of herbal medicine combined therapy in the treatment of COVID-19.
Jin et al., 2022[66]	WPR	Treatment	SR and MA (RCTs, quasi RCTs) / PubMed, Embase, AMED, Cochrane Register of Controlled Trials, CNKI, VIP, CBM, Wanfang data, KoreaMed, KMBase, RISS, OASIS	Patent herbal formula	Evaluate the effectiveness and adverse events of herbal medicines for the treatment of COVID-19.
Thakar et al., 2022[67]	SEA	Treatment	Living SR and MA (RCTs, analytical observational studies) / PubMed, Cochrane central register of controlled trials, WHO COVID-19 database, central trial registry-India, Digital Helpline for Ayurveda Research Articles and AYUSH research portal, Preprint repositories (MedRxiv, SSRN, OSF)	Ayurveda	Assess the effectiveness of AYUSH therapeutics on COVID-19 through a living systematic review and meta-analysis approach.
Wang et al., 2022[68]	WPR	Treatment	SR and MA (RCTs) / PubMed, CNKI, Wanfang data, (CENTRAL), Embase, World Scientific, SpringerLink	Patent herbal formula	Study the effectiveness and safety of Qingfei Paidu (QFPD) in the treatment of COVID-19.
Zhuang et al., 2022[69]	WPR	Treatment	SR and MA (RCTs, retrospective cohort studies) / Embase, PubMed, Cochrane Central Register of Controlled Trials, Web of Science, CNKI, CBM, Wanfang data, VIP database, Chinese Clinical Trial Registry (ChiCTR), clinicaltrials.gov	Patent herbal formula	Provide the theoretical basis and therapeutic evidence for the treatment of COVID-19 by integrated TCM and Western Medicine
Xu et al., 2022[70]	WPR	Treatment	SR and MA (RCTs) / PubMed, Medline, Web of Science, medRxiv, bioRxiv, Wanfang data, CNKI	Patent herbal formula	Investigate the clinical efficacy of TCM medicine in the treatment of COVID-19.
Javed et al., 2022[71]	SEA	Treatment	SR and MA (RCTs, quasi RCTs), PubMed, Medline, CAM-QUEST, Cochrane Central Register of Controlled Trials	Ayurveda, Homoeopathy	Compare the overall effect of AYUSH add-on regimen to standard of care for COVID-19.
Shafiee et al., 2023[72]	EMR	Treatment	SR and MA (RCTs) / Cochrane Library, MEDLINE via PubMed, Embase, clinicaltrials.gov	Curcumin	Assess the effect of curcumin on clinical outcomes in COVID-19 patients.
Shojaei et al., 2023[73]	EMR	Treatment	SR and MA (RCTs, intervention studies, clinical studies, NRCs) / PubMed, Scopus, Web of Science, Google Scholar Manual search of reference lists of papers	Curcumin	Summarize the findings of available clinical studies to assess nano-curcumin's influence on COVID-19 patients.
Si et al., 2019[74]	SEA	Treatment	SR and MA (RCTs) / PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang data, VIP	Patent herbal formula	Evaluate the clinical efficacy and safety of Jinhua QingganT granules combined with conventional Western medicine for the treatment of COVID-19.
Liu et al., 2022[75]	WPR	post-COVID	SR (RCT, cohort study, case series, case reports), WHO COVID-19 Research database, Cochrane Library, VIP, CNKI, Wanfang data, CBM	Glycyrrhizic acid monomer preparation (GAP), rather than the crude glycyrrhiza extracts	Critically review and analyze clinical evidence on the efficacy and safety of glycyrrhizic acid preparation (GAP) in the treatment of COVID-19 alone and COVID-19 with comorbid liver injury.

AMED=Allied and Complementary Medicine Database; AMR=Region of the Americas; CBM=Chinese Biomedical Literature Database; CHM=Chinese herbal medicine; CNKI=Chinese National Knowledge Infrastructure; CSTJ=China Science and Technology Journal; DHARA=Digital Helpline for Ayurveda Research Articles; EMR=Eastern Mediterranean region; EUR=European Region; MA=meta-analysis; NRC=non-randomized controlled trial; OSF=Open Science Framework; QFPD=Qingfei Paidu decoction; RCT=randomized controlled trial; RISS=Research Information Service System; SEA=South-East Asian region; SR=systematic review; SSRN=Social Science Research Network; TCM=traditional Chinese medicine; VIP=Chinese Science and Technique Journals Database; WPR=Western Pacific region.

TABLE 4 (Part 1 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Feng et al., 2021[35]	Herbal formulas as capsules, powders; Thyme essential oil; Curcumin capsules (160 mg)	ROR of various symptoms, ROC to severe disease, VALs, changes in imaging and laboratory values To reduce heterogeneity, authors limited analysis to RCTs only. Meta-analysis was not conducted due to methodological and outcomes heterogeneity.	12 / 1952	Average age 54; range 15–86. / males 50–60% range 32–77%	**Signif impr ROR** in 8/12. Risk of bias high. No severe ARR. **Lianhua Qinwen** capsules + CWM for Pneumonia sig. ROR $p<.05$. Not signif: ROC or VAL **Keguan-1 decoction** – sig ROR (fever, ↓ ARDS) $p<.05$ **Xuanfei Baidu decoction** (200 mL pouch BID + CWM signif ROR, impr in WBC, CRP, LYM, and ESR. ($p<.05$) **JHQG granules** (6 TID + CWM (arbidol) signif ROR and decreased viral nucleic acid detection + 7-day viral clearance rate signif ($p<.05$) **Thyme essential oil** (5 mL every 8 h) + CWM signif ROR, impr labs (urea nitrogen, neutrophils and calcium), LYM signif higher in Tx group ($p<.05$). **Nano-curcumin capsules** (40 mg 4x day) + CWM sig ↓ mRNA expression and cytokine secretion of IL-6 and IL-1β (both $p<.05$). No signif diff in IL-18 mRNA expression and TNF-alpha concentration ($p>.05$).
Jeon et al., 2022[36]	TCM medications		24 / 6231 (only 10 studies reported numbers)	NR / NR	
Du et al., 2021[37]	*Lonicera* / Jinyinhua / honeysuckle	ROR, imaging (lung CT) Heterogeneity using the χ^2 test and the I^2 statistical value; Subgroup analysis; Sensitivity analysis based on the leave-one-out method (Panahi et al., 2015[a]); When # of trials on outcome measure was >10, a funnel plot analysis was performed for reporting bias (Liu et al., 2020[b]). Statistical significance defined as $p<0.05$.	9 / 1286	Adults / Males – 680; Females – 606	**Signif impr ROR** (fever, cough reduction rate, cough, and fatigue) ($p<.05$). [5 trials, $n=815$, RR=1.21, 95% CI [1.12, 1.31], $I^2=19\%$, $p<.00001$]. **Reduced ROC** [6 trials, $n=965$, RR=0.50, 95% CI [0.33, 0.76], $I^2=0\%$, $p=.001$] **Signif impr in imaging:** lung CT [4 trials, $n=744$, RR=1.24, 95% CI [1.12, 1.37], $I^2=11\%$, $p<.0001$] **Signif impr in labs:** inflammatory biomarkers WBC, LYM, CRP, MD ($p<.05$). **No diff** in viral nucleic acid testing between honeysuckle alone and CHM formula No major ARR
Kumar et al., 2022[38]	HI plus standard CWM; HI alone compared with placebo plus standard CWM or placebo; HIs included granules, decoction, tablets/ pills, nasal drops, herbal injections	ROR, ROC (length of stay), imaging, labs (RT-PCR negativity); Assessment of heterogeneity based on χ^2 test of heterogeneity with significance level set at $p<0.10$ and applied the I^2 statistic after setting significance level ≥50%	32 / 3177	Average age 48.61 / 56.96% male and 43.03% female	Combined HI + CWM: **Signif impr ROR:** ↓ fever days (8 studies), cough (11/17 studies, $n=782$, RR 1.22; 95% CI [1.08, 1.37]), chest pain (3 studies, $n=177$, RR 1.12; 95% CI [0.75, 1.48]), sore throat ($n=387$, RR 1.0; 95% [CI 0.99, 1.19]); $I^2=22.1\%$; $p=.268$, fatigue: $n=700$, RR 1.27; 95% CI [1.11, 1.44]; $I^2=19.6\%$; $p=.269$.) **Signif Impr ROC:** ↓ recovery period **Insign ROC:** Duration of hospital stay – 6 studies MD + CI ($n=388$, MD –1.82; 95% [CI –3.84, 0.21]. Clinical effect rate – 0 studies evaluated clinical effect of herbal intervention as number of patients with improved effect rate – overall combined effect rate is significant – ($n=1810$, RR 1.13; 95% CI [1.08, 1.17]) **Improved imaging:** Chest CT: 13 studies, $n=1402$, RR 1.15; 95% CI [1.08, 1.23]; I2=29.9%; $p=.145$) HI compared with HI + CWM – "likely a good effect regarding RT-PCR negativity but stat insignificant"
Ang et al., 2020[39]	HI + CWM compared with CWM alone	Effectiveness, ROR, labs; High heterogeneity ($I^2=95\%$)].	7 / 855	Mean age 50.5; Range 42–65. / 472 male, 383 female	**Signif impr:** ROR and labs
Kang et al., 2022[40]	TCM or combination of TCM and CWM. No restriction to dosage of TCM. Control – CWM	ROC (mortality rate); Meta-analysis	29 RCTs, 28 RSs / 15,520	Adults / NR	**Signif impr ROC:** MA 7 RCTs demonstrated TCM lessen the proportion of patients progressing to severe cases [RR=0.45, 95% CI [0.29, 0.68], $I^2=0\%$, $p=.0002$]. In addition, 6 RSs [40, 42, 44, 47–49] evaluated this proportion

TABLE 4 (Part 2 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Zhang et al., 2022[41]	Three Chinese patent medicines – LHQW, JHQG, Xue-Bi-Jing; Three TCM prescriptions – QFPD, Xuan-Fei-Bai-Du (XFBD), Hua-Shi-Bai-Du (HSBD). Comparator – CWM drugs	Effectiveness, ROR (fever, cough, fatigue, respiratory rate, SOB, chest distress, rhinitis, rhinorrhea, sore throat, gastrointestinal symptoms muscle soreness, headaches), ROC, labs (nucleic acid negative rate, CRP, WBC, ARR); Heterogeneity: Random effects model when I^2 was >50%. I^2=NIL–51.9% depending on the outcome reported	18 / 2036	NR / NR	**TMTP**: signif increase clinical effect (RR 1.20; 95% CI [1.10, 1.31]). Signif ROR: fever (RR 1.49; 95% CI [1.30, 1.70]), cough (RR 1.72; 95% CI [1.38, 2.14]), and fatigue (RR 1.55; 95% CI [1.25, 1.93] Signif ROC: rate of recovery (RR 1.24; 95% CI [1.15, 1.35]). Impr expectoration (RR 2.05; 95% CI [1.28, 3.30]), SOB (RR 2.27; 95% CI [1.33, 3.86]), and chest distress (RR 2.24; 95% CI [1.47, 3.41]); Signif labs: decrease CRP (MD, −0.94; 95% CI [−1.79, −0.09]) **LHQW**: signif improved clinical efficacy, which was 1.22 times higher than that of CWM (RR 1.22; 95% CI [1.10–1.35]). Signif ROC: rate of recovery (RR 1.22; 95% CI [1.10–1.36]) **Xue-Bi-Jing**: No signif diff between Xue-Bi-Jing and CWM (RR 1.37; 95% CI [0.94, 1.99]) Signif ROC: rate of recovery (RR 1.36; 95% CI [1.06, 1.75]), **QFPD**: No signif diff between and CWM (RR, 1.10; 95% CI [0.91, 1.32]) on clinical effect. Signif ROC: rate of recovery (RR 1.26; 95% CI [1.10, 1.43]). ARR signif lower (0.72 times that of CWM (RR 0.72; 95% CI [0.58, 0.90]). **JHQG:** Impr ROR: expectoration, and its efficacy was 1.85 times higher than that of CWM (RR 1.85; 95% CI [1.01, 3.38])
Fan et al., 2020[42]	Treatment – Standard care + oral CHMs (decoction, extracted granules or capsules) for 5–15 days.	ROR, ROC, imaging (lung CT), lab (CRP, hs-CRP, PCT, IL-6, ESR, TNF-alpha, TNF-c, WBC, NEU, LYM, ARR, Hamilton anxiety scale, service satisfactory score; Heterogeneity based on the I^2 statistic. 50%+ reassessed by rechecking subgroup analysis; No heterogeneity detected for lung and CT scan. Signif heterogeneity found for symptoms and signs (I^2=94%) and inflammatory markers (I^2=97%)	7 / 732	>18 y / NA	**Signif ROR:** (−1.30 by SMD, 95% CI [−2.43, −0.16]; 3 studies; n=261, p=.03) **Impr lung CT scans:** (1.34 by risk ratio, 95% CI [1.19, 1.51]; 4 studies; n=489, p<.00001). **Signif impr labs:** CRP, mg/L; −11.82 by MD, 95% CI [−17.95, −5.69]; 5 studies; n=325, p=.0002 No signif ARR
Luo et al., 2021[43]	CHM – Decoction, granules, and/ or herbal injection with standard CWM treatment	Effectiveness, ROR (fever, cough, fatigue), ROC, imaging (CT scan), labs (RT-PCR) negative rate Heterogeneity based on I^2 varied from 0–99.5 depending on outcome measure.	19 / 1474	NA / NA	**Effectiveness**: MA showed overall clinical effectiveness (OR=2.67, 95% CI [1.83, 3.89], I^2=0%) **Signif ROR**: (fever, cough, and fatigue) **Signif ROC**: % turning to severe/critical (OR=0.40, 95% CI [0.24, 0.67], I^2=17.1%) **Insig ROC**: length of hospital stay (CWM=-0.46, 95% CI [–3.87, –2.95], I^2=99.5%) **Impr imaging**: CT scan (OR=2.43, 95% CI [1.80, 3.29], I^2=0%), **Impr labs**: reverse transcription-polymerase chain reaction (RT-PCR) negativity rate (OR=2.55, 95% CI [1.06, 6.17], I^2=56.4%) **No signif ARR:** OR=1.21, 95% CI [0.48, 3.07], I^2=43.5% The quality of evidence was very low to low.
Xiong et al., 2020[44]	CHM – decoction, tablet, pill, powder, pellet, granule, capsule, cream formula, oral liquid, plaster, and injection; The decoction of CHM was orally taken 1 dose every day, with about 400 mL in every dose.	ROR, ROC (length of hospital stay, clinical cure rate, death), imaging (lung CT), labs (TCM syndrome, viral nucleic acid testing, inflammatory biomarkers); When no statistical heterogeneity was identified (heterogeneity test, $p \geq 0.10$, or $I^2 \leq 50$ %), fixed-effects model was selected, otherwise random-effects model was applied; I^2 for each finding listed in previous column	18 / 2275	Average 50 years / 56% male, 44% female	**Signif impr lung CT**: 13 trials, n = 1402; RR = 1.23; 95% CI [1.15, 1.32]; I^2=31 %, p< .00001 **Signif ROR:** (2 trials, n=133; WMD: -1.84; 95 % CI [–3.10, –0.58]; I^2=0%, p=.004), fever reduction time (10 trials, n=1017; WMD: –1.36; 95 % CI [–1.80, –0.93]; I^2=58%, p< .00001), cough reduction (6 trials, n=422; RR=1.50; 95% CI [1.26, 1.78]; I^2=0%, p<.00001) **Signif ROC:** clinical cure rate (7 trials, n=1523; RR=1.18; 95 % CI [1.13, 1.24]; I^2=24%, p<0.00001), reduction length of hospital (2 trials, n=119; WMD: –1.99; 95% CI [–3.28, –0.70]; I^2=0%, p=.002)

TABLE 4 (Part 3 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Fei et al., 2021[45]	Integrated TCM and CWM Comparator – CWM TCM used in these studies, including Chinese patent medicine (n=14), Chinese herbal decoction (n=20), injection (n=1).	Effective rate, ROR (fever, cough, fatigue), ROC (disease progression, length of hospital stay), imaging (chest CT), labs (nucleic acid, lymphocyte count), ARR; Heterogeneity based on I^2 test; Significance $p<0.05$), subgroup analyses more effective outcomes in the HI + CWM than the control group.	35 studies – 19 RCTs and 16 observational studies / 3808	Approx. 53 years / Average men 53%; women 47%	**Signif ROR:** fever, fatigue and cough **Signif ROC:** disease progression, effective rate **Impr imaging:** chest CT Quality of evidence: very low to moderate
Sun et al., 2020[46]	CHM CPM Chinese medicine injections	Effectiveness, ROC, imaging (chest CT), labs (WBC, LYM, LYM%, CRP, IL-6, viral nucleic acid), ARR; Heterogeneity based on the I^2 and χ^2 test.	7 / 681	Age 51–75 / 34% female 66% male (both only reported in one study)	**Signif impr clinical efficacy** (RR=1.21, 95% CI [1.08, 1.36]) **Signif impr imaging**: reduced pulmonary inflammation (RR=1.27, 95% CI [1.12, 1.44]), **Signif impr labs**: WBC, MD=0.92, 95% CI [0.07, 1.76]; LYM, MD=0.33, 95% CI [0.08, 0.57]; LYM%, MD=2.90, 95% CI [2.09, 3.71]; CRP, MD=−12.66, 95% CI [−24.40, −0.92]), signif incr viral nucleic acid negative conversion rate (RR=1.49, 95% CI [1.13, 1.97]). **No increase** ARR: incidence of adverse reactions (RR=1.17, 95% CI [0.39, 3.52]).
Yin et al., 2021[47]	TCM (decoction, tablet, pill, powder, granule, capsule, cream, oral liquid, plaster, injection) with CWM Comparator – CWM alone.	Effective rate, ROR (fever, fatigue), imaging (chest CT), labs (CRP, ESR, PCT, CBC, WBC count, LYM)	19 / 1853	NA / NA	**Signif overall effective rate** (RR=1.17, 95% CI [1.10, 1.26], $p<.00001$) **Signif impr ROR:** ↓ fever rate (RR=1.25, 95% CI [1.04, 1.50], $p=.02$), fatigue (RR=1.28, 95% CI [1.00, 1.63], $p=.05$) **Signif impr imaging**: Chest CT (RR=1.24, 95% CI [1.14, 1.34], $p<.0001$) **Impr labs:** CRP (WMD=−4.14, 95% CI [−6.38, −1.91], $p=.0003$), WBC count (WMD=0.35, 95% CI [0.11, 0.58], $p=.004$). **Note:** Subgroup analyses showed that, when the treatment time is <2 weeks, the effect of integrated medicine treatment is more obvious.
Zhou et al., 2021[48]	TCM (granule, capsule, decoction, or oral liquid) with treatment range of 5–14 days + CWM; Comparator – CWM only	Effectiveness, ROR (cure rate, fever, cough), ROC, imaging; Subgroup analysis suggests heterogeneity in cure rate due to severity of disease.	10 / 1285	Lowest mean age 42.0; highest mean age 63.16 / 737 males, 556 females	**Incr cure rate:** ([RR] 1.15; 95% CI [1.04, 1.26]) **Signif imp ROR**: cough (RR 1.32; 95% CI [1.15, 1.52]), fever normalization (RR 1.10; 95% CI [0.94, 1.29]) **Signif imp ROC**: ↓ in disease progression (RR 0.58; 95% CI [0.43, 0.77]). **Impr imaging:** chest CT images (RR 1.23; 95% CI [1.11, 1.37]).
Liang et al., 2021[49]	Oral CPM formulas (pills, capsules or granules) either alone or combined. Comparators CWM recommended by the National Health Commission of the People's Republic of China, or placebo of CPM.	Effectiveness, ROR (fever, cough, fatigue), ROC (mortality), labs (nucleic acid test), ARR; Recovery rate: statistical heterogeneity (I^2=71%), involving JHQG and Lianhua Qingke	7 / Test: M=321 + F=270 Control: M=302 + F=249 /	Test=43.26–56.07 Control=42.0–53.09 / males & females	CPM + CWM **Impr effectiveness:** cure rate (RR = 1.20, 95 % CI [1.04, 1.38], involving LHQW and TJQW), reduced aggravation rate (RR = 0.50, 95 % CI [0.29, 0.85], involving LHQW, JHQG, LHQK and TJQW) **Impr ROC:** shortened the duration of fever, cough and fatigue, improved the recovery rate of cough and fatigue **Impr imaging:** chest CT manifestations. T Note: some differences in therapeutic effects among various CPMs for the same COVID-19 outcome. The use of TJQW and LHQG appeared not to increase the risk of adverse events, but JHQG may cause mild diarrhea.
Wang et al., 2021[50]	TCM + CWM	Effectiveness, ROR, ROC (mechanical ventilation, imaging (chest CT), labs (nucleic acid), ARR	25 / 2222	TCM + CWM=42.6–60.26 with one study 17–84 CWM=42.0–62.40 with one study 18–85 / males & females	**Signif incr effectiveness:** cure (risk ratio [RR]=1.20, 95% CI [1.04, 1.38], $p=.01$) **Impr ROC:** reduce clinical deterioration (RR=0.39, 95% CI [0.18, 0.86], $p=.02$), ARDS (RR=0.28, 95% CI [0.11, 0.69], $p=.01$), mechanical ventilation (RR=0.30, 95% CI [0.12, 0.77], $p=.01$), or death rate (RR=0.28, 95% CI [0.09, 0.84], $p=.02$). **Impr imaging:** chest CT (RR=1.22, 95% CI [1.07, 1.39], $p=0.01$) **Insig lab findings:** low confidence of a benefit of 5.4% in the negativity of SARS-CoV-2 nucleic acid test was also observed.

TABLE 4 (Part 4 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Yu et al., 2022[51]	CHM + CWM comparator – CWM	Effectiveness, ROR (fever, cough), ROC, imaging (chest CT), labs (viral nucleic acid) Heterogeneity assessed and subcategory analysis performed.	16 / 1645	NR / males & females	**Incr effectiveness:** (RR=1.24, 95% CI [1.16–1.33]) **Sign impr ROR:** fever (RR=1.24, 95% CI [1.09–1.42]), cough remission rate (RR=1.38, 95% CI [1.10–1.73]), feebleness (RR=1.45, 95% CI [1.18–1.77]), **Incr ROC**: clinical cure rate (RR=1.27, 95% CI [1.03, 1.56]), lower exacerbation rate (RR=0.36, 95% CI [0.25, 0.52]) **Signif impr imaging**: chest CT (RR=1.19, 95% CI [1.11, 1.28]). **Signif lab findings**: WBC rebounded significantly (WMD=0.35, 95% CI [0.16, 0.54]), recovery of LYM more obvious (WMD=0.23, 95% CI [0.06, 0.40]). **Insig lab findings**: rate of turning negative rate of viral nucleic acid (RR=1.20, 95% CI [0.78, 1.85]).
Wu et al., 2022[52]	Integrated TCM + CWM	Efficacy, ROR, ROC, imaging (lung CT), labs (viral assay conversion), ARR; Heterogeneity not signif: overall efficacy (p=0.24, I^2=27%), radiological lung recovery (p=0.24, I^2=27%); No heterogeneity: time to viral assay conversion (p=0.66; I^2=0%); High heterogeneity: laboratory indicators: except for WBC, LYM, and PCT	15 / Test=803; Control=666	Test=43.6–64.07; Control=41.3–58.29 / NR	**Signif impr efficacy:** RR=1.21; 95% CI [1.12, 1.30]; p<.01) **Signif ROR**: duration of chest distress (WMD=2.41; 95% CI [−2.99, −1.83]; p<.01) **Signif impr imaging:** lung CR (RR=1.30; 95% CI [1.19, 1.42]; p<.01) **Impr labs:** shortened the time to viral assay conversion (WMD=−1.38; 95% CI [−1.98, −0.78]; p<.01) and No difference in safety between groups: (RR=0.94; 95% CI [0.64, 1.39]; p=.76).
Pang et al., 2020[53]	CHM (including herbal decoction, CPM) compared with CHM + CWM, compared with CWM plus placebo	Efficacy, ROR (cough, fatigue, tachypnea, diarrhea, body pain), ROC (hospital stay, PaO2, mechanical ventilation, # severe and critical type, all-cause death), labs (RT-PCR), ARR	11 / 1259 (672 CMD + WM; 623 WM alone)	NR / NR	**Impr efficacy** **Impr ROR**: cough (RR 1.37, 95% CI [1.15, 1.64], p=.0004), fatigue (RR 1.37, 95% CI [1.02, 1.83], p=.04), and tachypnea resolution rate (RR 2.20, 95% CI [1.11, 4.39], p=.02). **Impr ROC**: ↓ # turned to severe and critical type (RR=0.47, 95% CI [0.32, 0.69], p<.0001), length of hospital stay (MD –7.95, 95% CI [–14.66, –1.24], p=.02), defervescence time (MD –1.20, 95% CI [–2.03, –0.38], p=.004) **Safety**: No significant difference between groups.
Shi et al., 2021[54]	CHM plus CWM	ROR (cough, fever, fatigue, and chest tightness), ROC, labs (LYM counts, CD4+, CD8+, CD4+/CD8+ ratio, CD3+, leukocyte counts, TNF-alpha, and IL-6). Heterogeneity assessed for subcategories.	30 / Intervention group=1677 Control group=1468	Intervention group: 33–65, 1 study 23–58 & 1 study 17–86; Control group: 38–66, 1 study 25–65 & 1 study 17–86 / NR	**Impr ROR**: fever (WMD −1.46, 95% CI [−2.60, −0.32]), cough (WMD of −1.74 (95% CI [−2.50, −0.99]), chest tightness (WMD −1.92, 95% CI [−2.20, −1.63]; I^2=3%), fatigue (WMD −2.14, 95% CI [2.47, −1.81]; I^2=0%). **Impr ROC**: decreased mortality (RR 0.33, 95% CI [0.20, 0.54], I^2=0%). **Signif impr labs**: LYM [WMD 0.37 (95% CI [0.14, 0.60]); p=0.002; I^2=98 %], CD4+ improvement (I^2=95%, p<.00001). CD8+ (95% CI, [−0.30, 1.23], p=.23; random effect model), CD4+/CD8+ improvement [WMD=0.46, p=.04; 95% CI ([0.02, 0.90]); random effect model]. CD3+ improvement. **No signif impr labs**: Leukocyte count (WMD=0.19, 95% CI [−0.12, 0.50], p=.23), combined WMD of TNF-alpha was −3.80 (95% CI [−5.96, −1.65], p=.0005; random effect model). uncertain decrease of IL-6 (WMD −0.59, 95% CI [1.29, 0.11], p=.10). No increase side effects between groups
Fan et al., 2021[55]	LHQW combined with CWM	Efficacy, ROR (fever, fatigue, and coughing and safety outcomes), ROC, imaging (chest CT). There was no statistical heterogeneity among the trials (p=0.92, I^2=0%), therefore, the data were synthesized using FEM (finite element modeling)	5 / Total Test group=424 & Total Control group=400	NR / total male=448 & total female=375	**Impr overall clinical efficacy** (RR=2.39, 95% CI [1.61, 3.55]) **Signif impr ROR**: fever (MD=-1.00, 95% CI [–1.17, –0.84]). **Impr ROC:** reduced the rate of conversion to severe cases (RR=0.47, 95% CI [0.29, 0.74]) **Signif impr imaging**: chest CT (RR=1.80, 95% CI [1.08, 3.01])

TABLE 4 (Part 5 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Liu et al., 2021[56]	LHQW CHM compared with CWM	Effectiveness, ROR, ROC, imaging (lung CT), labs, ARR Heterogeneity between trials was evaluated using I^2 statistics. The values of 25%, 50%, and 75% for the I^2 were indicated for low, moderate, and high statistical heterogeneity, respectively.	8 / 924	Test group=44.1–66.1; Control group=47.3–64.2 / 506 males	**Impr effectiveness**: (RR=1.16, 95% CI [1.04~1.30], p=.01) **Impr ROR**: shorter time to recovery of fever, fatigue coughing, sputum and shortness of breath, chest tightness, loss of appetite. **Signif impr ROC**: lower aggravation rate (RR=0.59, 95% CI [0.37~0.94]) **Impr imaging**: CT recovery rate (RR=1.21, 95% CI [1.02~1.43], p=.03) **Dec lab findings**: rate of liver function abnormal in the LH + CWM group. Further research indicated the longer the course of treatment (7 days vs 5), the more that laboratory indicators return to normal.
Zhuang et al., 2021[57]	LHQW Granules compared with controls	ROR, ROC; Heterogeneity was substantial with I^2=69%	3 / 245	NR/ NR	**Signif impr ROC**: reduced rate of severe or critical (RR = 0.38, 95% CI [0.17, 0.85], p<.05) and the fever time (SMD=-0.57, 95% CI [–0.96, –0.17], p<.05) **Signif impr ROR**: fever (RR = 1.36, 95% CI [1.14, 1.61], p<.05), cough (RR = 1.99, 95% CI [1.39, 2.86], p<.05), fatigue (RR = 1.52, 95% CI [1.15, 2.01], p<.05), expectoration (RR = 2.46, 95% CI [0.81, 7.51], p<.05).
Abdelazeem et al., 2022[58]	Curcumin versus placebo	Labs (lymphocyte count, cytokine levels, gene expression of transcription factors and cytokines); Heterogeneity not specified.	6 / 480	Mean age of 51 / 58% male, 42% female	**Signif impr labs:** LYM, T-helper 17 cells, downregulate T-helper-17 cell-related factors, reduce levels of T-helper-17 cell-related cytokines, yet increase the gene expression of the Treg transcription factor Forkhead box protein P3 (FOXP3), decrease T-Box transcription factor 21 (TBX21)
Kow et al., 2022[59]	Curcumin vs control	ROC (all-cause mortality); Heterogeneity substantial (50% and significance at p<0.10)	3 / 260	NR / NR	**Sig impr ROC:** reduced mortality (pooled odds ratio=0.23; 95% CI [0.09, 0.58])
Li et al., 2022[60]	WM, CHM, and other alternative therapies either alone or in combination; Placebo, no treatment, and standard care were included as control	Effectiveness, ROR, ROC, imaging (lung CT), labs (virological outcome, WBC, LYM, LYM%, CRP, PCT), ARR Heterogeneity based on χ^2 and I^2 quantitative tests. When p<0.10, I^2>50%, random-effects model for MA, p>0.10, I^2<50%, fixed-effect model was applied.	22 / 1789	Average 47 years / average 48% male and 52% female	**Signif incr efficacy**: (p<0.00001, OR=2.84, 95% CI [2.13, 3.78]). **Signif impr ROR**: fever, cough and weakness disappearance rate (p=.002, OR=3.63, 95% CI [1.58, 8.34]; p=.03, OR=2.52, 95% CI [1.12, 5.68]; p=.009, OR=3.32, 95% CI [1.34, 8.21]), dry throat, pharyngeal (p=.51, MD=0.05, 95% CI [−0.10, 0.20]; p=.003, MD=−0.76, 95% CI [−1.26, −0.27]). **Signif incr viral assay conversion:** CWM group: (I^2 >30%, p<.05, CHM + CWM (p=0.02, MD=−1.01, 95% CI [−1.83, −0.19]). **Signif impr imaging**: CT image (p<0.0001, OR=2.13, 95% CI [1.56, 2.89], I^2 <30%). **Signif impr in labs**: WBC and LYM (p=.005, MD=0.61, 95% CI [0.19, 1.03]; p=.0002, MD=0.37,95% CI [0.17, 0.56]), CRP (p<.00001, MD=−6.77, 95% CI [−8.47, −5.07]). LYM% (p<.00001, MD=1.96, 95% CI [1.30, 2.62]; p=.02, MD=4.49, 95% CI [0.73, 8.26]). Signif reduction PCT (p=.06, MD=−0.01, 95% CI [−0.01, 0.00]; p=0.01, MD=− 0.01, 95% CI [−0.02, −0.00]). **No signif diff in ARR:** (p=.0006, OR 0.63, 95% CI [0.48, 0.82; p=.0002, OR 0.42, 95% CI [0.27, 0.67]).
Zhang et al., 2022[61]	QFPD decoction + CWM, compared with CWM alone; QFPD decoction, with/without a CWM antibiotic.	Effectiveness, aggravation, ROC (duration of viral shedding, length of hospital stay), ARR Heterogeneity: based on I^2 statistic. I^2≤50%=low, fixed effects model, random effects model, subgroup analysis.	9 / 1108	23–89 / males & females	**Impr ROC**: reduced aggravation rate (AR) by 71% (RR 0.29, 95% CI [0.17, 0.51]), incr effective rate (ER) by 13% (RR=1.13, 95% CI [1.04, 1.22]), shortened 4.78 days of viral shedding (95% CI [-5.79, -3.77]) and 4.45 days of hospital stay (95% CI [-6.05, -2.86]) **No impr ROC**: mortality, length of hospitalization **Dec in ARR** by 56% (RR=0.44, 95% CI [0.22, 0.89])

TABLE 4 (Part 6 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Yang et al., 2022[62]	QFPD + CWM	ROC (length of hospital stay), labs (time for nucleic acid to become negative), ARR Heterogeneity based on I^2 test. I^2<50%=low, random effects model adopted when I^2>50%, subgroup analysis conducted as needed	4 / 390	NR / NR	**Impr in ROC:** length of hospital stay (3 trials, *n*=330, MD: –2.42; 95% CI [–3.87, –0.96]; *p*=.001) **Impr labs**: shorten the time of nucleic acid conversion (2 trials, *n*=318, MD: –4.78; 95% CI [–5.79, –3.77]; *p*=.02) **No ARR:** 2 trials, *n*=72; RR: 0.71; 95% CI [0.15, 3.42]; *p*<.00001
Rai et al., 2022[63]	AYUSH-64 (tablets / capsules given in dose of 1 g 2 or 3 times daily for 7 days to 12 weeks) vs standard CWM	ROR, QOL, ROC (hospital duration), imaging (chest CT), labs (negative RT-PCR assay, inflammatory markers and other biochemical parameters), ARR	5	NR	**Impr ROC**: clinical recovery (*n*=386, OR 2.35, 95% CI [1.33, 4.16], *p*=.003, I^2=18% with *p*=.3), recovery within 7 days (*n*=260, OR 2.75, 95% CI [1.09, 6.92], *p*=.03, I^2=0% with *p*=.67) No signif ROC: early clinical recovery (*n*=264, SMD=–0.67, 95% CI [–1.16, –0.18], *p*=.007, I^2=71% with *p*=.03), viral load clearance within 14 days. **Some impr ROC**: disease progression **Signif impr QoL** **Impr imaging**: chest CT (2 studies). Liver and kidney function WNL in both groups at end of study in all groups. **No signif impr labs:** pro-inflammatory markers (5 studies) **ARR**: none serious in intervention group, 2 studies serious ARR in control groups.
Ang et al., 2022[64]	Herbal medicine + CWM, compared with CWM alone	ROC (disease progression, hospital stay, mortality), Imaging (lung CT)	25 / 1192	Age ranges= male: 43.3–65.3 (1 study 17–84) and female: 41.7–67.2 (1 study 18–85) / male & female	**Impr ROR**: time to remission from fever (*p*<.00001), rate of remission from coughing (*p*<.0001), fatigue (*p*=.02), sputum production (*p*=.004) **No signif impro ROR**: rate of remission from fever, sore throat, nasal congestion and discharge, diarrhea, dry throat, chills, and the rate of conversion to a negative COVID-19 coronavirus test. **Impr ROC:** effective rate (*p*=.0001), progression to severe disease (*p*=.003), all-cause mortality (*p*=.003), time to a negative COVID-19 coronavirus test (*p*<.0001), duration of hospital stay (*p*=.0003). **Impr Imaging**: chest CT (*p*<.00001), No signif diff in ARR between groups.
Chien et al., 2022[65]	CHM with CWM, compared with CWM alone	ROR (coughing, fatigue), ROC, imaging, labs (viral conversion, CRP, other serum markers) Heterogeneity signif with CHM on viral conversion rate and viral conversion time (I^2=74%, and 93%, respectively), serum IL-6 level and CRP level (I^2=78%, and 93%, respectively).	40 / 5417	Intervention: 30.8–66.0; Control: 37.3–62.4; One study: 66 (median age); One study both Intervention and Control =15–80 / NR	**Signif impr ROR**: 1) cough (1.43 95% CI [1.21, 1.71], *p*=.0001), 2) fever (1.09 95% CI [1.00, 1.19], *p*=0.06), 3), fatigue (1.21 95% CI [1.10, 1.33], *p*=.0001); 4) **Signif impr imaging**: CT images (1.26 95% CI [1.19, 1.34], *p*≤.00001) **Signif impr labs**: viral conversion rates (1.22 95% CI [1.06, 1.40], *p*=.005) and 6) viral conversion times (−3.72 95% CI [−6.05, −1.40], *p*=.002), 7), IL-6 (1.97 95% CI [−0.72, 4.66], *p*=.15) and 8) CRP (−7.92 95% CI [−11.30, −4.53], *p*≤.00001).
Jin et al., 2022[66]	CHM + CWM, compared with CWM alone	Efficacy, ROR (TCM syndrome score), labs, ARR; Heterogeneity assessed using I^2 statistics.	7 / 855	Range 42.0–65.0. Mean age was 55.5 / 472 (55%) male and 473 (45%) female	**Signif impr efficacy** (RR 1.23, 95% CI [1.13, 1.34], *p*<.001, I^2=0%) **Signif impr ROR**: cough (RR 1.45, 95% CI [1.12, 1.89], *p*=.005, I^2=0%), sputum production disappearance rate (RR 1.73, 95% CI [1.19, 2.50], *p*=.004, I^2=0%). **Beneficial effects in TCM syndrome score** of cough (MD −1.18, 95% [CI −1.34, −1.03], *p*<.001, I^2=70%), fever (MD −0.62, 95% CI [−0.79, −0.45], *p*<.001, I^2=79%), dry and sore throat (MD −0.83, 95% CI [−1.45, −0.20], *p*=.009, I^2=97%), and fatigue (MD −0.60, 95% CI [−1.04, −0.17], *p*=.007, I^2=98%). **Impr labs:** WBC (I^2=76%), LYM (I^2=98%), LYM% (I^2=90%), PCT (I^2=0%), CRP (I^2=96%) **ARR**: CHM + CWM vs CWM (1^2=95%)

TABLE 4 (Part 7 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Thakar et al., 2022[67]	AYUSH modalities as standalone or adjunctive to CWM	Efficacy, ROR, ROC (clinical improvement, disease severity, mortality, use of oxygen therapy, use of ventilator, admission to ICU, duration of hospital stay), labs, (viral clearance), ARR	17 / 2199	NR / NR	AYUSH-64 vs CWM **Incr efficacy**: 3 studies, n=265, RR 1.94, 95% CI [1.01, 3.72], I^2=77%, moderate certainty of evidence. **Impr ROR**: symptom resolution (3 studies, n=287, MD –2.35 days, 95% CI [–4.05, –0.65], I^2=77%, moderate certainty of evidence). **No signif ROC**: disease severity **No signif change viral clearance**: (3 studies, n=179, RR 1.05, 95% CI [0.88, 1.26], I^2=0%, low certainty of evidence). **ARR**: No ARR in two studies, no additional risk in third study. No mortality in two studies reporting this as an outcome. Kabasura Kudineer vs CWM **Impr ROR**: symptom resolution (2 studies, n=278, MD –1.93 days, 95% CI [–2.28, –1.58], I^2=0%, low certainty of evidence). **Decr ROC**: Single trial decreased hospital stay without additional clinical improvement benefits (RR 1.02, 95% CI [0.83, 1.24]. **No signif change in viral clearance** (3 studies, n=211, RR 1.63, 95% CI [0.96, 2.76], I^2=73% with p=0.07, very uncertain level of evidence). Guduchi vs CWM **No signif ROC**: hospitalization duration (2 non-randomized studies, not statistically significant). **Reduced viral clearance** (2 studies, n=121, RR 3.57, 95% CI [2.31, 5.53], I^2=93%, uncertain quality of evidence). **ARR**: not reported, one non-randomized study
Wang et al., 2022[68]	QFPD granule or QFPD combined with CWM	ROR of various symptoms, ROC to severe disease, VALs, changes in imaging and laboratory values, adverse effects; Heterogeneity assessed using I^2 rates: lung CT, range from mild to critical, reduction of death, cough, fatigue, PCT (I^2=0%); Reducing adverse effects (I^2=21%); Time for nucleic acid conversion: (I^2=76%); Length of hospital stay: (I^2=98%); Fever: I^2=47%; WBC: I^2=80%; CRP: I^2=92%;	15 / 10,390	40.1–64.23 / male & female	**Signif Imp:** ROC: Clinical cure rate (8 trials, n=909); RR=1.15; 95% CI [1.10, 1.20]; p<.00001; length of hospital (9 trials, n=777); WMD=− 2.89; 95% CI [−3.04, −2.73]; disappearing time of cough (3 trials, n=175); WMD: –1.63; 95% CI [−1.89, −1.37] **ARR**: reduction in death (3 trials, n=9448); RR=0.23; 95% CI [0.17–0.33]; p<.00001; improvement on reducing adverse effects: (6 trials, n=3865); RR=0.8; 95% CI [0.68–0.95]; p=.01 **Lung CT:** (5 trials, n=465); RR=1.22; 95% CI [1.12, 1.33]; p<.00001 **Imp effect:** ROC (4 trials, n=347); RR=0.35; 95% CI [0.21, 0.60]; p=.0001; disappearing time of fatigue (2 trials, n=115); WMD: −1.47; 95% CI [−2.19, −0.75]; PCT: PCT (3 trials, n=112); WMD=−0.15; 95% CI [−0.81, −0.12]. **Labs:** shortened the time for nucleic acid conversion (5 trials, n=502); WMD=−4.08; 95% CI [−5.14, −3.02]; CRP: (4 trials, n=315); WMD: –4.39; 95% CI [−6.58, −2.20]; **No Sig Diff:** time of fever reduction (3 trials, n=175); WMD: −1.48; 95% CI [−1.84, −1.13]; WBC (5 trials, n=288); WMD: 0.50; 95% CI [−0.69, 1.69]

TABLE 4 (Part 8 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Zhuang et al., 2022[69]	TCM (single herbs, PCM, compound of several herbs irrespective of preparation) plus CWM	Efficacy, ROR (cough, fever, TCM syndrome score), ROC (rate of hospital stay, rate of severe or critical, time to defervescence), imaging (CT scan), labs (time of RT-PCR negativity, WBC, CRP), ARR	53 / 5425	NR / NR	**Incr efficacy**: 23 studies, RR 1.26, 95% CI [1.18, 1.35], $p<.00001$, $I^2=50\%$, random-effect model **Signif impr ROR**: cough (10 studies, MD=–2.11, 95% CI [–2.98, –1.25], $p<.00001$, $I^2=93\%$, random-effect model), fever (17 studies, RR 1.23, 95% CI [1.10, 1.38], $p<.00001$, $I^2=85\%$) **Impr TCM syndrome score** (12 studies, MD=–3.95, 95% CI [–5.07, –2.82], $p<.00001$, $I^2=92\%$, random-effect model) **Signif impr ROC**: rate to severe/critical (29 studies, RR 0.4, 95% CI [0.33, 0.49], $p<.0001$, $I^2=10\%$, $p=0.31$, fixed-effect model), time to defervescence (18 studies, MD=–1.45, 95% CI [–1.82, –1.07], $p<.00001$, $I^2=83\%$, random-effect model), length of hospital stay (15 studies, MD=–4.05, 95% CI [–5.24, –2.85], $p<.00001$, $I^2=91\%$, random effect model), **Impr Imaging**: CT scan (24 studies, RR 1.22, 95% CI [1.17, 1.28], $p<.00001$, $I^2=46\%$, fixed-effect model) **Impr labs**: ↓ time to RT-PCR negativity (7 studies, MD=–3.35, 95% CI [–4.74, –1.95], $p<.00001$, $I^2=92\%$, random-effect model), CRP (22 studies, MD=–9.23, 95% CI (–10.94, –7.52), $p<.00001$, $I^2=97\%$, random-effect model), WBC (16 studies, MD=0.07, 95% CI [–0.37, –0.51], $p<.00001$, $I^2=97\%$, random-effect model) **No signif diff in ARR** (31 studies, RR 0.85, 95% CI [0.71, 1.03], $p=.10$, $I^2=25\%$, fixed-effect model)
Xu et al., 2022[70]	TCM medicinal formulae combined with conventional treatment	ROR (fever, cough, fatigue, chest CT, hospitalization) biochemical markers, TCM symptom scale score, rate of deterioration Heterogeneity assessed using I^2 rates; Effective rate, deterioration rate, fever, cough, SOB, hospitalization time ($I^2=0\%$); Improvement in chest CT ($I^2=14\%$); Fever ($I^2=95\%$); Fatigue ($I^2=96\%$); Expectoration ($I^2=7\%$); WBC ($I^2=75\%$); Lymphocyte ($I^2=98\%$); TCM symptom scale score ($I^2=92\%$)	26 / 2981	18 or over / NR	**Signif impr ROR:** fever disappearance rate (OR 3.68, 95% CI [1.95, 6.96], $p<.0001$), fatigue disappearance rate (OR 3.15, 95% CI [1.60, 6.21], $p=.0009$), cough disappearance rate (OR 2.89, 95% CI [1.84, 4.54], $p<.00001$), expectoration disappearance rate (OR=5.94, 95% CI [1.98, 17.84], $p=.001$), disappearance rate of shortness of breath (OR=2.57, 95% CI [1.13, 5.80], $p=.02$); TCM symptom scale [SMD –1.22, 95% CI [–1.87, –0.57], $p=.0002$. **ROC:** improvement rate of CT image (OR=2.43, 95% CI [1.86, 3.16], $p<.00001$); reduction of the hospitalization time (MD=–3.16, 95% CI [–3.75, –2.56], $p<.00001$), and deterioration rate (OR 0.49, 95% CI [0.29, 0.83], $p=.007$) **Labs:** WBC (MD=0.30, 95% CI [0.03, 0.57], $p=.03$);
Javed et al., 2022[71]	Any AYUSH intervention along with Standard Care in one arm	ROR (fever, cough), ROC, labs (ferritin, TNF, LDH, Co-RADS-5), ARR; Heterogeneity based on I^2.	13 / AYUSH 1590; homeopathy prophylaxis 23,936	AYUSH 18–75; homeopathy prophylaxis 1–75 and 5–91 / male & female	**Impr ROR:** fever ($I^2=0\%$), cough ($I^2=78\%$) **Impr ROC**: recovery rate and period (RR=0.24, 95% CI [0.11–0.55] $p=.0007$, rate $I^2=82\%$, period $I^2=98\%$) (MD=−2.29, 95% CI [−4.62, 0.04], $p=.05$), respectively. **Impr labs**: cycle threshold value of qRT-PCR (MD=−2.16, 95% CI [−2.90, −1.43, $p<.00001$, $I^2=57\%$), IL-6 (MD=−0.31, 95% CI [−0.57, −0.05], $p=.02$), TNF-alpha (MD=−3.38, 95% CI [−4.25, −2.51], $p<.00001$), LDH (MD=−1.97, 95% CI [−2.57, −1.38], $p<.00001$). **Homeopathy preventive trial:** ↓ # occurrences of events were found (OR 0.12, 95% CI [0.03, 0.47], $p=.002$, $I^2=90\%$). ARR: $I^2=44\%$ RoB was unclear.
Shafiee et al., 2023[72]	Any "drug" with curcumin as its main ingredient	ROC (all-cause mortality, incidence of mechanical ventilation, incidence of hospitalisation, rate of positive COVID-19 RT-PCR test, and rate of patients with no recovery). Heterogeneity provided	13 / 991	NR / NR	**Signif impr ROC**: risk of mortality (RR 0.37; 95% CI [0.21, 0.65]; $p=.0005$), rate of recovery 7 studies (257 intervention, 252 control) (RR 0.55; 95% CI [0.43, 0.69], $p<.0001$), low heterogeneity. **No signif ROC:** mechanical intervention, Incidence of hospitalisation **Impr labs:** positive RT-PCR test rate: pooling of 3 studies (88 intervention, 72 control) (RR 0.55; 95% CI [0.40, 0.77], $p=.0004$)

TABLE 4 (Part 9 of 9) Overview of Results: Systematic Reviews

Study Information	Intervention	Outcomes measured / Heterogeneity	# of studies / participants	Age / Sex	Findings (*CHM and TCM interventions reported, unless otherwise stated*)
Shojaei et al., 2023[73]	Nano-curcumin, compared with placebo	Effectiveness, ROR, ROC, labs, ARRI Heterogeneity not specified	8 / 569	43–57 / 218 females, 351 males	**Improved ROR**: fever, cough, chills, myalgia, olfactory and taste disturbance, O2 saturation, sputum, chest pain, wheeze, dyspnea. **Improved ROC**: signif ↓ hospitalisation stay and mortality rate. **Sig impr labs:** LYM, gene expression of IL-6 and IL-1 beta **No signif diff labs:** CRP, hs-CRP, TNF-alpha, IL-6 No major ARR
Si et al., 2019[74]	JHQG combined with CWM, compared with CWM alone	Effectiveness, aggravation, ROR (fever, cough, fatigue, diarrhea, nausea and vomiting), imaging (chest CT), ROC, labs (nucleic acid test), ARR A comment is made that 1 of the 4 studies impacts intergroup heterogeneity due to the use of placebo only as a control.	4 / 582	34–56 / male & female	**Signif impr ROR**: fever **No signif ROR:** cough, nausea and vomiting, fatigue **Impr ROC:** prognosis, reduction in aggravation rate and better safety profile. **Impr labs**: serum levels of various cytokines and enhance immune function, particularly relating to IL-6, IL-1 β, CXCL8, CCL2, intercellular cell adhesion molecule-1, IL-10, IFNG, and IL-1A **Safety:** no difference between groups
Liu et al., 2022[75]	GAP combined with Vitamin C or CWM antivirals	ROC (hospital stay, mortality rate), labs (AST, ALT, ALP, GGT, TBIL, CRP, WBC, PCT, LYM, CD molecules); Lack of homogeneity between studies noted as reason for not performing meta-analysis.	13 / 598	30 to 75 / male & female	**Effectiveness:** GAPs (mainly diammonium glycyrrhizinate and magnesium isoglycyrrhizinate) improved liver function, inhibited inflammation, and strengthened the immunity of patients. **Impr labs:** reduction in liver enzymes (ALT, AST) and CRP and increase in LYM. **Mild ARR:** rash, nausea, vomiting, diarrhea, and abnormal liver function, but the impact of combining antiviral drugs cannot yet be excluded. **Concerns:** small sample sizes, lack of controls, selection bias across various studies

[a] Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. *Clin Nutr.* 2015;34:1101-1108. doi:10.1016/j.clnu.2014.12.019
[b] Liu M, Gao Y, Yuan Y, et al. Efficacy and safety of integrated traditional Chinese and western medicine for corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. *Pharmacol Res.* 2020;158:104896. doi:10.1016/j.phrs.2020.104896
ACE2 =Angiotensin converting enzyme 2; ALP=Alkaline phosphatase; ALT=Alanine transaminase; ARDS=acute respiratory distress syndrome; ARR=adverse reaction reporting; AST=aspartate aminotransferase; BID=twice a day; CBC=complete blood count; CD=cluster of differentiation; CHM=Chinese Herbal Medicine; CI=confidence interval; Co-RADs= COVID-19 Reporting and Data System; CPM=Chinese Patent Medicine / Chinese Proprietary Medicine; CRP=C-reactive protein; CT=computed tomography; CWM=Conventional Western Medicine; ESR=estimated sedimentation rate; GAP=glycyrrhizic acid preparation; GGT=gamma-glutamyl transferase; HI=herbal intervention; Hs-CRP=high sensitivity C-reactive protein; ICU=intensive care unit; IL-6=interleukin 6; Impr=improved; Insig=Insignificant; JHQG=Jin-Hua-Qing-Gan; LDH= Lactate dehydrogenase; LH=Lian hua qing wen (also LHQW); LHQG=Lian hua qing gan; LHQK=Lian hua qing ke; LYM=lymphocytes; MA=meta-analysis; MD=mean differences; MDA=Malondialdehyde; mRNA=messenger RNA; NA=not applicable; NEU=neutrophil; NR=not reported; OR=odds ratio; PCT=procalcitonin; QFPD=Qingfei Paidu; QOL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; ROC=rate of conversion; ROR=rate of recovery; RR=risk ratio; RS=retrospective studies; RT-PCR=Reverse transcription polymerase chain reaction; Signif=significant; SMD=standardized mean difference; SOB=shortness of breath; TBIL=total bilirubin; TCM=Traditional Chinese Medicine; TID=three times a day; TJQW=Toujie Quwen; TLR=toll-like receptor; TNF=tumour necrosis factor; Tx=treatment; VAL=viral assay level; WBC=white blood cell count; WBS=white blood cells; WM=Western medicine; WMD=weighted mean differences; WNL=within normal limits.

Analysis of Herbal Medicines

Curcumin

The two narrative reviews on curcumin[27,29] (derived from *Curcuma longa*) highlight the antiviral, immunomodulatory, and anti-inflammatory properties of curcumin. Other aspects identified which may contribute to therapeutic benefit in the prevention and/or treatment of COVID-19 are curcumin's antioxidant,[29] anticoagulant,[29] antiplatelet,[29] and cytoprotective[29] properties. The potential role of curcumin in the prevention and treatment of COVID-19 and the management of post-COVID syndrome were indicated as viral inhibition or inactivation by binding directly to receptors on the spike protein and ACE-2 receptors,[27,29] regulation of the PI3K/Akt/mTOR signaling pathway,[27] and alleviation of pulmonary fibrosis.[27]

Five systematic reviews evaluated the effects of curcumin supplementation on patients with COVID-19.[35,58,59,72,73] Studies reviewed included randomized controlled trials (RCTs), intervention studies, clinical studies, and non-randomised clinical trials. Two papers performed meta-analyses and two were descriptive studies. Dosage and type of intervention varied between the studies. All studies included curcumin as an adjunct to standard care. Four studies examined supplementation with nano-curcumin at dosages ranging between 40 mg and 240 mg for periods ranging from 7 to 21 days. Administration of other forms of curcumin supplementation (oral spray, tablet, AyurCov preparation) included dosages ranging from 40 mg to 950 mg, either as standalone or in combination with other NHPs, over durations ranging from 14 to 21 days. The outcomes examined included all-cause mortality,[58,75] effect on lymphocyte count,[58] cytokine levels,[58] gene expression

of transcription factors,[58] mechanical ventilation,[72] hospitalisation,[72] and positive RT-PCR.[72] Statistically significant differences between curcumin intervention and comparator showing the benefit of curcumin included reduction in mortality,[59,73] lower rate of positive viral PCR test,[73] and faster rate of recovery.[73] Improvements in lymphocyte count[58] were reported; however, the statistical significance of this effect was not reported. Supplementation with nano-curcumin was found to potentially reduce the duration of hospitalisation and provide symptomatic relief of COVID-19.[73]

Withania somnifera

The narrative review on *Withania somnifera*[23] highlighted its antiviral properties. The proposed role of *Withania* in the prevention and treatment of COVID-19 related to its major constituents of withaferin A (wifA) and withanone (win). The study reported that the cytotoxicity of the main proteases of SARS-CoV-2, (M^{pro}), which was vital for viral replication, was reduced by both wifA and win. Both components irreversibly inhibited 0.5 μM M^{pro} with IC50 values of 0.54 and 1.8 μM, respectively.

No systematic reviews reported solely on the use of *Withania somnifera* in the prevention or treatment of COVID-19. One systematic review reported on its use as a component of an Ayurvedic herbal treatment (see below).

Plants used in traditional systems of medicine (Chinese, Tibetan, and Ayurvedic medicine)

The ten narrative reviews[10,12-14,16,19,20,25,32,33] that examined herbs used in traditional Chinese,[10,12,13,14,16,19,32] Tibetan,[33] and Thai[10] medicine, and Ayurveda[12,20,25] highlighted the antiviral,[10,13,14,16,20,25,32,33] anti-inflammatory,[10,13,32,33] immunomodulatory,[12,13,14,16,20,33] and hepatoprotective[16] properties of a broad variety of herbs and formulations.

The potential role of these herbs in the treatment of COVID-19 included the multi-component nature of some traditional formulations, contributing to a multi-targeted action against viral infections, cytokine storms, endothelial injury, and micro-thrombotic impacts of variants of SARS-CoV-2.[16]

Systematic Reviews – Ayurvedic Medicine

Four systematic reviews reported on the effects of Ayurvedic medicine in the treatment of COVID-19.[38,63,67,71] The types of studies included were RCTs and quasi-RCTs. Herbal interventions included granules, decoctions, tablets, nasal drops, and injections. Studies included in the systematic reviews examined Ayurvedic herbal medicine as adjunct to standard care,[38,63,67,71] as a stand-alone treatment,[38,67] or compared with placebo or placebo plus Western medicine.[38]

Dosage and interventions varied across the studies. The polyherbal AYUSH-64 formulation was administered at a dosage of 1 g either twice or three times daily. Other formulations included Guduchi Ghanavati, two tablets (250 mg each), twice daily; Chyawanprash, 12 g twice per day for 30 days; and polyherbal approaches reported as AYUSH regimens, comprising different herbal combinations at varying strengths, administered twice daily (see Table S2 in the supplemental material). Duration of administration ranged from 7 days to 12 weeks.

Outcomes examined included effect on RT-PCR negativity, clinical symptoms (fever, cough, chest pain, throat, fatigue, chest computed tomography [CT]), duration of hospitalization, laboratory parameters (white blood cell [WBC] count, lymphocyte counts and percentages, C-reactive protein, IL-6, erythrocyte sedimentation rate [ESR]), disease progression (including resultant admission to high-dependency or emergency units), recovery time, and mortality. Adverse effects of herbal treatment were considered in two studies.[63,67]

Study results suggested that administration of Ayurvedic herbal formulations, including AYUSH-64, Guduchi, and Kabasura Kudineer, performed better as an adjunct to Western medicine when compared with Western care alone, particularly in mild, moderate, or asymptomatic cases.[38,67,71] Ayurvedic herbal medicine treatment when used as an adjunct showed improved symptom recovery rate, and improved laboratory parameters.[71]

Systematic Reviews – Traditional Chinese Herbal Medicine (CHM)

In total, 32 systematic reviews considered the role of patent herbal formulas in the treatment of COVID-19.[35,36,38-57,60-62,64-66,68-70,74] Herbal formulations studied included decoctions, granules, pills, patent formulas, or injections (see Table S3 in the supplemental material). All papers focused on treatment, with none reporting on prevention or management of post-COVID syndrome.

Reporting of patient data was inconsistent. Nine papers did not include patient age data, while 11 did not include gender information. Age reporting included various measures, such as mean age, age range, or average age. The average age ranged between 45 and 65, with an overall age range between 17 and 86 years. Where gender was reported, patients were predominantly male, although one paper reported higher female inclusion. Gaps in data availability were attributed to the number of studies only available in the Chinese language. All patients included were identified as having COVID-19 ranging from mild to critical.

All papers reported on the use of CHM as an adjunct to standard treatment. Three papers also reported on CHM as a stand-alone treatment compared with standard treatment.[57,60,62] Administration of interventions variously occurred over a duration ranging from 3 to 30 days, with dosages varying depending on the nature and type of CHM formulation.

Outcomes examined included clinical effects of herbal medicines as measured by changes in clinical symptoms, recovery time and rate, duration of hospitalization, changes in disease severity, and the progression of disease. Outcomes related to changes in laboratory measures and inflammatory markers, including WBC count, lymphocytes, C-reactive protein, IL-6, ESR, nucleic acids, and viral assays, were examined. Some studies also examined lung injury as evaluated by x-ray or chest CT. The safety of TCM interventions was examined, including adverse reactions, increased severity of disease, and mortality rates.

Results indicated that the use of TCM herbal interventions as an adjunct to Western treatment yielded better recovery rates for COVID-19 clinical symptoms and reductions in recovery time from COVID-19. Statistically relevant results included resolution

of COVID-19 symptoms,[38-40,42-45,47-49,51,53-55,57,65] improvement in lung function, inflammatory markers, and other laboratory results,[40,42-44,46,47,51,52,54,60,66,68] reduction in duration of hospitalization,[40,44,53,68] and improved clinical cure rate.[44,48-51,68]

Other Medicinal Herbs

The narrative reviews examining other medicinal herbs[14,15,26,28,34] also highlighted anti-inflammatory, antioxidant, antiviral, immune enhancing, immunosuppressive, central nervous system modulating, and immune modulating actions of medicinal herbs. The proposed mechanism of action of medicinal herbs in the treatment of COVID-19 was suggested as being due to the secondary metabolites present in these plants, including sterols, diterpenes, alkaloids, glycosides, and aliphatics.[14,34]

One systematic review[75] considered the role of glycyrrhizic acid preparation (GAP) in the treatment of COVID-19 alone and COVID-19 with comorbid liver injury, particularly in relation to its efficacy and safety.[75] The study reported that GAP contributed to a reduction in liver enzymes and CRP while improving liver function, inhibiting inflammation, and strengthening immunity. Some mild adverse reactions were reported although the impact of co-administration with antiviral drugs was not investigated.

Potential Toxicity

One narrative review[17] focussed on potential toxicity of herbs sometimes used in traditional medicine. This review highlighted the importance of use by appropriately qualified practitioners. No systematic reviews specifically examined the potential toxicity of herbal medicine in relation to treatment or prevention of COVID-19 or in the management of post-COVID recovery.

Herbal Medicine as Adjunct to Vaccination

Two narrative reviews examined the role of herbs as vaccination adjuncts against COVID-19.[30,31] These reviews considered preclinical studies of the use of plant proteins as immunoadjuvants in antiparasitic, antifungal, and antiviral vaccines. Immune-modulating and immune-enhancing properties were identified. The potential role of plant proteins in binding to carrier proteins may attenuate potential toxicity of some adjuvant immunization formulations for pediatric and immunocompromised patients[30]. It is proposed that the mechanism of action is related to immunostimulatory activity, such as enhancement of T lymphocyte proliferation,[30,31] and amplification of production of IL-12 and IFN-gamma.[30] No systematic reviews examined the use of herbal medicine for vaccination purposes.

DISCUSSION

Quality of Studies on Herbal Medicines

Over 50% of the original systematic reviews focusing on the use of herbal medicines for the prevention and/or treatment of COVID-19 were not included in the final papers as 49.5% did not meet the AMSTAR criteria set for this umbrella review and another 10.5% were removed during the data extraction phase as they did not meet inclusion criteria (not COVID [n = 4], duplicate [n = 2], not herbs [n = 2], not English [n = 1], wrong study type [n = 1]). Uncertainty about the quality of research on herbal medicines is a recognized concern[76] and impacts the understanding and acceptance of herbal medicines from all traditional medicine systems. For example, concerns exist regarding the variability of plant chemical compositions depending on the part used, botanical species, and growing and harvesting conditions, among others in herbal research.[76,77] Likewise, concerns about the level of methodological reporting, such as the absence of information about blinding, random allocation, and low sample sizes, have previously been identified.[77]

Herbal Medicines Integral to Systems of Traditional Medicine

Various studies included in this paper examined herbal medicines used in traditional medicine systems—particularly those of TCM and Ayurveda. Herbal medicines are used alone and in conjunction with conventional Western medicine for most health concerns, especially those related to acute infections and non-communicable diseases (NCDs).[77,78,79] Understanding the effectiveness and safety of herbal medicines is critical as they are used as an integral part of most traditional systems of medicine, including Indian systems of medicine [80] and Traditional Chinese medicine (TCM), and over 93% of the naturopathic medical workforce globally uses herbal medicines [2,81] and indicated that the study of herbal medicines was part of their naturopathic medical education. With the use of herbal medicines so integral to traditional medicine practices, it is concerning that, according to the *WHO Global Report on Traditional and Complementary Medicine 2019*, 110 member states indicated the use of herbal medicines, but only 24 indicated that there was any regulation.[3] The lack of regulation impacts the safety, quality, and efficacy of herbal medicines both for practitioners who use them in practice and the public that is self-prescribing.

Diverse Therapeutic Properties

The studies in this paper explored the pharmacological aspects of various herbal medicines in the prevention and treatment of COVID-19 and long COVID, including immunological, anti-inflammatory, anti-microbial, and antioxidant properties. The wide range of herbs investigated, and the diversity of the properties explored highlight the significant role that herbal medicines can play, especially in the treatment of acute conditions, such as COVID-19. Many papers highlighted the role of herbal medicine as an adjunct to Western care (n = 40). Herbal interventions, when used as an adjunct, demonstrated statistically significant improved recovery, including symptomatic resolution, improved inflammatory markers, reduced hospitalization, and improved clinical cure.

Various studies noted herbal medicine's inhibitory impacts on viral activity. This includes blocking of invasion pathways, suppression of cytokine storm potential and degradation of lymphocytes. Herbal constituents such as curcumin, essential oils, naringin, pectins and flavonoids can bind directly to receptors. The cytotoxicity of M^{pro} (required for viral replication) was inhibited

by constituents of *Withania*. The anti-inflammatory properties of herbal constituents, including sterols, diterpenes, alkaloids, glycosides, and cannabinoids, contribute to modulation of inflammatory processes, including ACE2 gene expression, and reduction of serum CRP, MDA, and TNF-alpha.

Enhancement of vaccination through adjunctive use of herbal medicines with immunomodulatory and immuno-enhancement properties was suggested by two studies in this review. This is an aspect of the potential of herbal medicine that warrants further study, given the immuno-stimulant activity of various herbs.

Herbal Interventions Indicated Improved Outcomes

A significant finding, particularly among the reviews of CHM interventions, was the added benefit of herbal treatment to patient outcomes when botanicals are combined with standard care or Western medicine. Objective laboratory measures showed statistical improvements within complete blood counts (CBC) (white blood cells [WBS], lymphocytes), CRP, and other measures of inflammation. Relief and reduction of COVID-19 symptoms and the rate of conversion, especially in relation to the duration of stay in hospital and viral clearance, was also evidenced. Combining herbal medicine with standard treatment thus may reduce overall cost of treatment through better patient response to treatment and improvements in recovery from illness.

Key Herbal Medicines Investigated with Respect to COVID-19

Although >60 individual herbs were included in the papers surveyed in this report (see Appendix S1 in the supplemental material), a few herbs stood out due to the frequency with which they were investigated (including as key components of herbal formulations in TCM and Ayurvedic preparations), the findings associated, and their widespread use in herbal medicine. Three key herbs highlighted are *Glycyrrhiza glabra/uralensis, Tinospora cordifolia*, and *Curcuma longa*.

Glycyrrhiza glabra/uralensis (licorice) is a key herb in seven of the TCM herbal formulations studied in this review. Its medicinal use has been documented in texts from ancient Assyria, Egypt, China, and India.[83] Glycyrrhizic acid (GA) is one of the main active ingredients in licorice. Studies have demonstrated the role of glycyrrhizic acid preparations (GAP) in inhibiting growth of coronaviruses,[82,83] influenza A,[82,83] and HIV.[82,83] GA has demonstrated activity in chronic liver disease, inhibiting collagen type 1 alpha 2 (COL1A2), and slowing the progression of liver fibrosis.[82] Anti-viral actions include interference with the S-protein, inhibiting viral entry to host cells, adsorption and membrane penetration during viral replication, and stimulation of IFN-gamma development by T-cells.[82] As an anti-inflammatory, GA inhibits translocation of nuclear factor-κB (NF-κB) and suppresses TNF-alpha.[83]

Tinospora cordifolia (guduchi) is widely used in Ayurvedic medicine.[84] Classical Ayurvedic texts indicate its usefulness in various disease conditions, including those characterised by fever, nausea, and cough.[84,85] It contains a variety of compounds, including alkaloids, glycosides, sterols, and polysaccharides.[85] Preparations of the dried stem have demonstrated an anti-inflammatory mode of action that resembles that of nonsteroidal anti-inflammatories.[84] Studies have indicated it can normalize liver function[84] and that it activates the immune system via actions of (1,4)-alpha-D-glucan on macrophages, activating them via TLR6, NF- κB and cytokine production.[84,85]

Curcuma longa (turmeric) is a key source of curcumin and has been used medicinally in many parts of the world.[86,87] While bioavailability has been identified as reducing the effectiveness of curcumin, most preparations contain such enhancers as piperine (also found in black pepper, *Piper nigrum*).[86,87] Evidence demonstrates that curcumin can address oxidative stress, which is a factor in chronic disease and inflammation.[86] Curcumin's anti-inflammatory actions have been shown to result from its capacity to block activation of NF- κB.[86] Potentially, it also increases the activity of antioxidants.[86] Curcumin has demonstrated activity targeting multiple signalling molecules.[86] It directly targets protein kinases, inflammatory molecules, carrier proteins and metal ions.[87] Indirectly, it targets enzymes, transcription factors, receptors, inflammation mediators, adhesion molecules, and growth factors.[87] This broad range of activities contributes to the role of curcumin in treating and preventing various conditions.

Safety of Herbal Medicines

Twenty systematic reviews in this paper considered the potential of adverse reactions in their study design.[41,42,45,46,49,50,52-56,60,63-67,73-75] Most (n = 17) reported adverse reactions that were either mild or "not serious." Reactions reported included diarrhea, vomiting, rash, and nausea. Two studies[56,75] reported abnormal liver function results; however, both reported that methodological limitations reduced the certainty of the impact on safety of herbal treatment when used in conjunction with standard treatment. Three studies[54,60,63] reported that inclusion of herbal medicine with standard treatment tended to reduce side effects. One study[75] specifically noted that the impact of combining herbal and chemical anti-viral drugs was not known.

As noted above, the global lack of regulation impacts the safety of herbal medicines.[3] A range of safety considerations have been identified, including lack of methodologically sound research regarding interactions between medications (herb–drug, and herb–herb),[77] adulteration of herbal material,[77] variable product quality,[76,77] and cultural contexts, such as communication gaps between patient and practitioner.[76,77]

Various factors contribute to herbal medicine safety. For example, chemical composition can vary depending on the growing conditions, parts used, how and when plants are harvested, preparation/extraction, and formulation of medicinal products.[76] Clinically based research demonstrates that naturopathic practitioners have a high level of knowledge regarding herbal safety issues, making them well-placed to provide support for patients in making appropriate choices.[2]

Limitations

There are some limitations to this review. The methodology for this umbrella review focused on papers with a strong methodology. Several of the papers reviewed reported poor methodological

quality, including risk of bias in the studies that they reviewed. Building a body of knowledge demonstrating the effectiveness and safety of herbal medicine requires increased attention to conducting high quality research. Another limitation was the wide variety of herbal medicines included in the review. While this provided a useful overview of the range of herbs that could be used for the prevention, treatment, and management of COVID-19, the range of interventions used made the identification of key herbs and treatment approaches challenging. The lack of systematic reviews considering the role of herbs in the prevention of COVID-19 highlighted a gap in research relating to the benefit of herbal medicine in enhancing the human immune system to prevent disease.

CONCLUSION

Herbal medicines are the most prevalent therapy used in most traditional medicine systems, yet there remain concerns about the safety of herbal medicines, the lack of regulation in many countries, and the quality of research conducted on herbal medicines. That being said, half of the studies in this paper reported on adverse research, 85% of which reported only "mild" or "not serious" reactions.

The papers included investigated over 60 herbs and highlighted a broad range of therapeutic properties, including immunological, anti-inflammatory, anti-microbial, and antioxidant properties as they highlighted the significant role of herbal medicines in the prevention and treatment of COVID-19 and long COVID and in vaccination enhancement. Three key herbs were highlighted: *Glycyrrhiza glabra/uralensis,* for its potential to inhibit the growth of coronavirus, the anti-inflammatory and immune-enhancing properties of *Tinospora cordifolia*, and the oxidative stress and anti-inflammatory properties of *Curcuma longa*. What appeared to be evident in this review is that herbal interventions, when used as an adjunct to standard care, demonstrated statistically significant improved recovery including symptomatic resolution, improved inflammatory markers, reduced hospitalization, and improved clinical cure.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that we have none.

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SUPPLEMENTAL MATERIAL

Supplemental material linked to the online version of the paper at https://doi.org/10.54434/candj.161:

- Table S1 Additional Citation Overlap Analysis: Papers with 5 or More Articles Cited More Than Once
- Table S2 AYUSH Regimens
- Table S3 Chinese Herbal/Traditional Formulations Studied by Number of Papers Reporting
- Appendix S1 Herbal Formulations and Singles

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APPENDIX 1: GLOSSARY OF TERMS

ACE2	Angiotensin converting enzyme 2
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMR	Region of the Americas
AMSTAR	A Measurement Tool to Assess systematic Reviews
ARDS	Acute respiratory distress syndrome
ARR	adverse reaction reporting
AST	aspartate aminotransferase
CBC	complete blood count
CBM	Chinese Biomedical Literature Database,
CCNM	Canadian College of Naturopathic Medicine
CD	cluster of differentiation
CHM	Chinese Herbal Medicine
CI	confidence interval
CNKI	Chinese National Knowledge Infrastructure
CPM	Chinese Patent Medicine / Chinese Proprietary Medicine
CRP	C-reactive protein
CSTJ	China science and technology journal
CWM	Conventional Western Medicine
ESR	estimated sedimentation rate
EMR	Eastern Mediterranean Region
EUR	European Region
GAP	glycyrrhizic acid preparation
GGT	gamma-glutamyl transferase
HI	herbal intervention
HIV	human immunodeficiency virus
Hs-CRP	high sensitivity C-reactive protein
IL-6	interleukin 6
Impr	improved
Insignif	Insignificant
LYM	lymphocytes
MA	meta-analysis
MDA	Malondialdehyde
M^{pro}	main protease
mRNA	messenger RNA
NCD	non-communicable diseases
NEU	neutrophil
NFKappaB	Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)
NHP	natural health products
NR	not reported
NRC	non-randomised controlled trial
OSF	Open Science Framework
PCT	procalcitonin
PICO	patient/population, intervention, comparison and outcomes
RCT	randomised controlled trial
QFPD	Qingfei Paidu decoction
RISS	Research Information Service System
RoB	risk of bias
ROC	rate of conversion
ROR	rate of recovery
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SEA	South-East Asia Region
Signif	significant
SR	Systematic Review
SSRN	Social Science Research Network
Standard Care	Treatment routinely offered in a hospital setting. Also conventional care. May include traditional plus Western biomedical/ pharmaceutical treatment
TBIL	Total bilirubin
TCM	Traditional Chinese Medicine
TLR	toll-like receptor
TNF	tumour necrosis factor
VIP	Chinese Science and Technique Journals Database
VAL	viral assay level
WBC	white blood cell count
WBS	white blood cells
WPR	Western Pacific Region