

Editor's Letter: WNF/COVID-19 Natural Therapies Special Edition

Marianne Trevorrow,¹ MA, ND



This letter will be relatively brief, as we also have a Guest Editorial for this edition from Lloyd, Cooley, and Steele introducing the work of the World Naturopathic Federation (WNF) research team behind the umbrella reviews that make up this Special Edition, our first on our new digital platform.

Instead, I'd like to reflect briefly on the journey we have taken at *CAND Journal* since we first discussed transitioning to a digital Open Journal Systems (OJS) platform in 2020. At the time, we knew we would have to build out a fully articulated set of Submission Standards and Guidelines suitable to a naturopathic medical publication, and after an extensive search, we were very grateful to have found a team at SG Publishing that was experienced with the unique challenges of defining our space as a science-based publication, while incorporating our naturopathic philosophy and extensive use of traditional, complementary, and integrative medicines (TCIM). As almost all our readers know, we began our new site build out in early 2021, and we were able to publish our first digital edition at the end of September 2021, right in the middle of the COVID-19 global pandemic.

Since that time, our small but very dedicated editorial team has carried out extensive outreach efforts in North America and overseas to try to bring attention to and build impact for *CANDJ*, both within and outside the profession. One of the most important ways we have done this is to make naturopathic doctor-led research freely available from point of publication on our Editor Selections page. The point of doing this is to showcase the outstanding work done by many of our Canadian colleagues, part of our mission at *CANDJ* since our digital inception.

Within these last two years, we have also undergone further updates to our Policies and Guidelines to include guidelines for the nomenclature of TCIMs (which we developed based on CONSORT guideline extensions relating to herbal and Chinese medicine)^{1,2} and to incorporate standards for Indigenous authorship, the use of Indigenous medicines, and citation standards for traditional Indigenous Knowledge Keepers.³

We are now entering our third year as a digital publication, and I'm delighted to be able to introduce this Special Edition, containing six umbrella reviews from the WNF, an international task force of researchers and clinicians supported by the Canadian College of Naturopathic Medicine (CCNM) and the Australian Research Consortium in Complementary and Integrative Medicine (ARCCIM). To reach as wide an audience as possible, *CANDJ* has agreed to make this entire edition an Open Access publication; in this way, we hope to demonstrate our commitment to publishing the work of naturopathic researchers, internationally as well as within Canada.

As this edition also brings us to the end of 2023, I would like to take this opportunity to wish everyone a very restful holiday season and peaceful new year.

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The Role of Traditional, Complementary, and Integrative Healthcare (TCIH) Therapies and Practices in the Prevention and/or Treatment of COVID-19: An Umbrella Review



Iva Lloyd,¹ ND, Kieran Cooley,² ND, and Amie Steel,³ ND, PhD

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the resulting coronavirus disease 2019 (COVID-19) infection have irrevocably transformed societies and health systems around the world. As of September 2023, more than 770 million cases and 7 million deaths have been attributed to COVID-19 globally,¹ and new SARS-CoV-2 strains are still emerging.² Three and half years after the onset of the COVID-19 pandemic, the search for effective COVID-19 treatments is still underway with an ongoing emphasis on biomedical treatments, while research on natural health products (NHPs) to support the prevention, management, and/or treatment of COVID-19 has been widespread. At the start of the COVID-19 pandemic, the global naturopathic community published ten rapid reviews in a Special Issue of *Advances in Integrative Medicine*.³ The issue outlined the historical role of natural therapies in the prevention and treatment of viral respiratory infections as one step in informing future research directions, leveraging knowledge in the naturopathic profession, and synthesizing evidence.³ Subsequently, a living evidence review of the efficacy and effectiveness of NHPs for COVID-19 was created and maintained by the World Naturopathic Federation (WNF) as a contribution to the evolving evidence base during the pandemic.⁴

Through these efforts, the naturopathic profession has assumed a key role in translating the emerging evidence regarding NHPs for COVID-19 for health practitioners, policymakers, and the general public. Naturopathic practitioners benefit from having a deep knowledge of traditional medicines (including NHPs) balanced with training in modern advances in biochemistry and pathophysiology. They are often trained as primary care practitioners and, as such, are excellently positioned to assess and interpret the clinical relevance and value of NHP research for a condition that affects so many in the community, such as COVID-19.⁵

Naturopathic practitioners employ a mix of contemporary research evidence and traditional knowledge to inform their

clinical decisions^{6,7} and this approach aids them in adapting to the ever changing external factors while still retaining the central tenets that guide naturopathic care.⁵ Even though naturopathic practitioners are well positioned to aid in public health efforts, barriers such as lack of regulation, government policies, and inadequate financial support, as well as a lack of formal linkages to public health organizations, have been identified as impediments to the naturopathic workforce being included as a valuable health-care resource.⁸

With the increased focus of the World Health Organization (WHO) on traditional, complementary and integrative medicine (TCIM), as demonstrated by the first Global Summit on Traditional Medicine held in India in August 2023,⁹ and the Astana Declaration's call for traditional medicines to be implemented into global health care,¹⁰ it is imperative that research investigating traditional, complementary and integrative health-care (TCIH) products and practices be considered in global healthcare strategies and in global healthcare crises, such as the COVID-19 pandemic.

OUR APPROACH TO THE UMBRELLA REVIEW

Aim of the Umbrella Review

This Special Focus Issue of the *CAND Journal* is a collation of six umbrella reviews examining the research focused on the contribution of TCIH NHPs and practices in the prevention and management of COVID-19. The WNF undertook this project with the support of the Canadian College of Naturopathic Medicine (CCNM) and the Australian Research Consortium in Complementary and Integrative Medicine (ARCCIM) as a means of providing health service providers, governments, and the wider community with a critical review of the NHPs and therapies that have received significant scholarship and research attention as they relate to the prevention and management of COVID-19.

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Yearly Live Review of NHPs and COVID-19 Research

Prior to the umbrella review process, the WNF Research Committee, in collaboration with the CCONM, conducted a year-long live review consisting of a monthly search for published peer-reviewed research pertaining to NHPs and natural therapies as they relate to the prevention and/or treatment of COVID-19 and post-COVID syndrome. The research publications collated through this live review included systematic reviews, narrative reviews, and other research papers. A summary of the systematic reviews was updated monthly on the WNF website (<https://worldnaturopathicfederation.org/live-review-of-natural-health-products-nhps-researched-with-respect-to-the-covid-pandemic/>), and an interim report of the systematic review characteristics was published in March of 2023.⁴ At the end of 2022, 308 systematic reviews and 93 narrative reviews had been collated through this live review. Due to the significant volume of research collected, and the overall increase in published works year over year, an umbrella review process was initiated, which included the critical appraisal of both the narrative reviews and the systematic reviews.

The Umbrella Review Task Force

The umbrella reviews were supported by a Task Force team of 46 individuals (researchers including research-active naturopathic clinicians) from seven educational institutions across seven countries and four WHO regions.

Target Audience

The reviews are intended to inform a broad range of stakeholders, including policymakers, researchers, biomedical health professionals and TCIH professionals, and the public. The Task Force’s intention was to leverage the strong pharmacognosy and nutritional knowledge and expertise of naturopathic practitioners and researchers to provide an up-to-date synthesis of available research evidence to identify treatment opportunities that warrant further consideration in the prevention, management and treatment of COVID-19, or rule out unlikely treatment options.

Potential Contribution

These reviews provide health policymakers, researchers, and clinicians evidence to identify the NHPs and natural therapies that

are supported by research in terms of COVID-19 prevention, treatment, and management options. Additionally, the engagement of the naturopathic profession in these reviews has provided early career researchers with experience in leading an international team of authors while offering clinician researchers additional experience and training in critical appraisal and scholarship. In doing so, it has contributed to one of the WNF’s primary aims: to support the building of naturopathic research capacity globally.⁵

Included Reviews

The Task Force identified and produced six umbrella reviews encompassing herbal medicine¹¹; vitamins¹²; minerals¹³; nutraceuticals (quercetin, n-acetyl cysteine, omega-3 fish oil, melatonin, probiotics, and propolis)¹⁴; diet and food¹⁵; and movement, exercise and breathing.¹⁶ As outlined in Table 1, the umbrella review started with 94 narrative reviews and 308 systematic reviews identified by the live review. After quality assessments (Phase 1) using the Scale for the Assessment of Narrative Review Articles (SANRA)¹⁷ and A Measurement Tool to Assess Systematic Reviews (AMSTAR 2)¹⁸ and screening against the eligibility criteria, 72 narrative reviews (76.6%) and 121 systematic reviews (39.3%) were selected for inclusion across the series of umbrella review manuscripts. The identified reviews were then allocated to authorship teams for each umbrella review for verification and inclusion in the respective umbrella review synthesis. As a result of this stage, some reviews were reallocated to a different umbrella review topic. An overview of the selection of manuscripts included in the different umbrella reviews for this Special Issue is presented in Table 1.

Limitations of the Evidence

The evidence presented in the umbrella reviews included herein is not intended to be a comprehensive exploration of all NHP treatments and practices commonly used in the prevention, management, or treatment of COVID-19. Neither is it intended to present a full picture of any one particular treatment or therapeutic approach. Each review is limited by the availability of evidence in the databases used in our search, and also influenced by the attention, funding, and opportunity to publish. The clinical expertise of naturopathic doctors in the form traditional

TABLE 1 Overview of Inclusion/Exclusion of Papers by Category

	NR – Pre-Phase 1	NR – Post-Phase 1	NR – Phase 2	% of NR Included	SR – Pre-Phase 1	SR – Post-Phase 1	SR – Post-Phase 2	% of SR Included
Herbal ¹¹	24	25	25	104.2%	99	51	41	41.4%
Vitamins ¹²	20	18	14	70.0%	92	59	44	47.8%
Minerals ¹³	12	8	8	66.7%	32	14	12	37.5%
Nutraceuticals ¹⁴	16	15	15	93.8%	43	20	15	34.9%
Diet and Food ¹⁵	13	9	7	53.8%	1	5	4	400.0%
Movement, Exercise and Breathing ¹⁶	9	8	3	33.3%	41	15	5	12.2%
Total	94	83	72	76.6%	308	164	121	39.3%

NR = narrative reviews; SR = systematic reviews.

knowledge, un-published clinical observations, or from the process of patient-centred clinical decision-making are not reflected.

Summary Statements

The umbrella reviews identified a range of important findings. The reviews by Murphy et al.,¹⁵ Remy,¹² and Van De Venter et al.¹³ found adequate nutritional levels of various vitamins and minerals were preventive against COVID-19 and numerous nutritional deficiencies were correlated with a decreased rate of recovery (ROR) from COVID-19 symptoms and worsened rate of conversion (ROC). Oakes et al.¹¹ reviewed the publications investigating herbal medicine and found therapeutic interventions that combined herbal medicines with conventional Western medical treatments showed significant improvements in both ROR and ROC. Although additional research is needed with respect to nutraceuticals, according to Karzon et al.,¹⁴ the current data suggests that the anti-inflammatory, anti-microbial, and antioxidant properties of various NHPs provided therapeutic value both preventively and in treatment of COVID-19. There are also a number of therapies which were reviewed by Carter et al.,¹⁶ such as breathing exercises, physical exercise, and mind-body exercises that are showing promise both from a preventive perspective and from a treatment perspective of COVID-19 due to their direct impacts on health and their indirect ability to modulate the immune system by decreasing stress. Overall, this series of umbrella reviews presents a growing body of evidence indicating that herbal medicines, vitamins, minerals, other natural health products/dietary supplements, diet, and other natural therapies are a significant therapeutic consideration in the prevention and management of COVID-19 and long-term sequelae. The series indicates that additional research is warranted.

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The Role of Minerals in COVID-19: An Umbrella Review

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ABSTRACT

Background: This umbrella review aims to synthesize the existing literature on the preventive and therapeutic benefits of minerals zinc, selenium, iron, copper, magnesium, phosphorus, and calcium in the context of COVID-19 prevention and management. The objective is to highlight the clinical applicability and identify avenues of future research.

Methods: A systematic search was conducted in PubMed and Google Scholar databases using predefined keywords for each mineral combined with COVID-19-related terms. Narrative and systematic reviews were included, following Cochrane guidelines. AMSTAR scoring was used to assess systematic review quality, while SANRA guidelines were used to evaluate narrative reviews. Data extraction and synthesis were performed, and reference overlap analysis was conducted (see Table S1 in the supplemental material).

Results: Narrative reviews highlighted the range of therapeutic properties of minerals including antimicrobial, antiviral, antioxidant, anti-inflammatory, and immune-modulating and the essential role they play in the prevention and treatment of many conditions, including acute respiratory conditions such as COVID-19. The systematic reviews highlighted that deficiency of key minerals such as zinc, selenium, iron, copper, magnesium, phosphorus, and calcium are associated with increased risk of infection and decreased rate of recovery. Iron supplementation may be beneficial as functional anemia is common in those with COVID-19. Zinc supplementation may shorten the duration of olfactory dysfunction.

Conclusion/Summary: Deficiency of minerals may increase the risk of infection and decrease the rate of recovery as it relates to COVID-19. Supplementation with and correction of zinc, iron and selenium deficiencies may improve clinical outcomes and immune responses in those with COVID-19.

Key Words Supplements, selenium, zinc, magnesium, iron, phosphorus, calcium, deficiency

INTRODUCTION

The prevention and treatment of the novel airborne virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; see Appendix 1 for a list of terms and acronyms used in this article) and its resultant coronavirus disease 2019 (COVID-19), as well as the management of COVID syndrome or long COVID has become a critical research priority due to the lack of evidence-based treatment protocols.¹ Natural health products such as vitamins, minerals, and herbal supplements are commonly used, widely available self-prescribed products.^{2,3} Improving overall health and maintaining health are frequently cited reasons for supplement use.⁴ Nutritional gaps are commonly present in the general population and deficiencies in micronutrients may lead to serious health problems.⁴ Nutritional counselling and guidance around supplementation are important services provided

by healthcare practitioners, such as naturopathic doctors, in the prevention and treatment of non-communicable and communicable diseases.^{2,5} Older people, immunocompromised people and those with underlying chronic conditions, all of whom are commonly associated with nutritional deficiencies, are at higher risk of developing critical forms of COVID-19, despite vaccination.^{6,7} A shift in consumer behaviour reflected research findings that mineral supplementation may contribute to the prevention and treatment of COVID-19, with a switch from mineral supplementation for treatment of viral infections (curative) to preventive use based on their immune enhancing properties.^{5,8,9} Forty-three percent of US consumers increased their intake of supplements with the intent of improving their immune function and wellness benefits during the COVID-19 pandemic. In China, 37.7% of survey participants reported the use of certain supplements to cope with COVID-19.¹⁰

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There are numerous studies focusing on the relationship between influenza-associated mortality, the incidence and duration of acute respiratory infections (ARIs) and baseline nutritional status.¹¹ Iron, zinc, magnesium, and selenium deficiencies are modifiable risk factors for poor immunogenicity and vaccine failure. Supplementation in institutionalized elderly patients resulted in higher antibody titres to the influenza vaccine.^{11,12} Supplementation could address immunosenescence and baseline inflammation in the elderly, resulting in decreased infection rates and improved responses to COVID-19 vaccines.¹¹⁻¹³ Patient education by practitioners is important to drive behaviour patterns of supplementation as a large-scale preventive tool, especially in high-risk populations. Informed decisions by self-medicating consumers should be guided by evidence-based research. This will help them to avoid adverse effects from prolonged use of high-dose minerals, polypharmacy, and drug interactions. High-dose adjunctive micronutrient supplement use should be encouraged only in clinical settings where monitoring for toxic effects can take place.^{10,14} Critically, inappropriate supplementation of ineffective minerals may delay the commencement of more effective treatment and allow COVID-19 progression.¹⁴

There is a need for research to provide an overview of the value of natural health products (NHPs) with regard to COVID-19. The objective of this study was to review the synthesis of literature on the use of minerals for the prevention and or treatment of COVID-19 and the management of COVID syndrome. Therefore, we conducted this comprehensive umbrella review to describe the published peer-reviewed literature and identify key areas to consider for research and clinical application.

METHODS

Design

Details of the ongoing living review preceding this study have been published in the Interim Report for the Live Review of Natural Health Products Researched with Respect to the COVID pandemic.¹⁵ The live review provides a continually updated and evolving summary of the available evidence. Updated information on the live review can be accessed on the World Naturopathic Federation website¹⁶: <https://worldnaturopathicfederation.org/live-review-of-natural-health-products-nhps-researched-with-respect-to-the-covid-pandemic/>. This study follows on from the interim report on the Living Systematic Review and forms part of a larger umbrella review on NHPs. The umbrella review provides a synthesis of the research included in the Live Review. The focus of this study is on the use of minerals with respect to the COVID pandemic.

Search Strategy

Reviews included in this study were identified by the Live Review, which followed the Cochrane Guidelines for Living Systematic Reviews.^{16,17} Monthly literature searches were conducted of the PubMed and Google Scholar databases between May 2022 and May 2023. The following search algorithm was used; “natur*,” “herb*,” “nutraceutical,” “botanical,” “medicinal plant,” “Ayurvedic,”

“Chinese medicine,” “herbal patent formula,” “vitamin,” “mineral,” combined with “prevention,” “prophylaxis,” “deficiency,” “treatment,” “management,” and “*COVID*,” “Coronavirus,” “SARS-CoV-2.” Terms cited in the literature such as individual herb names, compounds, vitamins, and minerals were included in the search. Identified articles were categorized based on the type of review, namely systematic, narrative, meta-analysis, and other.

Inclusion and Exclusion Criteria

This study includes systematic and narrative reviews included in the Live Review. Narrative reviews were reviewed by two independent reviewers and appraised for methodological quality using the Scale for The Assessment of Narrative Review Articles (SANRA) guidelines.¹⁸ Inclusion criteria for narrative reviews was if they had a scientific reasoning score of 1 and 2 and an overall total score of >5. Individuals providing data extraction were blind to the quality assessment criteria. Systematic reviews were reviewed by two independent reviewers and appraised for methodological quality using A Measurement Tool to Assess Systematic Reviews (AMSTAR) guidelines.¹⁹ Systematic reviews were included if the answer was “Yes” or “Partially yes” to question 9 and “Yes” to question 13 of the AMSTAR checklist.²⁰ Individuals performing data extraction were blinded to the quality assessment criteria for inclusion or exclusion of studies.

Any discrepancies for the inclusion of criteria were verified by a separate reviewer. Data was extracted only for those studies that were statistically significant and only for outcomes relevant to NHPs or natural therapies. A reference overlap analysis was used for the systematic reviews ensuring results were not over amplified for any single study included. Extracted data was captured and collated in online spreadsheets.

Data Extraction

Data extraction for the narrative reviews was performed as follows: study number, study identification—American Medical Association (AMA) style, author(s), date, journal, country/world region, review objective, details of any search conducted, area of focus (prevention, treatment, post-COVID), single category/mixed category, doses, therapeutic considerations including properties (anti-inflammatory, antiviral, etc., available at https://www.ndhealthfacts.org/wiki/Action_of_Herbs), associations (relationship to other vitamins/minerals, pathways), therapeutic considerations, additional clinical notes. Automation tools were not used in this process.

Data extraction for systematic reviews was performed as follows: study number, study identification—AMA reference style, author(s), date, journal, area of focus (prevention, treatment, post-COVID), review objective, review type (narrative, systematic, or meta-analysis), search date, search databases, study designs included, country of included studies, publication date range, tools for assessment of risk of bias, methods of synthesis/analysis, interventions relevant to NHPs/natural therapies, outcomes measured, number of studies included in the review, number of participants, age of included participants, sex of participants (percentage that are female), results/findings, heterogeneity

(only if a meta-analysis). Automation tools were not used during data extraction.

RESULTS

After the initial literature search and screening of the studies included in the Live Review was performed, 93 narrative reviews and 308 systematic reviews on NHPs were identified (Table 1). Of those, 12 narrative reviews and 32 systematic reviews pertained specifically to the use of minerals.

Narrative Reviews

Although narrative reviews are not usually included in umbrella reviews, they provide additional resources as well as an overview of the topic.²¹ Of the 12 narrative reviews initially identified, eight (67%) remained for the final umbrella review after exclusion criteria were applied (Table 2). Based on the country of residence of the first author, two of the reviews were conducted from the USA,^{22,23} while the others include one each from Australia,²⁴ Iran,²⁵ Italy,²⁶ Romania,²⁷ Serbia,²⁸ and Poland.²⁹ The minerals reviewed were

copper,^{25,27,28} iron,²⁸ magnesium,²⁵ selenium^{23,25-29} and zinc.²²⁻²⁸ Five of the narrative reviews focused on both prevention and treatment,^{22,24-27} two on prevention,^{23,29} and one on treatment.²⁸

Systematic Reviews

Of the 32 systematic reviews initially identified, 14 (44%) remained for data extraction after the AMSTAR analysis. Of those, 12 (86%) were included in the umbrella review after all exclusion criteria were applied and duplicates removed (Table 3). Based on the country of origin of the first author, reviews were conducted from five World Health Organization (WHO) regions; the Eastern Mediterranean region (Iran³⁰), the European region (Greece,³¹ Italy³², Netherlands,³³ Poland,³⁴ United Kingdom³⁵), the Region of the Americas (two studies in the USA^{36,37}), the South-East Asian region (Sri Lanka³⁸), and the Western Pacific region (Australia,³⁹ China,¹⁰ Singapore⁴⁰). The mineral therapies reviewed were calcium,^{31,40} iron,^{33,35,40} magnesium,^{31,40} phosphorus,³¹ selenium^{30-33,35,38,40} and zinc,^{10,31-34,35-40} with zinc being the most frequently represented mineral in the research. Six mineral reviews focused on the use of minerals for the prevention^{30,31,33,35,39,40} of

TABLE 1 Initial Findings of the Literature Search and Screening against Inclusion and Exclusion Criteria

	NR – Pre	NR – Post	% of NR included	SR – Pre	SR – Post	% of SR included
Vitamins	19	17	89.5%	92	59	64.1%
Minerals	12	8	66.7%	32	14	43.8%
Herbal	24	25	104.2%	99	51	51.5%
Nutrition	13	9	69.2%	1	5	500.0%
Other NHPs	16	15	93.8%	43	20	46.5%
Other Therapies	9	8	88.9%	41	15	36.6%
Total	93	82	88.2%	308	164	53.2%

NR – Pre=narrative reviews before screening against inclusion and exclusion criteria; NR – Post=narrative reviews after screening against inclusion and exclusion criteria; SR – Pre=systematic reviews before screening against inclusion and exclusion criteria; SR – Post=systematic reviews after screening against inclusion and exclusion criteria; NHP=natural health product.

TABLE 2 Main Characteristics of Included Narrative Reviews, Micronutrients and Area of Focus

Study No.	First Author, Year	Country	WHO Region	Mineral	Area of Focus
260	Notarbartolo et al., 2022 ²⁶	Italy	EUR	Zinc Selenium	Prevention, Treatment
262	Pisoschi et al., 2022 ²⁷	Romania	EUR	Copper Selenium Zinc	Prevention, Treatment
290	Prasad et al., 2022 ²²	USA	AMR	Zinc	Prevention, Treatment
300	Ahvanooei et al., 2022 ²⁵	Iran	EMR	Copper Magnesium Selenium Zinc	Prevention, Treatment
331	Paudel et al., 2022 ²⁴	Australia	WPR	Zinc	Prevention, Treatment
343	Kieliszek et al., 2022 ²⁹	Poland	EUR	Selenium	Prevention
344	Djordjevic et al., 2022 ²⁸	Serbia	EUR	Copper Iron Selenium Zinc	Treatment
348	Bell et al., 2023 ²³	USA	AMR	Selenium Zinc	Prevention

AFR=African region; AMR=region of the Americas; EMR=Eastern Mediterranean region; EUR=European region; SEAR=South-East Asian region; WHO=World Health Organization; WPR=Western Pacific region.

TABLE 3 Main Characteristics of Included Systematic Reviews, Micronutrients and Area of Focus

Study No.	First Author, Year	Country	WHO Region	Mineral	Area of Focus
502	Hunter et al., 2022 ³⁹	Australia	WPR	Zinc	Prevention
511	James et al., 2021 ³⁵	United Kingdom	EUR	Iron Selenium Zinc	Prevention
522	Wang et al., 2021 ⁴⁰	Singapore	WPR	Calcium Iron Magnesium Selenium Zinc	Prevention
532	Vlieg-Boerstra et al., 2021 ³³	Netherlands	EUR	Iron Selenium Zinc	Prevention
542	Pechlivanidou et al., 2022 ³¹	Greece	EUR	Calcium Magnesium Phosphorus Selenium Zinc	Prevention
556	Fakhrolmobasheri et al., 2021 ³⁰	Iran	EMR	Selenium	Prevention
608	Jayawardena et al., 2020 ³⁸	Sri Lanka	SEAR	Selenium Zinc	Treatment
609	Feng et al., 2021 ¹⁰	China	WPR	Zinc	Treatment
624	Balboni et al., 2022 ³²	Italy	EUR	Selenium Zinc	Treatment
625	Abioye et al., 2021 ³⁶	USA	AMR	Zinc	Treatment
706	Beran et al., 2022 ³⁷	USA	AMR	Zinc	Treatment
756	Olczak-Pruc et al., 2022 ³⁴	Poland	EUR	Zinc	Treatment

AFR=African region; AMR=region of the Americas; EMR=Eastern Mediterranean region; EUR=European region; SEAR=South-East Asian region; WHO=World Health Organization; WPR=Western Pacific region.

COVID-19 and five on treatment.^{10,32,34,36-38} The included systematic reviews cited 72 primary publications in 106 unique instances across all reviews, representing a Corrected Cover Area (CCA) of 4.545% ($CCA = 108-72 / (72 \times 12) - 72 = 0.04545$), indicating a slight overlap (see Table S1 in the supplemental material).

Calcium

No narrative reviews discussed calcium, for either the prevention or treatment of COVID-19. Both systematic reviews that included calcium assessed the impact of micronutrient deficiencies on intensive care unit (ICU) admissions and risk of death.^{31,40} One systematic review of 33 papers comprised of interventional (randomized controlled trials) and observational (cohort studies, cross-sectional studies, and case-controlled studies) studies, with relevant comparator groups and a total of 360,346 participants, assessed the impact of deficient micronutrients on the prevention of respiratory infection and on ICU admissions and risk of death. The paper concluded that calcium deficiency was not associated with clinical severity.⁴⁰ The second systematic review, which included 31 papers with 8,624 adult participants (mean age 61), found that calcium was a prognostic factor for COVID-19 patients. Normocalcemia and higher calcium blood levels were associated with higher survival rates. Low calcium blood levels were identified as a prognostic marker for the development of severe disease, significantly correlated with low chest computed tomography (CT) scores and higher numbers of ICU admissions.³¹

Copper

The three narrative reviews on copper highlighted the lower plasma levels found in COVID-19 cases²⁷ and its antimicrobial,^{25,28} antiviral, antioxidant,^{25,27,28} and immune-modulating²⁸ properties. The metabolic contribution of copper as an antioxidant enzyme²⁷ was also discussed. The proposed role of copper in the prevention and treatment of COVID-19 was indicated as an antioxidant defense.^{25,27,28} No systematic reviews included results for copper.

Iron

One narrative review highlighted iron's antimicrobial and inflammatory modulating properties.²⁸ Djordjevic et al.²⁸ emphasized iron's metabolism as being important to COVID-19's pathogenesis due to its role as a prooxidant and its role in the induction of ferroptosis. Three systematic reviews reported on iron. James et al.³⁵ discussed the role of iron deficiency, anemia, and iron concentration in iron-dependent host cellular processes involved in viral replication, pulmonary response to hypoxic stress, and the role of iron in inflammation and immune impairment. One systematic review highlighted varied results of iron supplementation on the incidence of respiratory tract infection; two included studies showed an increased risk and five studies showed no significant effect.³³ Depending on what iron level biomarker was measured, both increased and decreased risk of mortality were reported.⁴⁰ Both Wang et al.⁴⁰ and Vlieg-Boerstra et al.³³ highlighted increased

ferritin levels in patients with more severe cases of COVID-19 versus in those with milder cases.

Magnesium

One narrative review on magnesium discussed its role in shaping the innate and adaptive immune systems and its immune-modulating and anti-inflammatory properties; low magnesium levels activate inflammation, sensitize sentinel cells to harmful agents, and activate phagocytes.²⁵ One systematic review reported that COVID-19 survivors had significantly higher serum levels of magnesium and other nutrients at hospital admission than those who did not survive.³¹ Another systematic review, which reviewed the effect of micronutrient supplementation or deficiency on novel coronavirus incidence and severity, did not find any significance to magnesium nutritional levels.⁴⁰

Phosphorus

None of the narrative reviews reported on phosphorus. The one systematic review concluded that COVID-19 survival was associated with high blood levels of nutrients which included phosphorus.³¹ Significantly low phosphorus blood levels were commonly detected in severe COVID-19 disease. Significantly more patients with low phosphorus were admitted to ICU versus patients with normal levels of phosphorus. Low phosphorus levels were significantly correlated with low chest CT scores.

Selenium

Six narrative reviews discussed significant findings for selenium in the prevention and treatment of COVID-19 and the positive implications of supplementation.^{23,25-29} Selenium is an important immune modulator,²⁵⁻²⁸ antioxidant²⁶⁻²⁸ and antiviral.^{27,28} Lower blood concentrations of selenium were reported in COVID-19-infected adults versus non-infected adults,^{25,26,29} and higher mortality rates were noted in selenium-deficient patients.^{23,27} Deficiency was reported to lead to increased risk of infection^{27,28} and virulence of SARS-CoV-2.^{27,28} Supplementation has been proposed to improve selenoprotein profile, alleviate viral-induced oxidative stress, organ decay, and cytokine storm, and hinder the mutation to virulent variants of SARS-CoV-2.^{27,29}

Four systematic reviews reported significant findings for selenium.^{30,31,38,40} Selenium's anti-inflammatory, immune-boosting, antiviral, and antithrombotic effects were reported.^{30,38} Selenium deficiency was associated with worse clinical outcomes,³⁰ increased mortality risk,^{30,31,40} and higher SARS-CoV-2 viral genome mutation rate,³⁰ and selenium levels in COVID-19 patients were lower than in healthy individuals.^{30,31} Studies reviewed by Jayawardena et al.³⁸ showed mixed results for selenium and other multivitamin and mineral supplementation on the incidence and severity of ARIs in well-nourished, healthy adults.³⁸ Randomized controlled trials showed beneficial and detrimental effects of selenium supplementation in healthy adults with suboptimal selenium concentrations on the immune response to the influenza vaccine.³⁸ Beneficial effects included a dose-dependent increase in interleukin (IL)-8, IL-10, T-cell proliferation, and selenoprotein S (SEPS1) gene expression. Detrimental effects included lower

granzyme B content of CD8 cells.³⁸ Long-term supplementation of selenium sulphide (100 ug) and zinc sulphate (20 mg) in institutionalized elderly participants reduced the incidence of respiratory tract infections and increased antibody titres in response to influenza vaccines.³⁸

Zinc

One narrative review which included zinc did not report any evidence-based properties associated with COVID-19.²³ The six remaining narrative reviews that discussed zinc mentioned the following potential benefits and properties: antioxidant,^{22,24,26,27} anti-inflammatory,^{22,24-27} immunomodulatory,^{22,24,26,27} and antiviral.^{22,24-28}

Several narrative reviews highlighted zinc's role in modulating inflammatory cytokines,^{24,26,27} its ability to interfere with viral entry into the host's cell,^{24,26,27} its ability to decrease viral replication and coronavirus RNA polymerase,^{24,26-28} and its effect on ACE-2 receptor activity.²⁶ Its ability to alleviate cytokine storms was discussed.²⁷ Zinc's ability to inhibit nuclear factor (NF)- κ B signaling, its involvement in the recruitment, enhancement, and promotion of the activity of neutrophils, CD4+, and CD8+ T cells, and its triggering of IL-2 receptor expression were also discussed.^{24,27} Deficiency was shown to enhance the production of proinflammatory cytokines (IL-1 β , IL-6, and tumour necrosis factor [TNF]- α) and negatively affected the modulation of natural killer cells.^{22,27} Deficiency was also shown to increase the incidence of acute respiratory infections and was linked to higher rates of complications, prolonged hospital stays, and increased mortality.^{22,23,28}

Zinc supplementation was reported to reduce the incidence of infection in children and the elderly.^{22,38} Zinc supplementation in adults, combined with nitazoxanide, ribavirin, and ivermectin, was shown to clear SARS-CoV-2 from the nasopharynx in a shorter time period than symptomatic treatment alone (phase I clinical trial).²⁶ It improved gustatory sensitivity (randomized clinical trial) and lowered the duration of anosmia/hyposmia (prospective clinical trial, 220 mg zinc sulfate equivalent to 50 mg elemental zinc twice daily) when compared with those who did not receive zinc supplementation or therapy.²⁶ Zinc treatment showed decreased rates of mortality (three retrospective cohort studies, one randomized controlled study), a lower incidence of ventilation usage and ICU stays (one retrospective cohort study), as well as decreased hospital stay durations (one retrospective cohort study) and symptom severity (one retrospective review study, one non-randomized controlled study).²²

Of the 11 systematic reviews that included zinc, five investigated the impact of zinc nutritional status on the risk of infection and rate of recovery.^{10,32,33,36,39} Zinc supplementation was investigated as a sublingual or intranasal spray, oral supplementation, and intravenous administration.³⁶

Key findings include a reduction of symptom severity score,^{39,40} lower COVID-19 in-hospital mortality,^{31,34,35} and increased frequency of being discharged home when zinc was combined with azithromycin and hydroxychloroquine.³⁵ Zinc deficiency was associated with higher IL-6, a greater number of complications,³¹ higher incidence,⁴⁰ and poorer outcomes.³¹ One review found that sublingual zinc did not prevent clinical colds,³⁹ and another

review found that zinc sulfate is likely to shorten the duration of olfactory dysfunction.¹⁰ One systematic review found zinc supplementation may be beneficial in children under five by promoting an increase in interferon-gamma (IFN- γ) and IL-2.³⁸⁻⁴⁰ Zinc, along with selenium and other nutraceuticals, vitamins, and probiotics, was shown to have an immune-enhancing effect important in preventing or treating viral infections.^{10,38} There were mixed results as Beran et al.³⁷ and Balboni et al.³² did not find any significant associations for zinc and the prevention and/or treatment of COVID-19.

DISCUSSION

As a part of the larger umbrella review on NHP research with respect to the COVID pandemic, this comprehensive review reports evidence on minerals such as calcium, iron, magnesium, phosphorus, selenium, and zinc. Our findings demonstrate that micronutrient status is an important modifiable risk factor in the prevention and/or treatment of COVID-19. Important factors highlighted include the detrimental effects of low serum levels of certain minerals on COVID-19 severity and disease outcomes as well as the possible benefits of supplementation.^{30,31,38,40}

The association between nutrition and infection is well documented.⁴² Minerals such as selenium and zinc, along with other nutraceuticals and probiotics, have shown immune-enhancing effects for either preventing or treating viral infections such as polio, HIV and hantavirus, and influenza-like illness,^{30,35,38} and may contribute to the prevention and treatment of COVID-19.^{5,8,30,35,38} Minerals' status has the potential to influence susceptibility to the risk of COVID-19 infection through its role in immune functioning, shaping the innate and adaptive immune systems.^{30,35,38} Copper, iron, magnesium, selenium, and zinc's immune-modulating properties are well established.^{22,24-28} These minerals play an integral role in sensitizing and activating sentinel cell tissue, such as resident macrophages or dendritic cells, and innate immune functions mediated by natural killer cells and neutrophils in response to viral threats.²⁵⁻⁴³

It is well established that micronutrient supplementation has the ability to lower the incidence of ARIs and lessen their duration and severity.⁸ Based on our findings, supplementation is recommended for COVID-19 patients with mineral deficiencies.^{30,31,38,40} Healthcare providers should recommend supplementation only in cases where low serum levels are suspected or have been confirmed. Infections such as COVID-19 may adversely influence mineral status, which should be a consideration when managing patients with no history of deficiency.⁴² Almost 20% of the global population is affected by zinc deficiency.³⁶ This is a consideration when interpreting results from Beran et al.,³⁷ Fakhrolmobasheri et al.,³⁰ Jayawardena et al.,³⁸ Pechlivanidou et al.,³¹ and Wang et al.,⁴⁰ as these reviews included studies carried out in regions where zinc deficiency is endemic. The same consideration should be applied to results obtained from studies conducted in regions where selenium and iron deficiencies exist. No benefit of supplementation in COVID-19 patients with non-deficiency was found, and therefore supplementation in this population is not recommended.³¹ Patient education should include avoiding high doses of minerals, as they

can be toxic.⁴⁴ For example, excess amounts of selenium at doses above 0.9 mg/day may lead to hair loss, fatigue, gastrointestinal disorders, peripheral neuropathies, and increasing risk for type 2 diabetes.³⁰⁻⁴⁴ Magnesium doses in excess of 400 mg/day can cause diarrhea, and iron can cause constipation, nausea, and vomiting and reduce zinc uptake. Zinc toxicity can result in nausea and vomiting and immunosuppression, which would increase susceptibility to COVID-19 infection.⁴⁴

This umbrella review has shown that minerals have antiviral properties (copper, selenium, zinc) and antimicrobial properties (copper, iron). Selenium was shown to hinder mutation of SARS-CoV-2 to more virulent variants.^{27,28,30} These outcomes are in line with other research that indicates that nutritional status affects viral mutation and increased virulence as in the case of severe acute respiratory syndrome (SARS), acquired immune deficiency syndrome (AIDS),⁴⁵ swine-fever, dengue virus, influenza virus, and norovirus, among others.⁴⁶ Once viral mutations occur, patients with normal nutritional status become vulnerable to newly virulent viruses.⁴⁵ The public health implications are increased rates of the infection ($R_0 > 1$), higher patient loads and hospital admissions, as well as a threat to vaccine effectiveness, since mutations could give rise to vaccine-resistant strains over time.⁴⁷ Our understanding as healthcare practitioners of the underlying mechanisms and potential interventions for the SARS-CoV-2 virus are continuing to evolve. Novel therapies for the prevention and treatment of COVID-19 will continue to emerge. We recommend future studies include as-yet unstudied minerals for their potential use in the COVID pandemic.

High-risk populations associated with impaired immunity, such as the aged, immunocompromised, those with chronic disease, and those with nutritional deficiencies, are at a higher risk for COVID-19 infection and may have more severe disease outcomes.^{6,7,48,49} This is supported by previous research showing positive outcomes for mineral supplementation in obese patients, resulting in improved immune functioning.⁴⁹ This umbrella review found that normal blood level ranges of calcium, magnesium, selenium, and zinc were associated with reduced disease severity and improved survival.^{22,31} Ventilation use and ICU stays were also reduced,²² as was number of days spent in hospital.^{22,23,28} COVID-19-related hospitalizations place a tremendous burden on public health-care systems,⁵⁰ and hospitalization can have negative psychological and socio-economic effects on patients.^{51,52} Many patients are only partially insured or have no medical insurance which covers hospitalization or costs associated with COVID-19.⁵³ Hence interventions which reduce the severity of COVID-19 have a wider reaching societal impact than just preventing and or treating the illness itself.

The majority of viruses do not cause severe disease or severe inflammation in humans.⁵⁴ But we know that inflammation is a key feature of COVID-19.⁵⁵ Severe to critical illness in COVID-19 patients is linked to an excessive systemic inflammatory response that may result in lung damage, respiratory failure, the development of acute respiratory distress, and organ damage.²² Long COVID symptoms are linked to inflammation, and more than half of patients affected by long COVID exhibit persistent

inflammatory protein signatures (TNF, IL-6, IFN- γ).⁵⁶ This has an impact on the global burden of disease, as chronic inflammation and unchecked oxidation are etiological factors in the development of non-COVID-19-related diseases.⁵⁷ The use of minerals as an effective treatment approach to control COVID-19-induced inflammation and oxidation is supported by the findings of this umbrella review. There were significant findings to support zinc and selenium's anti-inflammatory and antioxidant properties, and further research is warranted to establish recommendations for standardized interventions for their use as stand-alone and/or adjuvant therapies in clinical settings. Zinc sulphate has also been found to improve sleep duration, efficiency, and latency. Approximately 74.8% of people with COVID-19 have sleep-related problems. It is thought that underlying inflammation is the cause of COVID-19-related sleep disturbances. Zinc could be useful in treating sleep disturbance related to acute COVID-19 infection as well as persistent sleep disturbances associated with long COVID cases or post-COVID syndrome.⁵⁸ Easily accessible mineral supplementation can be used as prevention therapy, especially in cases of deficiency, or as complementary self-treatment in mild cases of COVID-19.^{11,12}

Addressing nutritional deficiencies could be a cost-effective, low-risk strategy in the prevention and management of infectious disease.^{42,59,60} The primary preventive strategy for COVID-19 is the global vaccine program and its success relies on individuals' ability to mount an appropriate vaccine response.⁵⁹ In vulnerable populations who are prioritized to receive vaccines, such as the elderly or those with comorbidities, deficiency is common. Micronutrient deficiencies may affect vaccine responses. Selenium supplementation was shown to improve the vaccine response to a live, attenuated polio vaccine in healthy adults from the United Kingdom who were marginally selenium deficient. This was coupled with a lowered incidence of genetic mutation in recovered excreted polio viruses.⁶¹ Anemia and iron deficiency were associated with reduced antibody responses to diphtheria, pneumococcal, and pertussis vaccinations, and a multi-nutrient supplementation containing iron improved the immune response to measles vaccinations in Kenyan infants when compared with the use of multi-nutrient iron-free powder.⁵⁹ Acute viral infection leads to functional iron deficiency and anemia of inflammation, and approximately 80% of hospitalized patients in Austria were functionally anemic at admission.³⁵ Calcium deficiency was associated with more severe COVID-19 disease progression.³¹ Hence COVID-19 patients should be screened for deficiencies, which should be addressed to potentiate improved clinical outcomes. Prophylactic screening should be considered for at-risk populations. In 2020, the global dietary supplement market, which includes NHPs, had a market value of approximately US\$220.3 billion. There is a need for high-quality research to produce clear, consolidated guidelines on the use of minerals as adjuvant therapy in clinical settings or over-the-counter treatments for the prevention and treatment of COVID-19 for widespread dissemination among healthcare practitioners and the general public.¹⁰

This study had limitations. No raw data was analyzed as this was beyond the scope of this review. Results were often based on

highly heterogeneous effect sizes and therefore yielded conflicting outcomes.³⁸ There was a lack of information on therapeutic dosing, and when available, these differed vastly between studies.^{31,38} Many of the narrative reviews referred to the same pool of studies, which is to be expected until the body of research expands over time. Many preclinical studies, animal-based models and *in vitro* studies were included.³⁸ It is difficult to infer recommendations for human use from such studies. Safety and efficiency in humans also remain inconclusive.³⁸ Mixed associations with outcomes could be attributed to the use of different biomarkers.⁴⁰ Confounding variables were not addressed by this review. Many of the study participants included in the reviews were elderly. Malnutrition and mineral deficiencies (zinc and selenium), which are common in the elderly,⁶² and increasing age as an independent variable,⁶³ may result in impaired immune functioning, which is associated with increased morbidity and mortality in COVID-19. The prevalence of malnutrition and mineral deficiencies in people receiving long-term care or in hospitalized patients is well established.⁶⁰ Wang et al.⁴⁰ and Pechlivanidou et al.³¹ identified and recruited participants from hospitals, clinics, and patient registries. The significant outcomes in these reviews were ICU admissions and the risk of death, both of which could have been confounded by pre-existing mineral deficiencies.

A strength of this study is that a team of reviewers conducted all of the tasks, reducing the risk of errors and inconsistencies. Another strength of this study is that a Corrected Cover Overlap was calculated for the systematic reviews, ensuring significant results were not overstated.⁶⁴ Almost all of the studies included in our review had a low risk of bias based on quality assessment. Evidence drawn from peer-reviewed publications employing study designs that include comparison to adequate control groups, such as randomized controlled trial designs, are increasingly called for by critics of complementary approaches to health care and from those who hope to enable evidence implementation.⁶⁵⁻⁶⁸ It is our hope that this review of minerals in the context of NHP use for the prevention and treatment of COVID-19 will enable evidence implementation in clinical practice.

CONCLUSION

Reducing mineral deficiencies for the prevention of COVID-19 should be viewed as a public health priority. Supplementation of certain minerals, such as selenium, iron, and zinc, in those with clinical deficiencies could lead to improved COVID-19 outcomes. Further research should be undertaken on these minerals to ascertain efficacy, safety, and the optimum dose ranges for therapeutic effect with the least potential for side effects, ideally in randomized trials among COVID-19 patients.³⁶

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CONFLICTS OF INTEREST DISCLOSURE

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SUPPLEMENTAL MATERIAL

Supplemental material linked to the online version of the paper at <https://doi.org/10.54434/candj.164>:

- Table S1

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APPENDIX 1: GLOSSARY OF TERMS

AIDS	acquired immune deficiency syndrome
AMA	American Medical Association
AMSTAR	a measurement tool to assess systematic reviews
ARI	acute respiratory infection
CCA	Corrected Cover Area
COVID	coronavirus disease
CT	computed tomography
ICU	intensive care unit
IL	interleukin
IFN- γ	interferon-gamma
NHP	natural health product
SANRA	scale for the assessment of narrative review articles
SARS-CoV-2	severe acute respiratory syndrome of the coronavirus-2
SEPS1	selenoprotein S
TNF	tumour necrosis factor
WHO	World Health Organization

Vitamins for the Prevention and/or Treatment of COVID-19: An Umbrella Review



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ABSTRACT

Objective: This umbrella review synthesizes the existing literature on the role of vitamins for COVID-19 prevention and management. The objective is to elucidate potential preventive and therapeutic dimensions of these vitamins, highlight clinical applicability, and identify avenues for future research.

Methods: A systematic search was conducted using PubMed and Google Scholar, with predefined key words for each vitamin combined with COVID-19-related terms. Narrative and systematic reviews were included, following Cochrane guidelines. AMSTAR scoring was used to assess systematic review quality, while SANRA guidelines were used to evaluate narrative reviews. Data extraction, synthesis, and reference overlap were conducted.

Findings: Narrative reviews ($n=14$) revealed preclinical benefits of vitamins A, B group, C, D, and E (no research on vitamin K found) in COVID-19 management, with potential for immune modulation and anti-inflammatory responses. Of the systematic reviews ($n=44$), none included vitamins A or E. Some B vitamins exhibited potential, with significant associations between vitamin C supplementation and reduced COVID-19 severity. Many significant findings were also found between vitamin D deficiency and heightened COVID-19 risks, as well as promising effects of vitamin D supplementation.

Conclusion: Vitamins A, B group, C, D, and E hold mechanistic rationale for combating COVID-19, as suggested by narrative reviews. In systematic reviews, vitamin D deficiency underscores its role in COVID-19 severity, while vitamin C and D supplementation show potential benefits as adjunct therapies. This umbrella review highlights the comprehensive research on the efficacy of vitamins in addressing COVID-19, with challenges that warrant further investigation.

Key Words Umbrella review, naturopathic medicine, complementary and alternative medicine, SARS-CoV-2, nutrients

INTRODUCTION

Coronavirus disease (COVID-19; see Appendix 1 for a glossary of terms and acronyms used in this manuscript), instigated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, ushered in a global crisis. The World Health Organization's (WHO's) proclamation of COVID-19 as a public health emergency of international concern in January 2020, swiftly followed by its characterization as a pandemic in March 2020, underscored the gravity of the situation.¹ With almost 700,000,000 cases and close to 7,000,000 fatalities reported worldwide within 2 years,² COVID-19's impact on global health is profound. Its symptoms encompass fever, cough, fatigue, headache, diarrhea, arthromyalgias, and serious interstitial pneumonia, among others, which can culminate in acute respiratory distress syndrome, sepsis-induced coagulopathy, and multi-organ dysfunction.³ The disease's progression incites a cytokine storm,⁴⁻⁶ marked by an overproduction of pro-inflammatory cytokines, further contributing to its complexity.⁷⁻⁹

Due to the severity of the pandemic, various nutrients and natural therapies were investigated to determine their potential benefits in preventing and treating COVID-19 as part of naturopathic treatment. Among these, vitamins are essential micronutrients with wide accessibility, safety, and affordability that garnered special focus. Vitamin supplementation is known for offering a feasible avenue for bolstering immune responses,¹⁰ particularly for vulnerable populations. The safety of vitamins is well established, with low instances of adverse effects when consumed within recommended limits.¹¹ These factors collectively contribute to the potential of vitamins as a holistic approach to addressing the challenges posed by COVID-19. Despite this, controversy and misinformation about natural treatments, including vitamins, were widely discussed in the early days of the pandemic.¹²⁻¹⁴

Prior to the pandemic, the significance of vitamins was already established through their physiological roles in immune and overall health. Vitamin A bolsters interferon-based defenses against RNA viruses, impeding viral replication, and thus maintains immune

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homeostasis and boosts innate responses.¹⁵⁻¹⁷ Vitamin B, integral to cellular function, energy metabolism, and immune activation, has potential to fortify immune competence.^{18,19} Vitamin C contributes to chemotaxis, phagocytosis, and tissue repair. Vitamin D's functions in immune regulation²⁰⁻²³ have been associated with decreased risk of acute respiratory tract infections. Lastly, Vitamin E's antioxidants potentially heighten adaptive immunity against viruses.^{24,25} Such mechanisms of action were also shown to be beneficial in a number of rapid reviews specifically for COVID-19.²⁶ The previously published interim report²⁷ (see the methods section) on various naturopathic interventions in the prevention and treatment of COVID-19 did not find narrative and systematic reviews using vitamin K as an intervention, and therefore it was not included in this review.

Considering the controversy and misinformation about the potential role vitamins can play in preventing and treating COVID-19, the objective of this umbrella review is to compile synthesized literature on the role of vitamins vis-a-vis COVID-19, thus elucidating the state of evidence on preventive and therapeutic dimensions and clinical applicability. Peer-reviewed insights are distilled, informing the feasibility of naturopathic treatments. We aim to pinpoint avenues for future research and clinical application, enriching the arsenal against COVID-19.

METHODS

Design

This study commenced as a continuous, high-level monitoring effort involving systematic reviews on natural health products (NHPs) and natural treatments for COVID-19 prevention and management, including post-COVID conditions. To capture new significant evidence in this emerging domain, monthly searches were conducted for over a year, starting in May 2022. Results were published in an interim report.²⁷ Adhering to Cochrane Guidelines,²⁸ monthly meetings ensured refinement of research design, search terms, and inclusion/exclusion criteria, following the principles of living systematic reviews.

Upon completion of the data collection process as fully outlined in the interim report,²⁷ the methodology transitioned into an umbrella review design.^{29,30} An umbrella review methodically synthesizes evidence from multiple systematic reviews, permitting a comprehensive evaluation of the available evidence's quality and consistency across different interventions.

Search Strategy

Following the Cochrane guidelines for a living systematic review, PubMed and Google Scholar databases were searched using keywords "natur*", "nutraceutical," "prevention," "prophylaxis," "COVID," "Coronavirus," "SARS-CoV-2," combined with vitamin-specific terms for each of the vitamins:

Vitamin A: Vitamin A, retinol, retinoid, carotene, alpha carotene, beta carotene, carotenoid

Vitamin B group: Vitamin B1, thiamine, vitamin b2, riboflavin, vitamin b3, niacin, vitamin B5, pantothenic acid, vitamin b6,

pyridoxine, vitamin b7, biotin, vitamin b9, folate, folic acid, vitamin b12, cobalamin

Vitamin C: Vitamin C, ascorbic acid, ascorbate

Vitamin D: Vitamin D, cholecalciferol, hydroxycalciferol

Vitamin E: Vitamin E, tocopherol

Vitamin K: Vitamin K, vitamin K1, phylloquinone, phytonadione, vitamin K2, menaquinone, vitamin K3, menaphthone, menadione

Inclusion and Exclusion Criteria

Encompassing reviews without language restrictions, the study targeted structured database searches, transparent methodological criteria, and cumulative outcome conclusions. Additionally, relevant narrative reviews were collected if their reporting was similar to a systematic review with only some missing criteria for inclusion.

PICO eligibility criteria requirements for study inclusion were as follows:

Population: Clinical/observational (humans of any age/gender, any setting), in vivo (including animals), in vitro, or in silico studies.

Intervention: Vitamins A, B group, C, D, E and K.

Comparison: No comparator limitation.

Outcome: Symptoms, biological markers, diagnostic criteria, or viral traits related to severe acute respiratory syndrome, viral respiratory tract infections, or COVID-19.

Secondary analyses, literature reviews, editorial discussions, best practice guidelines, book chapters, and publications referring to COVID but using data prior to 2019 were excluded.

Data Mining

To truly address the objective of highlighting the preventive and therapeutic roles of vitamins with their clinical applicability, narrative reviews were included to extract therapeutic considerations and medicinal properties of vitamins, their relationship to other natural health products or pathways, and doses used. However, narrative reviews were excluded if they did not actually review studies directly related to COVID-19, but only hypothesized therapeutic applications.

Systematic reviews and meta-analyses were examined for the types of interventions and populations included, outcome measures and statistically significant results as well as their clinical relevance. Systematic reviews that did not examine studies on COVID-19 but other similar respiratory conditions or viral infections were excluded.

Data extraction and summarization of systematic and narrative reviews were conducted by eight trained independent volunteers

(doctors/researchers in naturopathic medicine), following specified data mining criteria. Only statistically significant results with outcomes relevant to NHPs and COVID-19 prevention and management were included. Finally, a reference overlap analysis was conducted to identify common citations across systematic and narrative reviews.

Data Analysis

Narrative reviews were assessed by two independent reviewers based on the Scale for the Assessment of Narrative Review Articles (SANRA). Individuals providing data extraction were blind to the quality assessment criteria for inclusion / exclusion. Reviews were excluded if they did not have a scientific reasoning score of 1 or 2 AND an overall total sum >5.

Systematic reviews were assessed for risk of bias and quality grading using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) and were reviewed by two individuals for accuracy.

Discrepancies were addressed by a third reviewer. Volunteers were blind to the quality assessment criteria for inclusion/exclusion. Reviews were excluded if they did not get full marks in question 9 and question 13.

Microsoft Excel was used to collate the data using a pre-tested, revised template tailored to the two review types.

RESULTS

Study Selection

Figure 1 shows the study selection and screening results.

Narrative Reviews

Narrative reviews were included in this project to provide a broader perspective and complement the systematic reviews, facilitating a comprehensive exploration of the landscape of vitamins for COVID-19 prevention and management.

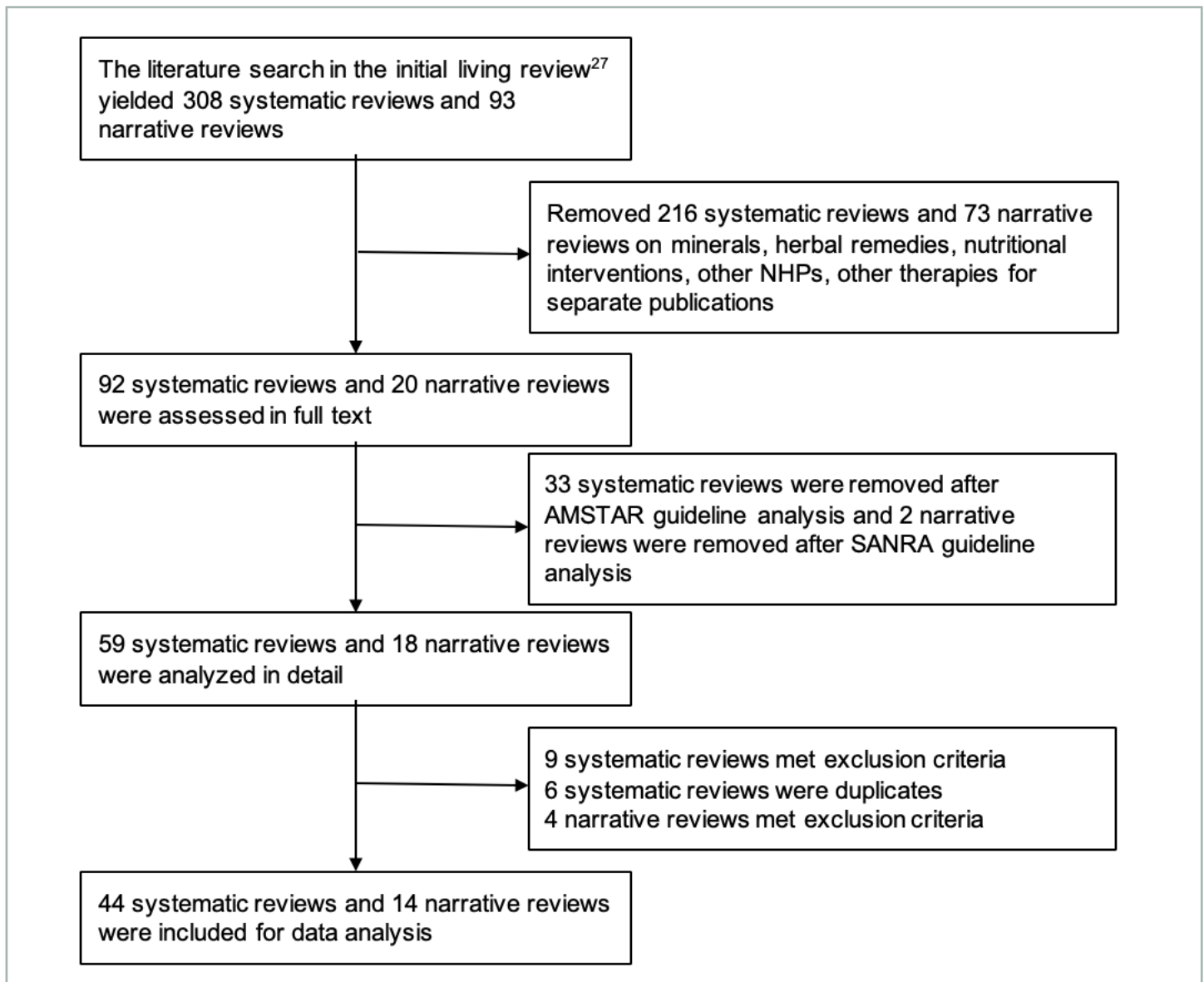


FIGURE 1 Study Selection and Screening against Inclusion/Exclusion

Of the 20 narrative reviews initially included, 18 (90%) remained for data extraction, and 14 (70%) remained for the final umbrella review after removing all reviews that met exclusion criteria (see Table 1).³¹⁻⁴⁴ Based on WHO regions of the country of residence of the first author, four of these reviews were from the Americas (AMR), four were from the European region (EUR), and two each were from the Eastern Mediterranean Region (EMR), the Western Pacific region (WPR) and South-East Asian region (SEA). With regard to the narrative reviews on vitamins, six were on vitamin A, four on the group of B vitamins, eight on vitamin C, 12 on vitamin D and four on vitamin E. As previously mentioned, vitamin K did not have relevant narrative reviews for this study. Considering most narrative reviews covered multiple NHPs, the total number of papers on vitamins ($n=34$) exceeds the number of papers reviewed ($n=14$).

Systematic Reviews

Of the 92 systematic reviews initially included, 59 (64%) remained for data extraction after the AMSTAR analysis. Of those, 44 (48%) were included in the umbrella review after removing all that met

TABLE 1 Narrative Reviews Included in the Umbrella Review

Narrative Review	Country	Region	SANRA Score	Vitamins
Base Medicine Task Force (2020) ³¹	USA	AMR	11	Vitamin C Vitamin E
Pisoschi et al. (2022) ³²	Romania	EMR	6	Vitamin A Vitamin D
Ahvanooei et al. (2022) ³³	Iran	EMR	8	Vitamin A Vitamin B Vitamin C Vitamin D Vitamin E
Michael et al. (2022) ³⁴	USA	AMR	10.5	Vitamin D
Paudel et al. (2022) ³⁵	Australia	WPR	7	Vitamin C Vitamin D
Djordjevic et al. (2022) ³⁶	Serbia	EUR	9.5	Vitamin A Vitamin B Vitamin C Vitamin D
Bahat et al. (2021) ³⁷	Turkey	EUR	8	Vitamin D
Inchingolo et al. (2021) ³⁸	Italy	EUR	7	Vitamin D
Bell et al. (2023) ³⁹	USA	AMR	7	Vitamin A Vitamin C Vitamin D Vitamin E
Stafford et al. (2023) ⁴⁰	USA	AMR	6	Vitamin D
Park et al. (2023) ⁴¹	Korea	SEA	10	Vitamin A Vitamin B Vitamin C Vitamin D Vitamin E
Huang et al. (2023) ⁴²	Singapore	WPR	12	Vitamin B Vitamin C
Chatterjee et al. (2022) ⁴³	India	SEA	8	Vitamin A Vitamin C Vitamin D
Del Giudice et al. (2022) ⁴⁴	Italy	EUR	7	Vitamin D

AMR = region of the Americas; EMR = Eastern Mediterranean region; EU = European region; SANRA = Scale for the Assessment of Narrative Review Articles; SEA = South-East Asian region; WPR = Western Pacific region.

exclusion criteria and duplicates (see Table 2).⁴⁵⁻⁸⁸ Based on WHO regions, 17 of the systematic reviews were from the European region (EUR), eight were from the South-East Asian region (SEA), seven were from the region of the Americas (AMR), eight were from the Western Pacific region (WPR), three were from the Emirates (EM) and one was from the African continent (AFR). There were no eligible systematic reviews on vitamin A, vitamin E, or vitamin K. Three systematic reviews were included for the group of B vitamins, 11 for vitamin C, and 33 for vitamin D. Due to systematic reviews covering multiple vitamins, the total number of papers on vitamins ($n=47$) exceeds the number of papers reviewed ($n=44$).

Vitamin A

Of the six narrative reviews that mentioned vitamin A, only two discussed its potential benefits and properties.^{33,36} These reviews referred to vitamin A's pulmonary, immunomodulatory, antimicrobial, and anti-inflammatory effects. This is mainly as a result of proliferating T lymphocytes by increasing interleukin-2 (IL-2). One narrative review focused more on carotenoids, with specific reference to their antioxidant, anti-inflammatory, and immunomodulatory potential.³²

Since none of the systematic reviews on vitamin A specifically addressed its direct effects on COVID-19, no conclusions can be drawn.

Vitamin B

Three of the narrative reviews examined the effects of B vitamins in relationship to COVID-19. Discussing the role of B vitamins in regulating cell function, energy metabolism, and immune functions, B12 was highlighted for its benefits to patients requiring oxygen support (when combined with other interventions),³⁶ and B9 (folate) for its antiviral ability to inhibit furin protease and inactivate 3C-like protease.⁴¹

One systematic review that included vitamin B in its search found a single case-control study on 200 participants who may have had more severe symptoms due to vitamin B6 or B9 deficiency ($\leq 5 \mu\text{g/L}$ and $\leq 4 \mu\text{g/L}$, respectively).⁵⁴ Another review on the prognostic role of micronutrients included only one retrospective study on B12 with no clinically helpful results.⁶¹ A third systematic review looked at any pharmaceutical and complementary intervention on the psychological wellbeing of people with long COVID, finding one study on 100 participants receiving a daily dose of 2000 mg nicotinamide mononucleotide (vitamin B3) for 22 weeks, but this study is ongoing.⁸⁸

All other B vitamins do not have adequate research to draw any conclusions regarding their potential benefits for COVID prevention, its treatment, or on long-COVID management. The group of B vitamins, therefore, do not have sufficient evidence to support their supplementation in COVID-19 cases. However, ensuring nutritional adequacy may theoretically prevent disease severity.

Vitamin C

Of the eight narrative reviews that covered the effects of vitamin C in relation to COVID-19, four discussed its antioxidant potential,^{31,33,35,42} six reviewed its anti-inflammatory

TABLE 2 (Part 1 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Liu et al. (2021) ⁴⁵	China	Observational studies	Newcastle-Ottawa scale I^2 : 64.9%–93.6%	Vit D: serum levels	Incidence	10 (376,596)	Age range: > 50 years Male: 25.2%–54.3% (not reported = 2)	Increased risk of COVID-19 associated with vitamin D deficiency or sufficiency (OR=1.43, 95% CI 1.00–2.05); Average vitamin D level was lower in COVID-19-positive patients (serum 25(OH)D: -0.37, 95% CI -0.52 to -0.21); nmol/L: -7.90, 95% CI -13.41 to -2.38)
Pereira et al. (2022) ⁴⁶	Brazil	Observational studies	Research Triangle Institute Item Bank (RTI – Item Bank) I^2 : 35.7%	Vit D: serum levels	Symptom severity, LOS, mortality	27 (372,332)	Mean age: 35.58 years (not reported = 1) Female: 26%–65% (not reported = 1)	Severe cases of COVID-19 present more with vitamin D deficiency than mild cases 65% (OR=1.65, 95% CI 1.30–2.09). Vitamin D insufficiency below 75 nmol/L increased hospitalization (OR=1.81, 95% CI 1.41–2.21) and mortality from COVID-19 (OR=1.82, 95% CI 1.06–2.58).
Bassatne et al. (2021) ⁴⁷	Lebanon	Observational studies and RCTs	Newcastle-Ottawa scale I^2 : 94%	Vit D: 357 IU/day to 60,000 IU/day, from one week to 12 months	Mortality	34 (19,080)	Age range: 42–81 years Female: 20%–67% (not reported = 2)	Mean serum 25(OH)D levels were 5.9 ng/mL significantly lower in COVID-19 positive, compared with negative patients (MD=-5.9, 95% CI -9.5 to -2.3)
Munshi et al. (2020) ⁴⁸	USA	Observational studies	Not reported	Vit D: serum levels	Disease severity, ICU admission, mortality	6 (1,368)	Mean age: 63.8 years Male: 58.6%	Patients with poor prognosis (N=150) had an adjusted standardized mean difference of -0.58 (95% CI -0.83 to -0.34, $p < .001$) serum 25(OH)D levels compared with those with good prognosis (N=161); Larger differences between ICU and floor admission (SMD=-0.84, 95% CI 1.32 to -0.36, $p = .001$); Larger differences by severity (SMD=-0.50, 95% CI -0.78 to -0.22, $p < .001$)
Teshome et al. (2021) ⁴⁹	Ethiopia	Observational studies	JBI, GRADE I^2 : 79.1%	Vit D: serum levels	Incidence	14 (91,120)	Not reported	Serum 25(OH)D deficiency was associated with an 80% increased risk of COVID-19 infection (OR=1.80, 95% CI 1.72–1.88)
Szarpak et al. (2021) ⁵⁰	Poland	Observational studies	Cochrane RoB 2 tool I^2 : 99%	Vit D: serum levels	Incidence	13 (14,485)	Mean age: 70.3 years Male: 58.6%	Mean serum 25(OH)D levels were 17.7 ± 6.9 ng/mL in COVID-19 negative patients, compared with positive patients 14.1 ± 8.2 ng/mL (MD=3.93; 95% CI 2.84–5.02; $p < 0.001$)
Kiyumi et al. (2021) ⁵¹	Oman	Observational studies	NOS I^2 : 67%	Vit D: serum levels	Incidence, disease severity, mortality	43 (254,963)	Age range: > 35 years Sex not reported	Higher prevalence of vitamin D deficiency and insufficiency in COVID-19 positive patients (59.0% and 40.1%, respectively) A significant association between 25(OH)D and symptom severity (OR=3.38, 95% CI 1.94–5.87, $p < .0001$) and mortality (OR=2.30, 95% CI 1.47–3.59, $p < .00001$)
Dramé et al. (2021) ⁵²	France	Observational studies	NOS I^2 : Not reported	Vit D: serum levels	Symptom severity, mortality, oxygen therapy, IMV	11 (1,008)	Age range: > 60 years Female: 29.6%–77.3%	Those without vitamin D deficiency had better primary clinical outcomes (death rate, the severity of the disease, oxygen therapy requirement, ICU support). Serum vitamin D level was also higher in COVID-19-negative patients.

TABLE 2 (Part 2 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Crafa et al. (2021) ⁵³	Spain	Observational studies	PRISMA I^2 : 84–98%	Vit D: serum levels	Incidence, disease severity, mortality	30 (380,172)	Mean age: 35.2–83.4 years Male: 38.7%–100% (not reported = 2)	Serum levels of 25(OH)D were significantly lower in COVID-19-positive patients (MD -3.99 (-5.34, -2.64); $p < .00001$; $I^2 = 95\%$) Serum level of 25(OH)D was lower in patients with severe disease (MD -6.88 (-9.74, 4.03); $p < .00001$; $I^2 = 98\%$) and in those who died (MD -8.01 (-12.50, -3.51); $p = .0005$; $I^2 = 86\%$) Patients with Vitamin D deficiency had an increased risk of developing severe disease [OR=4.58 (2.24, 9.35); $p < .0001$; $I^2 = 84\%$].
Wang et al. (2021) ⁵⁴	Singapore	Observational studies	NHLBI, RoB 2 I^2 : 84.9%	Vit B: serum levels; Vit D: serum levels	Incidence, disease severity, mortality, ICU admission, progression to respiratory-related complications	33 Tot: 360346 Vit B: 50 Vit C: 0 Vit D: 557,048	Mean age: 32–87.7 years Male: 22.7%–71.4% (not reported = 2)	The absence of micronutrient deficiency reduced COVID-19 incidence (pooled OR=0.37, 95% CI 0.18–0.78).
Chiodini et al. (2021) ⁵⁵	Italy	Observational studies	NOS, Funnel plot, Egger's test I^2 : 0–89.6%	Vit D: serum levels	Mortality, hospital admission, LOS, ICU admission	17 (2,756)	Age range: >42 years Female: 28.6%–63% (not reported = 1)	Low level of 25(OH)D is associated with COVID-19 mortality (OR=2.47, 95% CI 1.50–4.05; $I^2 = 30.5\%$), higher rates of hospital admissions (OR=2.18, 95% CI 1.48–3.21; $I^2 = 0\%$) and longer hospital stays (0.52 days; 95% CI 0.25–0.80; $I^2 = 89.6\%$)
Dissanayake et al. (2021) ⁵⁶	Sri Lanka	Observational studies	NOS I^2 : 73–92%	Vit D: serum levels	Incidence, disease severity, mortality	76 (1,976,099)	Age range: >32 years Male: 23%–80.2% (not reported = 8)	Vitamin D deficiency increased the odds of developing COVID-19 (OR=1.46; 95% CI 1.28–1.65; $p < .0001$; $I^2 = 92\%$), severe disease (OR=1.90; 95% CI 1.52–2.38; $p < .0001$; $I^2 = 81\%$), and death (OR=2.07; 95% CI 1.28–3.35; $p = .003$; $I^2 = 73\%$) Lower 25(OH)D levels in COVID-19-positive patients (MD=-3.85 ng/mL; 95% CI -5.44 to -2.26; $p \leq .0001$), and in patients with severe COVID-19 symptoms (MD=-4.84 ng/mL; 95% CI -7.32 to -2.35; $p = .0001$) and in non-survivors (MD= -4.80 ng/mL; 95% CI -7.89 to -1.71; $p = .002$)
Ebrahimzadeh et al. (2021) ⁵⁷	Iran	Observational studies	NOS I^2 : 0–80.6%	Vit D: serum levels	In hospital mortality	13 (2,208)	Age range: 34–102 years Male: 44.4%–67%	There was a significant positive relationship between vitamin D deficiency and risk of COVID-19 in-hospital mortality (OR=2.11; 95% CI 1.03–4.32).
Tentolouris et al. (2022) ⁵⁸	Greece	Observational studies and RCTs	RoB 2 I^2 : Not reported	Vit D: 1000 IU up to 14 days to 400,000 IU orally one time	Mortality, ICU admission	10 (2,078)	Mean age: 53.1–88 years (not reported = 4) Sex not reported	There was a beneficial role of vitamin D supplementation on ICU admission (OR=0.326; 95% CI 0.149–0.712; $p = .005$).
Shah et al. (2022) ⁵⁹	India	Systematic reviews	AMSTAR, GRADE, Egger's test, Begg's test, Mazumdar's test, Funnel plot I^2 : Not reported	Vit D: 400 IU to 400,000 IU	Mortality, ICU admission, LOS, IMV	10 (548,458)	Not reported	Vitamin D supplementation reduced the risk of mortality (OR=0.48, 95% CI 0.346–0.664; $p < .001$); Reduced ICU admission (OR=0.35; 95% CI 0.28–0.44; $p < .001$); Reduced mechanical ventilation (OR=0.54; 95% CI 0.411–0.708; $p < .001$)

TABLE 2 (Part 3 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Bignardi et al. (2022) ⁶⁰	Italy	Observational studies and RCTs	NOS, RoB 2 I^2 : 0%	Not reported (mixed serum levels and supplementation)	Mortality, hospitalization, ICU admission, IMV	17 (3,108)	Age range: 35–88 years Sex not reported	Low 25(OH)D levels associated with mortality (RR=1.42, 95% CI 1.14–1.71, I^2 =0.0%), need for ICU admission (RR=1.76, 95% CI 1.03–2.49, I^2 =0.0%), and need for ventilation (RR=3.58, 95% CI 1.45–5.70, I^2 =0.0%).
Pechlivanidou et al. (2022) ⁶¹	Greece	Observational studies and interventions	Risk of bias tools not reported I^2 : Not reported	Wide range of studies with mixed serum levels and supplementation	Mortality, survival	31 Vit B: 1 Vit C: 2 Vit D: 13 Vit E: 1 Tot: 8,624 Vit B: 310 Vit C: 212 Vit D: 2,334 Vit E: 110	Mean age: 52–70 years Female: 20%–59%	Supports the therapeutic use of vitamin D, insufficient data on other micronutrients to draw conclusions.
Dadras et al. (2022) ⁶²	Thailand	Observational studies and RCTs	NOS I^2 : Not reported	Vit D: serum levels	Disease severity, disease duration, mortality	35 (unclear how many on vitamin D) Total population not reported	Age range: 60–93 years Sex not reported	Deficiency in 25(OH)D predicted a poorer prognosis and mortality in the elderly and is associated with more severe lung involvement and longer disease duration.
Migliorini et al. (2022) ⁶³	Germany	Observational studies and RCTs	NOS, Jadad I^2 : Not reported	Not reported	Incidence, disease severity, disease progression	23 Tot: 3,443 Vit C: 1,488 Vit D: 3,443	Mean age: 45–74 years Male: 50%–52%	Supports the use of Vitamin C or Vitamin D supplementation.
Mishra et al. (2022) ⁶⁴	India	Observational studies	PRISMA, NIH, NHLBI, Funnel plot, Egger's test I^2 : 94.2%	Vit D: serum levels	Comorbidities with COVID-19 infection	16 (386,631)	Age range: 2–82 years Female: 53.16%	Lower serum 25(OH)D levels in COVID-19-positive patients (MD=-1.70; 95% CI -2.74 to -0.66; p =.001) with a 95% prediction interval of -5.85 to 2.45.
Mazaheri-Tehrani et al. (2022) ⁶⁵	Iran	Observational studies	Egger's test I^2 : 93.07%	Vit D: serum levels	Incidence, disease severity	7 (1,799)	Mean age: 27–32 years Female: 100% (pregnant)	No significant difference in serum vitamin D levels between COVID-19 cases and healthy controls (WMD=-2.55, 95% CI -6.85 to -1.74). Serum vitamin D levels are significantly lower in severe cases (WMD=-2.71, 95% CI -4.18 to -1.24). Vitamin D deficiency prevalent amongst most participants.
Sloan et al. (2022) ⁶⁶	Brazil	Observational studies, interventions and RCTs	RoB 2 I^2 : Not reported	Vit D: 2000 IU/day–200,000 IU one time	Not reported	10 (Not stated)	Age range: 18–71 years Sex not reported	Recommend serum vitamin D levels greater than 30 ng/mL, preferably 40–60 ng/mL. Large bolus doses seemed to have little significant effect.

TABLE 2 (Part 4 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Petrelli et al. (2023) ⁶⁷	Italy	Observational studies, interventions and RCTs	Egger's test I^2 : 77% for severity, 50% for mortality	Vit D: 357 IU/day–60,000 IU/day (others specified)	Incidence, ICU admission, mortality	27 (1,276,7045)	Not reported	Low levels of D3 were significantly associated with severity (OR=1.97, 95% CI 1.55–2.51, $p < .01$; $I^2=77\%$, $p < .01$) and mortality (OR=1.83, 95% CI 1.55–2.16, $p < .01$; $I^2=50\%$, $p < .01$) risk due to COVID-19. Low levels of vitamin D3 were associated with a significant risk of COVID-19 (OR=1.72, 95% CI 1.51–1.97, $p < .01$; $I^2=76\%$, $p < .01$). After diagnosis of COVID-19, vitamin D supplementation was associated with significantly reduced infection severity (e.g., ICU admission) (OR=0.38, 95% CI 0.28–0.5, $p < .01$; $I^2=0\%$, $p = .71$).
Feng et al. (2021) ⁶⁸	China	RCTs	RoB 2 I^2 : Not reported	Vit D: 200,000 IU/day dissolved in 10 mL peanut oil solution	LOS	12 Vit D: 1 Tot: 1,952 Vit D: 237	Mean age: 56.2 years Sex not reported	Insufficient data
Ao et al. (2022) ⁶⁹	China	Observational studies and RCTs	Jadad, NOS I^2 : 26% for severity, 0% for mortality	Vit C: 2–24 g IV for 3–7 days	Mortality, disease severity	7 (807)	Age range: 36–78 years Male: 33%–66.7%	No statistically significant results found
Kwak et al. (2021) ⁷⁰	Korea	Observational studies and RCTs	Funnel plot, Egger's test I^2 : 20.9% for mortality, 94.6% for length of hospital stay	Vit C: 1–12 g/day or 50–100 mg/kg/day; from every 6 hrs up to 10 days	Hospital mortality, LOS	8 (1,021)	Not reported	No statistically significant results found
Stroehlein et al. (2021) ⁷¹	Germany	RCTs	RoB 2 I^2 : Not reported	Vit D: 0.532 mg orally up to 7 days, to 200,000 IU one time	All-cause mortality, IVM, LOS, serum vitamin D status, ICU admission, adverse events (any grade).	3 (356)	Age range: 42–64 years Male: 6%–69%	Low certainty of evidence
Varikasuvu et al. (2022) ⁷²	India	RCTs	RoB 2, Funnel plot, Begg's test, Egger's test I^2 : >50%	Vit D: 1,000 IU–80,000 daily up to 2 weeks; or 200,000 IU orally one time	ICU admission, mortality, RT-PCR positivity	6 (551)	Age range: 18–56 years Male: 44%–59%	Vitamin D reduced the rates of RT-PCR positivity (RR=0.46, 95% CI 0.24–0.89, $Z=2.31$, $p=.02$, $I^2=0\%$). Vitamin D is associated with fewer rates of ICU admission, mortality events, and RT-PCR positivity (relative risk, RR=0.60, 95% CI 0.40–0.92, $Z=2.33$, $p=.02$, $I^2=48\%$).
Argano et al. (2022) ⁷³	Italy	Systematic reviews and meta-analyses	AMSTAR I^2 : Not reported	Wide range of studies with mixed serum levels and supplementation	Inflammatory process in patients affected by DM	6 (1,594)	Not reported	Supports the therapeutic administration of supplemental vitamin D in diabetic patients to reduce COVID-19 respiratory complications.
Rawat et al. (2021) ⁷⁴	India	RCTs	RoB 2 I^2 : 0% for mortality, 0% for duration, 92% for LOS, 0% for IMV	Vit C: 50 mg/kg/day up to 24 g/day	Mortality, ICU LOS, hospital LOS, IMV incidence.	6 (572)	Age range: 36–79 years Sex not reported	No statistically significant results found in the meta-analysis

TABLE 2 (Part 5 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Gavrielatou et al. (2022) ⁷⁵	Greece	Observational studies and RCTs	RoB 2 I^2 : 74%	Vit C: high-dose IV	Vasopressor-free days, continuous renal replacement therapy-free days, ventilator-free days, ICU-free days, ICU-mortality	11 (1,807)	Age range: 41–81 years Female: 24.8%	No statistically significant results found in the meta-analysis.
da Rocha et al. (2021) ⁷⁶	Brazil	RCTs and interventions	RoB 2 I^2 : Not reported	Vit D: 0.532 mg to 200,000 IU	Duration of IMV, mortality rate, adverse events	3 (385)	Age range: 40–71 years Sex not reported	Supports the therapeutic use of supplementary vitamin D to mitigate respiratory complications associated with COVID-19 or to preemptively mitigate the severity of COVID-19 in the event of infection.
Bania et al. (2022) ⁷⁷	Greece	Observational studies, interventions and RCTs	RoB 2 I^2 : Not reported	1000 IU/day to 50,000 IU/wk to 120,000 IU/mo to 200,000 one time	LOS, IMV/intubation, ICU admission, mortality	11 (1,070)	Age range: 27–89 years Sex not reported	Supports the therapeutic use of supplementary vitamin D to mitigate respiratory complications associated with COVID-19 or to preemptively mitigate the severity of COVID-19 in the event of infection.
Hariyanto et al. (2022) ⁷⁸	Indonesia	Observational studies, interventions and RCTs	Funnel plot I^2 : <25%–>50%	Vit D: 25,000 IU/month up to 200,000 IU/day for 2 days	ICU admission, IMV, mortality	11 (2,265)	Age range: 31–97 years Sex not reported	Vitamin D supplementation reduced ICU admission (OR=0.27, 95% CI 0.09–0.76, p =.010, I^2 =70%, random-effect modelling); Reduced the need for mechanical ventilation (OR=0.34, 95% CI 0.16–0.72, p =.005, I^2 =61%, random-effect modelling); Reduced mortality from COVID-19 (OR=0.37, 95% CI 0.21–0.66, p <.001, I^2 =50%, random-effect modelling).
Hosseini et al. (2022) ⁷⁹	Canada	Observational studies, interventions and RCTs	RoB 2 I^2 : >50%	Vit D: <1000 IU/day–10,000 IU/day	Incidence, hospital admission, ICU admission, mortality	23 (5,870,189)	Age range: 15–100 years Sex not reported	Vitamin D supplementation was significantly associated with a reduced risk of ICU admission (RR=0.35, 95% CI 0.20–0.62) and mortality (RR=0.46, 95% CI 0.30–0.70).
Beran et al. (2022) ⁸⁰	USA	Observational studies and RCTs	Jadad, NOS, Egger's test, Funnel plot I^2 : Not reported	Vit C: 1 g–8 g oral or 50 mg–24 g IV up to 18 days Vit D: wide range of dosages and durations	Mortality, intubation rate, LOS	26 (5,633)	Age range: 29–79 years Sex not reported	No sig effects with vitamin C; Vitamin D adequacy reduced intubation rate (RR=0.55, 95% CI 0.32–0.97, p =.04, I^2 =48%) and LOS (MD=-1.26; 95% CI -2.27 to -0.25; p =.01, I^2 =0%).
Aldhafiri et al. (2022) ⁸¹	Saudi Arabia	Observational studies, interventions and RCTs	Forest plot, Funnel plot I^2 for Vit C 0%–96%; for Vit D 94.31%	Vit C: 24–168 g for 5–7 days; Vit D: serum levels only	Incidence, duration	27 (11,711)	Not reported	Serum levels of vitamin D are low in COVID-19–positive patients (p <.001). No significant variations found for vitamin C supplementation.
D'Ecclesiis et al. (2022) ⁸²	Italy	Observational studies and interventions	NOS, RoB2, Egger's test, Begg's test, Funnel plot I^2 : <50%	Vit D: 1000 IU daily to 400,000 IU one time (mixed studies with serum and supplementation)	Symptom severity, ICU admission, IMV/intubation, LOS, mortality	38 (205,565)	Mean age: 35.6–90 years Male: 32%–92%	Vitamin D supplementation was associated with a reduced risk of disease severity (SRR=0.38, 95% CI 0.20–0.72, 6 studies) and mortality (SRR=0.35, 95% CI 0.17–0.70, 8 studies), particularly in older individuals and at higher latitudes.

TABLE 2 (Part 6 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Olczak-Pruc et al. (2022) ⁸³	Poland	Interventions	RoB 2, ROBINS-I I^2 : Not reported	Vit C: ≤ 1 g/day– > 10 g/day	Mortality, LOS, ICU admission	19 (1,817)	Age range: ≥ 18 years Sex not reported	Vitamin C supplementation reduced the risk of in-hospital mortality (OR=0.59; 95% CI 0.37–0.95; $p=.03$). The ICU length of stay was longer in patients treated with vitamin C vs. standard therapy, 11.1 (7.3) vs. 8.3 (4.7) days (MD=1.91; 95% CI 0.89–2.93; $p<.001$).
Kümmel et al. (2022) ⁸⁴	Germany	RCTs	Funnel plot, Begg's test, Egger's test I^2 : 0% for mortality, 66% for ICU admission, 24% for length of hospitalization	Vit D: 0.5 µg–5,000 µg	Mortality, ICU admission, LOS	8 (657)	Mean age: 39.7 years Female: 100%	Trend for reduced mortality (OR=0.74, 95% CI 0.32–1.71, $p=.48$), with even stronger effects, when vitamin D was administered repeatedly (OR=0.33, 95% CI 0.1–1.14).
Huang et al. (2022) ⁸⁵	Korea	Observational studies and RCTs	RoB 2, NOS, Funnel plots, Egger's test I^2 : >50%	Vit C: 500 mg orally–24 g IV	Mortality, ICU duration, LOS, IMV	19 (949)	Age range: ≥ 60 years Sex not reported	Vitamin C supplementation reduced the risk of mortality (RR=0.81, 95% CI 0.62–1.07; $I^2=58\%$; $Q=40.95$; $p<.01$); no significant differences in LOS, ventilation, ICU duration
Kow et al. (2023) ⁸⁶	Malaysia	RCTs	RoB 2 I^2 : Not reported	Vit C: 200 mg–8 g orally daily or 6 g–28 g IV daily	Mortality	11 (939)	Mean age: 42–67 years (all ≥ 18 years) Sex not reported	Vitamin C supplementation reduced the risk of all-cause mortality (pooled OR=0.53; 95% CI 0.30–0.92), especially in patients with severe COVID19 (pooled OR=0.47; 95% CI 0.26–0.84).
Vollbracht et al. (2021) ⁸⁷	Germany	Observational studies, interventions, RCTs, pre-clinical	NA I^2 : Not reported but heterogeneity mentioned	Vit C: > 1 g IV daily	Symptom severity, oxygen status	9 (720)	Not reported	Supports the therapeutic use of high dose vitamin C to improve oxygen status and mitigate the severity of COVID-19.
Hawke et al. (2022) ⁸⁸	Canada	RCTs and interventions	RoB 2 I^2 : Not reported	Vit B3: 2000 mg daily for 22 weeks		42 Vit B: 1 Tot: 5,814 Vit B3: 200	Age range: <18–65+ Sex not reported	Insufficient data

AMSTAR=a measurement tool to assess systematic reviews; CI=confidence interval; DM=diabetes mellitus; GRADE=grading of recommendations, assessment, development and evaluations; ICU=intensive care unit; IMV=invasive mechanical ventilation; IV=intravenous; JBI=Joanna Briggs Institute critical appraisal tool; LOS=length of stay; MD=mean deviation; NHLBI=National Heart, Lung and Blood Institute quality assessment tool; NIH=National Institutes of Health; NOS=Newcastle-Ottawa scale; OR=odds ratio; PRISMA=preferred reporting items for systematic reviews and meta-analyses; RCT=randomized controlled trial; RoB 2=Cochrane risk of bias tool; ROBINS-I=risk of bias in non-randomized studies – of interventions; RR=relative risk; RT-PCR=reverse transcription-polymerase chain reaction test; SMD=standardized mean difference; SRR=standardized rate ratio; WMD=weighted mean difference.

effects,^{33,35,36,39,41,42} and three covered its immunomodulatory benefits.^{33,35,36,42}

The systematic reviews of vitamin C generally found positive associations between its therapeutic supplementation and reduced COVID-19 severity. Eleven of the 13 systematic reviews included a meta-analysis, but only three of them found significant results. In Huang et al. (2022),⁸⁵ vitamin C supplementation reduced the risk of mortality (relative risk [RR] = 0.81, $p < 0.01$). In Olczak-Pruc et al. (2022),⁸³ vitamin C supplementation reduced the risk of in-hospital mortality (odds ratio [OR] = 0.59, $p = 0.03$) but the researchers also found that the length of stay in the intensive care unit (ICU) was greater in patients treated with vitamin C compared with standard therapy alone, with an average of 11.1 days compared with 8.3 days (mean deviation [MD] = 1.91, $p < 0.001$). In Kow et al. (2023),⁸⁶ vitamin C supplementation reduced the risk of all-cause mortality (pooled OR = 0.53; 95% confidence interval [CI] 0.30–0.92), especially in patients with severe COVID-19 (pooled OR = 0.47; 95% CI 0.26–0.84).

The doses of vitamin C administered in the included studies ranged substantially and covered both oral and intravenous (IV) applications within the same systematic reviews. With regard to oral doses, these ranged from 200 mg to 8 g daily, while doses for IV application ranged from 6 g to 28 g daily. None of the reviews examined the dose–effect relationship. As for the duration, IV therapy was administered between 1 and 10 days, but oral therapy had prolonged durations.

Vitamin C, therefore, demonstrates potential benefits in the prevention and treatment of COVID-19, but the strength of evidence remains uncertain. Given the wide variability in vitamin C dosing and administration observed across these studies, many non-significant findings among the systematic reviews may be due to methodological issues in the research.

Vitamin D

Vitamin D had the greatest number of narrative reviews ($n=12$), 11 of which provided an extensive evaluation of its mechanisms, its properties, and its applicability related to COVID-19. Three studies discussed vitamin D as an antioxidant,^{32,35,40} eight as an anti-inflammatory,^{33–36,38,40,41,44} nine as an immunomodulator,^{32–39,44} and two as an antiviral.^{35,37} In most cases, the reviews focused on the importance of addressing deficiency as measured by serum status of 25-hydroxy vitamin D or 25(OH)D.

None of the systematic reviews discussed any severe adverse effects or therapeutic concerns with regard to vitamin D. In fact, the general consensus is that there is a clinical value in measuring serum 25(OH)D levels because deficiency and inadequacy are associated with increased COVID-19 incidence, severity of symptoms, length of stay in hospital, ventilation requirements, and mortality.

For the 28 studies that conducted a meta-analysis, findings were consistently supportive of maintaining adequate levels of 25(OH)D and/or the therapeutic use of vitamin D supplementation. For example, 11 reviews found statistically significant associations between low levels of 25(OH)D and the incidence of getting a COVID-19 infection,^{45,47,49–51,53,55,56,64,67,81} and eight with disease

severity.^{46,48,51,53,55,56,65,67} Inadequate levels of 25(OH)D were also reported to have a significant association with COVID-19–related mortality in nine of the systematic reviews.^{46,48,51,53,55–57,60,67}

With regard to vitamin D supplementation, five reviews found significant associations with a reduced risk of ICU admission,^{58,59,72,78,79} and five found it reduced the risk of mortality.^{59,72,78,82,84}

As for vitamin D dosing, the wide range from 357 IU/day to 400,000 IU as a single bolus complicates the effectiveness of data analysis. Though some studies described loading doses compared with maintenance doses, three studies highlighted that repeated administration of smaller doses would provide better effects than single large bolus doses.^{60,66,84}

In summary, the most fitting take-home message would be to ensure the patient reaches adequate serum levels, preferably 100–150 nmol/L (40–60 ng/mL),⁶⁶ with appropriate vitamin D supplementation and dosing for the patient to reach desired serum levels.

Vitamin E

Of the narrative reviews, only one outlined the antioxidant, anti-inflammatory, and immunomodulatory components of vitamin E in relation to COVID-19 specifically.³³ The authors discussed vitamin E's ability to reduce the production of nitrogen oxide and downregulate inflammation (prostaglandin E2 and cyclooxygenase), while modulating the Th1/Th2 balance and protein kinase C.

In the absence of systematic reviews specifically investigating the impact of vitamin E on COVID-19, definitive conclusions cannot be reached.

Overlap Analysis

Calculating the Corrected Covered Area at 2.31%, we found there was only a slight overlap across all systematic reviews. We further examined 15 reviews containing more than 10 articles cited more than once across all included reviews, particularly for the topics on vitamin D. Nonetheless, the impact any occurrence of overlap would have on our review findings was slight.

DISCUSSION

The synthesis of narrative and systematic reviews in this umbrella study presents a comprehensive overview of the potential roles of vitamins A, B group, C, D, and E in the context of COVID-19 management. The inclusion of narrative reviews alongside systematic reviews enhances the breadth of understanding, providing a holistic exploration of vitamins for COVID-19 prevention and management. Although only a subset of the initially included narrative and systematic reviews was retained for final analysis, these reviews collectively shed light on potential benefits and mechanisms associated with various vitamins.

Vitamin A emerges as a theoretical candidate for immunomodulation, anti-inflammatory action, and antimicrobial effects. The absence of systematic reviews specifically focusing on vitamin A highlights the need for more comprehensive investigations. Similarly, the activity of the vitamin B group in cell function regulation, energy metabolism, and immune response modulation

(particularly vitamins B6, B9, and B12) warrant attention. Unfortunately, the limited number of systematic reviews on the vitamin B group as a treatment option for COVID-19 leave these water-soluble vitamins as theoretical aids that require further research. Finally, discussion of vitamin E within narrative reviews underscores its potential antioxidant and anti-inflammatory effects. However, the absence of systematic reviews limits our ability to draw definitive conclusions regarding its impact on COVID-19 outcomes and thus emphasizes the need for dedicated research in this area.

In contrast, the systematic reviews available for vitamins C and D offer clearer insights into their effects, but the strength of evidence is far greater for vitamin D. Narrative reviews consistently discussed vitamin C's antioxidant, anti-inflammatory, and immunomodulatory properties, but the evidence remains rather theoretical. As to vitamin D's significance in addressing deficiency-related COVID-19 risks, it is confirmed to be an important antioxidant, anti-inflammatory, immunomodulator, and an antiviral agent. The mechanisms of action discussed for vitamin D are then effectively put into practice in multiple trials.

The systematic reviews on vitamin C reveal a notable pattern: while all of them discussed positive associations between vitamin C supplementation and reduced COVID-19 severity, only a few presented statistically significant results. A closer examination may elucidate why 70% of studies found no statistically significant results. First, these systematic reviews and meta-analyses all had a small number of studies on vitamin C included (ranging from two to 11 studies) with an insufficient population size to obtain statistical power for significant findings. The systematic reviews with a greater number of studies also had the greatest heterogeneity (I^2 from 74% to 96%), reducing the confidence in the pooled estimate or effect size. Further discrepancies could be attributed to variations in study populations, methodologies, and outcome measures among the included studies in the systematic reviews. One of the main reasons for this high level of heterogeneity is that the doses of vitamin C administered in the included studies ranged substantially, with both oral and IV applications within the same systematic reviews complicating the interpretation of outcomes. On the one hand, the lowest dose included in a study (200 mg daily taken orally), was based on the maximum absorption efficiency^{89,90} and was suggested by some authors as an optimal dose for primary prevention of disease.⁹¹ On the other hand, studies had up to 8 g taken orally in daily divided doses, presenting a drastic difference in oral treatment regimens. Similarly, 6 g to 28 g of IV administration in the studies included presents such a wide range of dosing approaches that a dose-response relationship warrants further study. Such an analysis would have been especially valuable considering that IV vitamin C bypasses intestinal absorption for higher plasma concentrations to be achieved but renal excretion can restore vitamin C to baseline within hours.⁹² These pharmacokinetics must be considered for clinically relevant interpretation of the research findings.

There is also the concern that baseline measures of plasma vitamin C concentration were not considered in these studies. Because of the intricate way in which the body will absorb, distribute,

metabolize, and eliminate vitamins to regulate plasma levels, the outcomes of vitamin C supplementation can vary significantly based on an individual's vitamin C status. This divergence is particularly notable between those who have sufficient vitamin C levels (plasma concentrations near saturation) and those with sub-optimal (plasma concentrations <50 $\mu\text{mol/L}$), marginally deficient (plasma concentrations <23 $\mu\text{mol/L}$), or severely deficient (plasma concentrations <11 $\mu\text{mol/L}$) levels.⁹³ Future research on vitamin C should ensure that interventions or statistical analyses consider serum levels. Similarly, clinical application should be carried out with due consideration of the individual's baseline vitamin C status. In summary, the research on vitamin C suggests it has potential benefits in the prevention and treatment of COVID-19, but the heterogeneity of included studies invites careful consideration of the precise dosing and administration protocol for patients.

With respect to vitamin D, this essential nutrient emerges as a central theme within the body of systematic reviews, underscoring its role in both the prevention and treatment of COVID-19. Systematic reviews consistently highlight the significance of maintaining adequate vitamin D levels in addressing the multifaceted challenges posed by the pandemic. The recurring findings across these reviews provide compelling evidence that optimizing vitamin D status could substantially mitigate the risks associated with COVID-19, spanning from disease incidence to severity and mortality.

Nevertheless, the diverse outcomes observed in the systematic reviews suggest a complex interplay of factors, including variations in dosing and formulations, study populations, methodologies, and geographical contexts. The intricate pharmacokinetics of vitamin D contribute to the nuanced interpretation of outcomes, as its metabolism is influenced by factors such as age and body mass,⁹⁴ as well as skin pigmentation, latitude, sun exposure, and dietary intake.⁹⁵⁻⁹⁷ This diversity of factors inevitably results in a wide range of dosing strategies aimed at achieving individualized 25(OH)D sufficiency. Consequently, the observed mixed outcomes in systematic reviews are reflective of this personalized approach, with dosage variations aligning well with the distinct requirements of diverse patient profiles.

The challenge lies in striking a balance between establishing an effective dosing regimen that attains the desired therapeutic effects while minimizing potential adverse outcomes. The reviewed systematic studies clearly lean towards vitamin D being an effective vitamin for COVID-19 prevention and treatment. Nonetheless, the optimal dosing protocol remains an area of ongoing investigation, meriting further research and refinement. Despite this complexity, repeated dosing seems to yield superior outcomes compared with a single large bolus dose.

Clinical Relevance and Implications

The synthesis of narrative and systematic reviews has implications for practitioners, policymakers, and researchers. Clinicians should consider the varying levels of evidence and the specific contexts in which these vitamins are being administered.

Vitamin D's significance in addressing deficiency-related risks presents a strong rationale for incorporating 25(OH)D assessment

into clinical practice, considering vitamin D deficiency is strongly associated with worse COVID-19 outcomes. Supplementation strategies in clinical practice must emphasize personalized dosing to reach the ideal serum levels of 100–150 nmol/L (40–60 ng/mL). The fundamental role of vitamin D in immune modulation signifies its potential to become a vital adjunct in the fight against the pandemic in hospitalized and outpatient settings. Optimal administration strategies to achieve and maintain optimal vitamin D levels require further fine-tuning with future research endeavours.

The evidence for vitamin C is weaker than it is for vitamin D. Concerns over the heterogeneity of included studies point to the strong need for further research on oral and IV treatments in separate research studies. Nonetheless, study results are leaning towards controlled dosing regimens to enhance immunity and mitigate the impact of COVID-19 in hospitalized or ICU settings. Therefore, in clinical practice, vitamin C may be carefully considered as a possible adjunct for COVID-19 treatment.

The lack of comprehensive systematic exploration of the group of B vitamins and the speculative nature of findings for vitamins A and E necessitate caution in their clinical application for COVID-19 management. Furthermore, added caution is required for special populations. Though several studies focused specifically on the elderly, and one on pregnant women, discretion should also be used in the application of any vitamin therapy to children or other subpopulations (e.g., immunocompromised, other comorbidities) because of a lack of research on these specific groups.

Strengths

Though it is not typical to include narrative reviews in an umbrella review, the inclusion of high-quality narrative reviews, according to SANRA guidelines, provides a complement to systematic reviews in their provision of clinically relevant treatment options. The collected systematic reviews also underwent a rigorous quality assessment, aligning with AMSTAR scoring tools. Using such quality assessments ensured robustness and minimized potential biases. By scrutinizing overlapping references and outcomes across systematic reviews, a cohesive framework emerged, enabling the identification of overarching patterns and discrepancies among the various systematic reviews. This umbrella review allowed for a holistic understanding of the synthesized evidence, empowering the extraction of meaningful insights that helped formulate comprehensive conclusions in the context of the potential role vitamins can play in COVID-19 prevention and management.

Limitations

At the beginning of the COVID-19 pandemic, researchers found a very limited number of relevant studies to include in their systematic reviews and were therefore hindered in drawing effective conclusions or running meta-analyses. In comparison, researchers who waited for more data to be published had stronger evidence to present. Many studies relied on the treatment of upper respiratory tract infections (URTIs) to hypothesize on the mechanisms of action of vitamins on COVID-19. Unfortunately, such URTI treatment often fails to acknowledge the unique cytokine

storm that COVID-19 triggers, which is why studies that did not specifically address COVID-19 were excluded. Furthermore, according to the reference overlap table, several systematic reviews used the same studies. This suggests a potential for limited diversity and breadth of evidence, which could impact the robustness and comprehensiveness of the conclusions drawn from those reviews. We also cannot ignore great variations in heterogeneity and publication bias among the systematic reviews in this umbrella review. Moreover, occasional disparities in data interpretation among extraction volunteers introduce a methodological limitation.

Of important note, some studies claimed significant results based on *p* values, despite the 95% confidence interval crossing the 1,^{83,85} ultimately contradicting themselves and reducing the level of trust readers can have in their data interpretation. Studies that did not account for variations in the dose (or ignored vitamin dosing as a factor) were less likely to find clinically relevant results. Future studies need to consider separating serum levels of a nutrient from its therapeutic supplementation in their methodological criteria. Similarly, studies should analyze results from oral and IV administrations separately, considering their dose and delivery affect the pharmacokinetics and pharmacodynamics of vitamin therapy. Closer attention to the dose–response relationship, along with cross-correlations to the stage of disease (prevention, early stage, mild vs severe cases, and post-COVID), also warrant further investigation. Since low doses may be ineffective and high doses have a higher likelihood of adverse effects, future research needs to control for dosing variability and report accordingly.

CONCLUSION

Several noteworthy findings emerge from this comprehensive examination of the potential roles vitamins play in COVID-19 prevention, treatment, and management. While narrative reviews suggest promising attributes of vitamins A, B, C, D, and E in combating COVID-19, the absence of systematic reviews on certain vitamins hinders conclusive insights. Vitamin B exhibits theoretical benefits in cell regulation and immunity, yet its role lacks comprehensive systematic investigation. Vitamins A and E showcase intriguing properties but require further systematic exploration specifically related to COVID-19. Small sample sizes and high heterogeneity among the included studies on vitamin C devalue the aggregated results. Nonetheless, there were sufficient systematic reviews on vitamin C to suggest possible associations between its adjunct supplementation and a reduced risk of COVID-19 severity, despite varying dosages and forms of administration complicating the interpretation relevant to clinical application. Conversely, results on vitamin D were much more conclusive. Vitamin D warrants substantial attention, as its deficiency correlates with heightened COVID-19 risks. The systematic reviews confirm serum adequacy leads to reduced risks of COVID-19 infection, severity, and mortality. Personalization of vitamin D dosing is suggested to reach ideal serum levels. Overall, this analysis underscores the need for meticulous research to establish more robust conclusions.

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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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APPENDIX 1: GLOSSARY OF TERMS

25(OH)D	25 hydroxy vitamin D
AMSTAR	Assessment of Multiple Systematic Reviews
CI	confidence interval
COVID-19	coronavirus-19 (aka SARS-CoV-2, novel coronavirus)
CRP	C-reactive protein
EF	Endothelial function
FBF	forearm blood flow
FMD	flow mediated dilation
FoxP3	Forkhead box P3
GRADE	grading of recommendations, assessment, development and evaluations
ICU	intensive care unit
IL-6	interleukin-6
IV	intravenous
JBI	JBI critical appraisal checklist
LOS	length of stay
NHLBI	the national heart, lung and blood institute quality assessment tool
NIH	National Institutes of Health (NIH) quality assessment tools
NOS	Newcastle-Ottawa scale
OR	odds ratio
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RoB 2	Cochrane risk of bias tool
ROBINS-I	risk of bias in non-randomized studies – of interventions
RR	relative risk
SARS-CoV-2	severe acute respiratory syndrome of the coronavirus 2
TNF- α	tumor necrosis factor- α
URTI	upper respiratory tract infections
WHO	World Health Organisation

The Role of Movement, Exercise, and Breathing in the Prevention and Treatment of COVID-19: An Umbrella Review



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ABSTRACT

Objective: To identify the published review literature regarding movement, exercise, and breathing in the prevention and/or treatment of the coronavirus 2019 disease (COVID-19) and long COVID, with the goal of describing the literature and identifying areas for further research and clinical application. Movement and exercise incorporate sedentary behaviours, various forms of exercise, breathing and respiratory therapies, and yoga-asanas (postures).

Methods: This paper progresses from a live review and incorporates systematic reviews and narrative reviews. A literature search occurred monthly using PubMed and Google Scholar from May 2022 to May 2023. A measurement tool to assess systematic reviews (AMSTAR) scoring assessed systematic review quality, while the scale for the assessment of narrative review articles (SANRA) guidelines were used to evaluate narrative reviews. Only information and data focused on movement and exercise relevant to COVID-19 prevention and/or treatment were extracted from each review.

Results: Three narrative reviews and five systematic reviews were included. Sedentary behaviours increased significantly during the pandemic. Decreased physical activity level was associated with risk of hospitalization from COVID-19. Physical activity and breathing exercises, whether conducted face-to-face (F-2-F) or via telerehabilitation were associated with improvement in dyspnea (shortness of breath), exercise capacity, lung function, fatigue, and quality of life (QoL). Extreme exercise is best avoided for at least 2 to 3 weeks after severe COVID-19 symptoms.

Conclusion: Sedentary behaviour and lack of regular physical activity is correlated with an increased risk of COVID-19. Various forms of movement, exercise, and breathing may be beneficial in the treatment of COVID-19 and in long COVID. Further research and understanding of the importance of movement, exercise, and breathing as it relates to immune health is warranted.

Key Words Physical activity, isometrics, calisthenics, inhalation, respiration, remedy

INTRODUCTION

The advent of the coronavirus disease 2019 (COVID-19; see Appendix 1 for a list of terms and acronyms used in this article) hampered the continuity of essential health services throughout the world during 2021–2022,¹ with the broader impacts of COVID-19 accounting for over 760 million confirmed cases worldwide since December 2019, affecting people of all ages.² Efforts during this tumultuous period were focused on identifying effective and efficient treatments for COVID-19,^{4,5} improving rates of recovery,^{6,7} and preventing transmission through public health initiatives.⁸ Some of the prevention measures, such as the

lockdowns and closures of many services, resulted in high levels of stress, and individuals across the globe not only delayed but entirely forwent health services when needed.⁹ Individuals often changed their lifestyle behaviours and the frequency and type of interactions that they had with others.^{10,11} COVID-19 strained the capacity for health systems worldwide to sustain the provision for essential health services. This pressure on health systems ultimately initiated the rapid roll-out and uptake of technology-assisted essential health services and lifestyle guidance via virtual telehealth appointments.^{12,13}

Fatigue, shortness of breath, weakness, and other respiratory symptoms are common symptoms of COVID-19¹⁴ and long

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COVID.¹⁵ As sedentary lifestyles and lack of exercise are well known to be correlated with respiratory symptoms,¹⁶ it stands to reason that the impact of movement and exercise should be explored as a preventive measure that may improve both immune health¹⁷ and mental health¹⁸ in the treatment of COVID-19 and long COVID.

The aim of this paper was to identify the published review literature regarding movement, exercise, and breathing in the prevention and/or treatment of COVID-19 and long COVID and the impact of the pandemic. The aspects of movement, exercise, and breathing that are included are sedentary lifestyles, various forms of aerobic and resistance exercises, various Western breathing exercises, yogic breathing (pranayama), and yoga asanas (postures). This review also analyzed the difference between face-to-face (F-2-F) and telerehabilitation interventions with the goal of describing the literature and identifying areas to consider for future research and clinical application.

METHODS

Design

This paper progresses from a live review of systematic reviews⁴⁰ which explored natural health products (NHPs) and natural therapies in the prevention and/or treatment of COVID-19. Along with five other papers, this is an umbrella review encompassing narrative reviews and systematic reviews that were collected as part of the live review completed in order to provide a comprehensive evaluation of various NHPs and natural therapies studied.

Search Strategy

A live literature search occurred monthly in PubMed and Google Scholar databases from May 2022 to May 2023, as guided by the Cochrane guidelines for a live systemic review.⁴¹ A primary search strategy for the overarching live review was conducted utilizing some of the following search terms “natur*,” “herb*,” “nutraceuti,” “botanical,” “medicinal plant,” “Ayurvedic,” “herbal patent formula,” “vitamin,” “mineral,” “exercise,” “traditional medicine,” “medicine, traditional Chinese,” “lifestyle medicine,” combined with “prevention,” “prophylaxis,” “deficiency,” “treatment,” “management,” and “*COVID*,” “Coronavirus,” “SARS-CoV-2”; these search terms were filtered for meta-analysis, review, or systematic review (refer to Table S1 in the supplemental material). Individual therapies cited in the literature were searched and were subsequently added to the search criteria, for example “exercise,” “meditation,” and “breathing.” This manuscript presents the results of a subset of studies identified through the live review focused on movement, exercise, and breathing.

Articles identified by the living review search strategy were then grouped based upon the type of review as stated in the abstract (1) systematic review/meta-analysis, (2) narrative, and (3) other.

Inclusion and Exclusion Criteria

This umbrella review includes systematic reviews and narrative reviews. Both review types were appraised by at least two reviewers for inclusion/exclusion and any discrepancies were assessed by

an independent third reviewer. Systematic reviews were assessed according to A Measurement Tool to Assess Systematic Reviews (AMSTAR) guidelines⁴² and narrative reviews according to the Scale for The Assessment of Narrative Review Articles (SANRA) guidelines.⁴³ Systematic reviews were included if the review authors, at least partially, accounted for risk of bias (RoB) in individual studies and used a satisfactory technique for assessing the RoB. Narrative reviews were included if the scientific reasoning score was 1 or 2 and the overall total sum >5.

Population, intervention, comparator, outcome (PICO) eligibility criteria requirements for study inclusion were as follows:

Population: Clinical/observational (humans of any age/gender, any setting), in vivo (including animals), in vitro, or in silico studies.

Intervention: Sedentary, movement, exercise, breathing

Comparison: No comparator limitation.

Outcome: Symptoms, biological markers, diagnostic criteria, or viral traits related to COVID-19.

Due to the potential for a bidirectional relationship between exercise and COVID-19, studies were also considered for inclusion when the outcome was the intervention.

Excluded were secondary analyses, literature reviews, editorial discussions, best practice guidelines, and book chapters. Only results that reported statistically significant outcomes relevant to COVID-19 prevention and/or treatment were extracted from each review. Any discrepancies for inclusion were verified by a separate reviewer.

Data Extraction

Narrative reviews were included to highlight the therapeutic considerations and known mechanisms of action of each criterion. The data extracted from the narrative reviews included study number, American Medical Association (AMA) style, author(s), date, journal, country/World Health Organization (WHO) region, review objective, details of any search conducted, area of focus (prevention, treatment, long COVID), and therapeutic considerations including properties (anti-inflammatory, antiviral, etc.) were extracted based on therapeutic properties outlined on https://www.ndhealthfacts.org/wiki/Action_of_Herbs.

The data extracted from the systematic reviews of this review includes study number, study identification, author(s), date, journal, area of focus (prevention, treatment, long COVID), WHO region, review objective, search date, search databases, study designs, included country, included studies, publication date range, tools for assessment of RoB, methods of synthesis/analysis. Data extracted for the systematic reviews for the study results includes relevant study interventions, relevant outcomes measured, number of studies, number of participants, age of included participants, sex of participants (percentage female), results/findings, heterogeneity (only if a meta-analysis).

RESULTS

The primary review identified 401 papers of which 155 (38.6%) were excluded as not meeting the primary review criteria, including critical appraisal thresholds. After additional deduplication and extraction, a further 40 additional studies were excluded, leaving 206 studies that were allocated amongst the various subsets that are reported as unique umbrella reviews. Specific to this subset, 50 studies were selected as potentially relevant for this subset analysis and further screened, through which 42 (84.0%) were removed as not meeting the criteria, resulting in 8 included for review in this manuscript: 5 systematic reviews and 3 narrative reviews.

Systematic Reviews

Of the 41 initially identified systematic reviews in this section, 5 papers were included in the final write-up⁴⁴⁻⁴⁸ (Table 1). The included systematic reviews were conducted in the following WHO regions: the Western Pacific region (WPR) ($n = 3$), region of the Americas (AMR) ($n = 1$), and Eastern Mediterranean region (EMR) ($n = 1$). Movement and exercise were explored as they relate to being a comorbidity for COVID-19,⁴⁶ the impact of COVID-19 public health measures on movement and exercise,⁴⁷ physical activity (PA) as a prevention for COVID-19,⁴⁴ the impact of pulmonary respiratory muscle exercises (PRME) as an adjunct treatment for COVID-19,⁴⁵ and the value of respiratory muscle training (RMT) in long COVID.⁴⁸

Narrative Reviews

Narrative reviews were included in this umbrella review to provide a broader perspective on the therapeutic considerations and to complement the details of the systematic reviews (Table 2). Of the nine narrative reviews initially included, eight remained for data extraction and three papers were included in the final write-up.^{21,49,50} The three papers in the narrative reviews included the following WHO regions: European region (EUR) ($n = 2$) and South-East Asian region (SEAR) ($n = 1$). One of the narrative reviews focused on the impact of yoga asanas (postures) and yogic breathing (pranayama) on prevention and treatment of COVID-19. The other two narrative reviews discussed various forms of exercise for the treatment of long COVID.

Initially the systematic reviews and narrative reviews identified for this paper included all non-ingestible therapies that were not included in the other umbrella review papers. For example, systematic reviews on mind-body therapies, body-based therapies, Ayurveda, and acupuncture were included. The diminutive evidence base for some therapies in the prevention and treatment of COVID-19 is reflected in the high number of papers excluded from the final manuscript; papers that were not focused on COVID-19 were also excluded.

Symptom Severity and Hospitalization

Two systematic reviews discussed the correlation between activity level and the risk of COVID-19.^{44,46} Luo et al. (2022)⁴⁶ concluded that the level of physical exercise correlated with an increased risk

of COVID-19 and found that moderate-to-high PA may be associated with lower risk of COVID-19 severity, yet self-reported moderate-to-vigorous physical activity was not associated with lower risk. The meta-analysis by Li et al. (2023), involving 17 studies and over 1 million participants self-reporting on level of PA found a 40% reduction in the risk of COVID-19 hospitalization between those reporting a high dose of PA compared with those reporting a low level of PA. Although an increase in moderate-intensity PA was found to be beneficial in all groups, the benefit was greater in those that were initially doing less than 10 metabolic equivalents of task per-hour (Met-h)/week. Met-h is an objective measure of the energy cost for metabolic activity or the rate at which a person expands energy for PAs or exercise capacity.⁵²

Impact of the Pandemic on Movement

The meta-analysis by Gigli et al. (2022)⁴⁷ involving 34 studies and 9,433 males and females looked at the self-reported impact of COVID-19 on various lifestyle behaviours and found that the lockdowns and school closures may have resulted in an increase in unhealthy lifestyle behaviours for most people. Between 36.5% and 43% respondents indicated that they did not engage in PA, or they experienced a significant reduction in PA during the lockdowns. The studies also indicated that adults over 40 with children, unemployed persons and those living in a macroeconomic region were more likely to engage in unhealthy behaviours. Children and adolescents were significantly affected, with one study indicating that PA in children and adolescents decreased from 540 min/week before the pandemic to 105 min/week during the pandemic and the other study indicating that the prevalence of physical inactivity in students increased from 21.3% to 65.6%. The studies also showed that screen time increased as PA decreased. There is also some indication that telemedicine may reduce the impact of unhealthy lifestyle behaviours.

Movement as an Adjunctive Treatment for COVID-19

One narrative review and one systematic review discussed movement as an adjunctive treatment for COVID-19. The narrative review by Umesh et al. (2022) discussed yoga asanas (postures), yogic breathing (pranayama), and meditation as a prophylaxis and an effective adjunctive therapy for COVID-19.²¹ The paper outlined the anti-inflammatory and antioxidant impacts of yoga and presented the results from a range of studies, including a clinical trial to support their findings. When yogic meditation, moderate-intensity exercise, and a control group were compared, findings suggested that the yoga group had a lower mean severity score for respiratory symptoms compared with the exercise group, and both the yoga group and the exercise group fared better than the control group.

The systematic review by Ahmed et al. (2022) involved eight studies and 449 participants and assessed the impact of PRME conducted either F-2-F or via telerehabilitation on a number of COVID-19 rate-of-recovery (ROR) markers.⁴⁵ The study suggested that PRME produced significant improvements in exercise capacity. The results were better for those with acute symptoms

TABLE 1 (Part 1 of 2) Systematic Reviews: Movement, Exercise, and Breathing

First Author, Year of Publication	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention/ Exposure	Participants: Number / Age / Sex	Outcomes Reported	Readings/Findings
Luo et al., 2022 ⁴⁶	Prevention WPR / Europe, East Asia	50 / Meta-analysis NR / PubMed, EMBASE, MEDLINE No tools, relied on 3 main IV assumptions: relevance, independence, and exclusion.	Exercise along with a number of other characteristics and comorbidities were assessed.	NR / NR / NR	Risk of COVID-19.	The role of physical activity in the risk of COVID-19 was inconsistent. Moderate-to-high physical activity may be associated with lower risk of COVID-19 severity, yet self-reported MVPA was not.
Gigli et al., 2022 ⁴⁷	Prevention AMR / China, Italy, UAE, Poland, Iraq	34 / meta-analysis / December 2021–April 2022 PubMed, Scopus, Science Direct, Scielo, Google Scholar Cochrane risk of bias tool	Impact of COVID-19 on lifestyle behaviours.	9,433 / males and females	Self-reported changes in lifestyle behaviours including exercise and screen time generally through online questionnaires. Note: the dietary behaviour changes are not included in this paper.	Observational studies reveal between 38.5% and 43% did not practice PA or reported sig decrease in PA and 36.2% to 49% significantly increased their screen time for entertainment during the pandemic. Most reported an increase in physical and emotional exhaustion, irritability and tension, as well as sleep disturbances. Children/adolescents showed sig altered lifestyle behaviour globally, including increased sedentary behaviour (median time spent in PA decreased from 540 min/wk before pandemic to 105 min/wk during the pandemic) and increased mental health outcomes. During the pandemic, the prevalence of physically inactive students increased from 21.3% to 65.6% and screen time averaged 30 hours per week during the pandemic.
Li et al., 2023 ⁴⁴	Prevention WPR / UAE, Canada, Slovenia, Sweden, UK, Iran, Palestine, Korea, Spain, Luxembourg, France, Brazil, USA, South Africa, China	17 / Meta-analysis / 1980–April 2022 PubMed, Web of Science	PA	1,038,768 / 18 to 69 / males and females	Self-reported PA level and its impact on hospitalization. Measurement based on MET-h MVPA, VPA	Several studies evidenced that for a small percentage of the participants, the pandemic resulted in improved lifestyle behaviours. Those with the highest PA dose showed a 40% (RR 0.60, 95% CI [0.48, 0.71]) reduction in the risk of COVID-19 hospitalization compared with the lowest dose of PA. When PA < 10 Met-h/week, an increase of 4 Met-h/week (1 hour of moderate-intensity or 1/2 hour of high-intensity) was associated with a 14% reduction in the risk of hospitalization for COVID-19 (157 $p < .01$, RR = 0.86, 95% CI [0.85, 0.87]). When PA > 10 Met-h/week, the risk of hospitalization for COVID-19 decreased by 11% for each 158 additional 4 Met-h/week ($p < .01$, RR = 0.89, 95% CI [0.87, 0.90]). A 4 Met-h/week PA is equivalent to 1 hour MPA or 1/2 hour MVPA.

TABLE 1 (Part 2 of 2) Systematic Reviews: Movement, Exercise, and Breathing

First Author, Year of Publication	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention/ Exposure	Participants: Number / Age / Sex	Outcomes Reported	Readings/Findings
Ahmed et al., 2022 ⁴⁵	Treatment EMR / Spain, Saudi Arabia, Brazil, Turkey, China	8 / Meta-analysis / January 2020–April 2022 / PubMed, Web of Science, Cochrane Cochrane risk of bias tool	PR muscle exercise, device-based threshold positive expiratory pressure, airway cleaning exercises, Telerehabilitation or F-2-F	449 / NR / males and females	ROR exercise capacity (6-MWT), lung function FVC, dyspnea severity index, dyspnea 12, (mMRC), fatigue (Borg scale of perceived exertion) QoL (anxiety, depression based on SF-12, SF-36), squat test and grip strength Comparison of F-2-F telerehabilitation for all markers.	PR program was superior to no intervention in improving dyspnea, exercise capacity, lung function, and fatigue in patients with COVID-19. Exercise capacity: PR produced sig improvement in exercise capacity based on 6-MWT (8 studies, MD 65.85 M 95% CI [42.86, 88.83]; $p < .001$). PR effective in both acute (5 studies, MD 8269 95% CI [56.30, 109.07], $p < .001$) and chronic COVID-19 patients (3 studies, MD 44.16, 95% CI [20.30, 68.02], $p < .001$). Improvement in acute was better than chronic and PR was effective both with mild and moderate/severe COVID-19 patients. Telerehabilitation: Both F-2-F (2 studies, MD 41.46, 95% CI [24.28, 58.63], $p < .001$) and telerehabilitation (6 studies, MD 75.95, 95% CI [49.05, 102.84], $p < .001$) were effective in improving exercise capacity. Dyspnea: PR sig improvement dyspnea (5 studies, SMD -2.11, 95% CI [-2.96, -1.27], $p < .001$) and exercise capacity (MD 65.85 m, 95% CI [42.86, 88.83], $p < .001$) in patients with both acute and chronic COVID-19 with mild to severe symptoms. Benefits were identified with both F-2-F and telerehabilitation. Fatigue: improvement via telerehabilitation in acute patients having mild symptoms (4 studies, MD 2.42, 95% CI [-2.72, -2.11], $p < .05$) Lung function: only F-2-F improved FVC in acute patients with mild symptoms (MD 0.26 L, 95% CI [0.04, 0.48], $p < .05$) QoL: The effect of PR on QoL was inconsistent across studies, yet 1 study found that F-2-F PR for 2 weeks improved QoL in patients with COVID-19 (SMD 2.89, 95% CI [2.04, 3.75], $p < .05$) PR was found to be safe and feasible for patients with COVID-19.
Chen et al., 2022 ⁴⁸	Post-COVID WPR / China, Saudi Arabia	3 / meta-analysis / NR PubMed, EMBASE, Chinese Science and Technology Journal full-text database (CNKI), Wan Fang Data, Chinese Biomedical Literature Database (VIP) Cochrane risk of bias tool	Three studies all employed RMT, with or without endurance training. Two studies adopted device-based threshold PEP, which can increase airway diameter and enhance mucus clearance by generating a force for flow obstruction that allows flow only when PEP reaches the requisite threshold level. One study also applied lower LMS exercises to improve muscle mass and strength, and one study integrated stretching exercise for body posture and flexibility. All three studies adopted the interval training approach.	233 / 48 to 69 / 58% male and 42% female with mild-to-moderate lung function impairments after COVID-19.	Exercise capacity: 6-MWT; PF: based on spirometry, lung volumes and diffusion capacity; QoL: SF Health Survey SF-12 and SF-36, ADL; Anxiety and depression: SDS and SAS	Exercise capacity: Sig improvement based on 6-MWT (50.41, 95% CI [34.34, 66.48], $p < .0001$) in treatment group. RMT sig improved exercise capacity, regardless of types of interventions (F-2-F or remote, with device-based or not, with endurance training or not). Dyspnea: improved in treatment group Pulmonary function: various parameters were used and interventions across the studies making improvements in PF difficult to assess. QoL: various inventories used. Sig improvement in all studies. One study used the SF-36 and indicated at 6 weeks sig improvement in all domains, yet no sig improvement in ADL. Another study using the SF-12 reported sig improvement on physical components at 6-weeks, but no sig improvement on the mental component. Anxiety and Depression: assessed in one study and indicated sign improvement in SAS, but not in SAD.

ADL=activities of daily living; AMR=region of the Americas; CI=confidence interval; EMR=European region; F-2-F=face to face; FVC=forced vital capacity; h=hour; IV=instrumental variable; LMS=limb muscle strength; MD=mean difference; MET-h=metabolic equivalents of task per hour; mMRC=modified Medical Research Council; MPA=moderate physical activity; MVPA=moderate to vigorous physical activity; MWT=minute walk test; NR=not reported; PA=physical activity; PEP=positive expiratory pressure; PF=pulmonary function; PR=pulmonary respiration; QoL=quality of life; RMT=respiratory muscle training; ROR=rate of recovery; RR=risk ratio; SAS=self-rating anxiety scale; SDS=self-rating depression scale; SF=short-form; sig=significant; SMD=standardized mean difference; UAE=United Arab Emirates; UK=United Kingdom; USA=United States of America; VPA=Vigorous physical activity; WHO=World Health Organization; WPR=Western Pacific region.

TABLE 2 Narrative Reviews: Movement, Exercise, and Breathing

First Author, Year of Publication	Area of Focus	WHO Region	Search Details	SANRA Score	Therapies Investigated	Properties / Association	Therapeutic Considerations
Umesh et al., 2022 ²¹	Prevention, treatment	SEA	PubMed	8	Yoga	Physical inactivity and other lifestyle factors impact immune health.	Yoga: preventive strategy for COVID-19. Yoga asanas (postures) may increase anti-inflammatory neuro-hormonal substances and thereby reduce the severity of infection. A RCT of 8-week yoga program (postures, breathing – paranyama, and meditation) matched moderate intensity exercise to a control group and a yoga group and identified a lower mean severity of respiratory symptoms for the yoga group than the exercise group. Both the yoga group and exercise group reported lower mean severity of respiratory symptoms than the control group. Yoga was found to be effective in other conditions with a respiratory factor, e.g., HIV, anti-tuberculosis treatment, pulmonary tuberculosis and in increasing lung capacity. A number of RCT yoga studies have demonstrated improvement in inflammatory markers and antioxidant status.
DeLuca et al., 2022 ⁴⁹	Long COVID	EUR	Cochrane Library, PEDro, PubMed, and Google Scholar	9	Physical function: 2 sessions, 6 weeks, aerobic exercise (walking/treadmill based), strength training of upper and lower limbs. Virtual reality exercises = 6 weeks, max 30 minutes/day. Brain stimulation: 9 over 3 weeks (20 mins/session)	Not specified / None	Studies suggest yoga may reduce the severity of infections by regulating the immune responses. Cognitive imperative in long COVID requires a multifaceted treatment approach including addressing physical functions using various means. Physical function: Endurance and balance training had significant improvements in walking capacity, symptoms of fatigue, cognition, and respiratory symptoms. Virtual reality exercise at home was well tolerated resulting in positive health, and QoL improved in time, whereas cognitive function seemed unaltered.
Scurati et al., 2022 ⁵⁰	Long COVID	EUR	Not specified	8.5	Exercise: various forms of exercise including, American College of Sports Medicine FITT-VP protocol Assessment of METs Aerobic, resistance training, exercises. Breathing exercises, stretching etc.	Anti-inflammatory, immune modulating, builds muscle mass, ameliorates cognitive function. Exercise mobilizes and activates innate immune cells, including neutrophils, inflammatory monocytes, dendritic, and NK cells Improved QoL	Consideration of exercise prescriptions as a concurrent treatment to modulate the molecular phenotype of long COVID. Exercise plays a preventive role and should be part of a long COVID treatment regimen. FITT-VP should start within 30 days after acute phase. Exercising over three METs should be avoided until 2/3 weeks after overcoming severe symptoms or 1 week after mild/moderate COVID-19. With mild COVID-19 symptoms only prolonged and exhaustive activity must be avoided. Avoid exercise in the acute phase of COVID-19. Once recovered, progressive increase in exercise recommended.

COVID-19=coronavirus disease 2019; EUR=European region; FITT-VP= frequency, intensity, time, type, volume and progression; MET-h=metabolic equivalents of task per hour; NK= natural killer; QoL=quality of life; RCT= randomized controlled trial; SEA=South East Asia region.

than for those with chronic symptoms and were more effective with mild versus moderate-to-severe patients. There were significant improvements in shortness of breath for both acute and chronic patients with mild-to-severe symptoms, though PA only improved fatigue in acute patients with mild symptoms. Physical activity only improved lung function in acute patients with mild symptoms when PA was in person F-2-F. Telerehabilitation may be effective in improving exercise capacity, shortness of breath, and fatigue.

Movement and Long-COVID

Two narrative reviews^{49,50} and one systematic review⁴⁸ discussed exercise in the treatment of long COVID. DeLuca et al. (2022) discussed physical function exercises for the improvement of cognition and associated mental health symptoms.⁴⁹ These exercises were comprised within a rehabilitation program consisting of two supervised sessions over 6 weeks incorporating aerobic exercise (walking/treadmill-based), strength training of upper and lower limbs, or virtual reality exercises, at no more than 30 min/day. Significant changes in walking times ($p < .01$) were reported post-rehabilitation for both walking tests.

Scurati et al. (2022) discussed the use of various types of exercise to mobilize and activate innate immune cells, including neutrophils, inflammatory monocytes, dendritic, and natural killer cells in long COVID.⁵⁰ The exercise programs discussed included the American College of Sports Medicine FITT-VP (frequency, intensity, time, type, volume, and progression) exercise protocols, the assessment of metabolic equivalents of task (METs), and the use of aerobics, resistance training, breathing exercises, and stretching.

The paper recommended that FITT-VP should start within 30 days after an acute COVID-19 infection and that exercising over 3 METs should be avoided until 2 or 3 weeks after overcoming severe symptoms or 1 week after mild/moderate COVID-19.

Chen et al. (2022) explored pulmonary rehabilitation (PR) and impaired respiratory function associated with COVID-19 and provided evidence of improved exercise capacity when measuring a 6-minute walk test among 233 patients with long COVID.⁴⁸

DISCUSSION

The results of this paper highlight the importance of movement and exercise in the prevention and/or treatment of COVID-19 and long COVID. Movement and exercise are also highlighted as important considerations for COVID-19 comorbidities, such as non-communicable diseases (NCDs).

Movement and Exercise as Part of Prevention Strategies

The WHO recommends that a combination of moderate and high-intensity activities equivalent to 10 MET hours/week is the most effective at reducing the risk of COVID-19 and/or risk of hospitalization from COVID-19.⁵⁴⁻⁵⁶ Exercise serves several purposes and is a strong indicator for health. For example, exercise capacity is an important index for measuring overall health and the ability of the body to cope with external stressors.⁵⁷ Exercise

and physical activity have beneficial effects on the immune system resulting in enhanced immunosurveillance, reduced systemic inflammation, improved regulation of the immune system, and delayed onset of immunosenescence.^{55,56} Proper breathing is also a key consideration for optimizing immune health and respiratory health.^{58,59}

Movement and Exercise as Part of a COVID-19 Treatment Regimen

Although research indicates that physical exercise is not advisable during the acute phase of COVID-19,⁵⁰ both physical exercise and PRME may improve the rate of recovery from COVID-19 and long COVID.^{44,45,47} Shortness of breath, fatigue, and decreased exercise tolerance are commonly associated with symptoms of mild-to-severe COVID-19.⁴⁵ Research also indicates that physical exercise may have some preventive impact and may decrease the risk of hospitalization.⁴⁴

Link Between Movement and Exercise and NCDs

Sedentary behaviour and lack of movement or exercise are strongly associated with increased risk of NCDs. Physical inactivity is often associated with other unhealthful lifestyle behaviours such as imbalanced diet, smoking, increased alcohol consumption, and the risk of a higher body mass index (BMI). Movement is an integral component of a healthful lifestyle and is a call to focus on salubrious lifestyles and diets⁶⁰ due to lifestyle factors being tied to chronic diseases and adverse health outcomes, for parents and children.^{61,62} NCDs often manifest as chronic comorbidities or as a multimorbidity⁶³ and have been linked to worsening COVID-19 symptoms and prognosis.⁶⁴ Although many NCDs can be averted,⁶⁵ health states stemming from unbalanced lifestyle choices may well be attributing to instances of COVID-19 as evidence indicates that patients with chronic illness such as diabetes, hypertension, respiratory illness, or renal or hepatic illness are more likely to be affected by COVID-19.⁶⁶ Non-communicable diseases are a major threat to humankind and present a substantial global disease burden.⁶⁷ Even though initiating lifestyle changes takes time and may be challenging to evaluate in a short-term study, these studies highlight the importance of focusing on movement and exercise as part of a healthful lifestyle.

Mental health issues are considered an NCD⁶⁸ and have greatly increased during the pandemic due to the lockdowns,⁶⁹ the trend towards working from home,⁷⁰ the stress and fear associated with COVID-19 itself,^{69,71} and as a long COVID symptom.⁷² There is a significant body of research linking the risk of mental health and the lack of PA and an increase in sedentary behaviour.⁷³⁻⁷⁵ Engaging in regular movement and exercise is an integral part of both preventing and treating mental health concerns.⁷⁶

The breadth of this paper captures the role of movement in the prevention and treatment of COVID-19. Nevertheless, this paper has some limitations which should be considered when interpreting the findings. The search strategy for this study was based on a primary search strategy for a live review, reiterated monthly and using numerous search terms not relevant to this study. Also, literature may exist outside of the date ranges, databases, or search

language used to identify potential studies for inclusion. Movement as part of overall wellness requires longer-term studies to elucidate the true importance or impact.

CONCLUSION

This study synthesizes evidence related to the potential role of movement, exercise, and breathing in the prevention and treatment of COVID-19 and long COVID. During the pandemic, the level of PA decreased, especially in children and adolescents. Various types of movement and exercise including pulmonary respiratory exercises, aerobic and resistance exercises, yoga asanas (postures) and yogic breathing (pranayama) indicated benefit in the prevention of COVID-19 and in the treatment of long COVID resulting in an improvement in exercise capacity and lung function and a decrease in shortness of breath and fatigue. Physical activity is best avoided during acute COVID-19 but should be started within 2 to 3 weeks after the acute phase is resolved depending on a patient's symptoms and health status. Indeed, movement, exercise, and breathing are primary areas of interest for future research when exploring viral infections.

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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.163>:

- Table S1 Live Review Search Strategy

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APPENDIX 1: GLOSSARY OF TERMS

AMA	American Medical Association
AMR	Americas WHO region
AMSTAR	a measurement tool to assess systematic reviews
BMI	body mass index
COVID-19	coronavirus disease 2019
EMR	eastern Mediterranean WHO region
F-2-F	face to face
FITT-VP	frequency, intensity, time, type, volume, and progression.
MET	metabolic equivalent of task
Met-h	metabolic equivalents of task per hour
NCD	non-communicable disease
NHP	natural health product
PA	physical activity
PICO	population, intervention, comparator, outcome
PRME	pulmonary respiration muscle exercise
RCT	randomized controlled trial
RMT	respiratory muscle training
RoB	risk of bias
ROR	rate of recovery
SANRA	scale for the assessment of narrative review articles
SEAR	South-East Asian WHO region
WHO	World Health Organization
WPR	Western Pacific WHO region

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 compresses².

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 2020⁴ 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), <i>in vivo</i> (including animal studies), <i>in vitro</i> , or <i>in silico</i> (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 reviews¹⁰⁻³⁴ 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 (<i>Nerium oleander</i>), Datura, <i>Aconitum carmichaelii</i> (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	<i>Radix isatidis</i> , Ban-lan-gen, <i>Bupleurum</i> , <i>Coptis</i> , 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	<i>Withania somnifera</i>	Explore the potential of <i>Withania somnifera</i> in preventive and therapeutic interventions for COVID-19.
Lu et al., 2022 ²⁴	WPR	Prevention, Treatment	<i>Crocus sativus</i> , saffron, <i>Gardenia jasminoides</i>	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	<i>Andrographis paniculata</i> , <i>Artemisia annua</i> , <i>Artemisia afra</i> , <i>Cannabis sativa</i> , <i>Curcuma longa</i> , <i>Echinacea purpurea</i> , <i>Olea europaea</i> , <i>Piper nigrum</i> , and <i>Punica granatum</i> and phytochemicals 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	<i>Curcumae</i> rhizoma	Provide an overview of the active constituents of <i>Curcumae</i> rhizoma, their applications and mechanisms in infectious diseases.
Pérez et al., 2022 ²⁸	AMR	Treatment	<i>Cannabis sativa</i>	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, <i>Trypanosoma cruzi</i> , leishmania, and <i>Paracoccidioides brasiliensi</i>	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 reviews³⁵⁻⁷⁵ 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 review³⁸ 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	<i>Lonicera</i>	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, <i>Withania</i>	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, <i>Ephedra</i> , <i>Scutellaria</i> , <i>Zingiber</i> , 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 Qinqwen 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-1 β (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	<i>Lonicera</i> / 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 ³); When # of trials on outcome measure was > 10 , a funnel plot analysis was performed for reporting bias (Liu et al., 2020 ³). 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 $\geq 50\%$	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]; $I^2=29.9\%$; $p=.145$) 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 ≥0.10, or I^2 ≤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]) Signif 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, PaO ₂ , 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 ($p<.00001$), 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 ($p<.00001$), 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], $p\leq.00001$) 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], $p\leq.00001$).
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 ($I^2=95\%$)

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 cytoprotective²⁹ 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 count⁵⁸ 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 Thai¹⁰ 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 hepatoprotective¹⁶ 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 review⁷⁵ 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 review¹⁷ 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 pre-clinical 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 patients³⁰. 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 concern⁷⁶ 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 medicine⁸⁰ 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- α .

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 [WBC], 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- γ development by T-cells.⁸² As an anti-inflammatory, GA inhibits translocation of nuclear factor- κ B (NF- κ B) and suppresses TNF- α .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 function⁸⁴ and that it activates the immune system via actions of (1,4)- α -D-glucan on macrophages, activating them via TLR6, NF- κ B 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- κ B.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 study⁷⁵ 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 methodological. 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	NEU	neutrophil
ALP	Alkaline phosphatase	NFKappaB	Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)
ALT	Alanine transaminase	NHP	natural health products
AMR	Region of the Americas	NR	not reported
AMSTAR	A Measurement Tool to Assess systematic Reviews	NRC	non-randomised controlled trial
ARDS	Acute respiratory distress syndrome	OSF	Open Science Framework
ARR	adverse reaction reporting	PCT	procalcitonin
AST	aspartate aminotransferase	PICO	patient/population, intervention, comparison and outcomes
CBC	complete blood count	RCT	randomised controlled trial
CBM	Chinese Biomedical Literature Database,	QFPD	Qingfei Paidu decoction
CCNM	Canadian College of Naturopathic Medicine	RISS	Research Information Service System
CD	cluster of differentiation	RoB	risk of bias
CHM	Chinese Herbal Medicine	ROC	rate of conversion
CI	confidence interval	ROR	rate of recovery
CNKI	Chinese National Knowledge Infrastructure	RT-PCR	Reverse transcription polymerase chain reaction
CPM	Chinese Patent Medicine / Chinese Proprietary Medicine	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CRP	C-reactive protein	SEA	South-East Asia Region
CSTJ	China science and technology journal	Signif	significant
CWM	Conventional Western Medicine	SR	Systematic Review
ESR	estimated sedimentation rate	SSRN	Social Science Research Network
EMR	Eastern Mediterranean Region	Standard Care	Treatment routinely offered in a hospital setting. Also conventional care. May include traditional plus Western biomedical/ pharmaceutical treatment
EUR	European Region	TBIL	Total bilirubin
GAP	glycyrrhizic acid preparation	TCM	Traditional Chinese Medicine
GGT	gamma-glutamyl transferase	TLR	toll-like receptor
HI	herbal intervention	TNF	tumour necrosis factor
HIV	human immunodeficiency virus	VIP	Chinese Science and Technique Journals Database
Hs-CRP	high sensitivity C-reactive protein	VAL	viral assay level
IL-6	interleukin 6	WBC	white blood cell count
Impr	improved	WBS	white blood cells
Insignif	Insignificant	WPR	Western Pacific Region
LYM	lymphocytes		
MA	meta-analysis		
MDA	Malondialdehyde		
M ^{pro}	main protease		
mRNA	messenger RNA		
NCD	non-communicable diseases		

The Role of Nutraceuticals in the Prevention and/or Treatment of COVID-19: An Umbrella Review

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ABSTRACT

Background: To identify the results of published review literature regarding nutraceuticals, including probiotics, melatonin, poly-unsaturated fatty acids (PUFAs), quercetin, N-acetyl cysteine (NAC), and propolis as they relate to the prevention and/or treatment of COVID-19 (CV) and/or long COVID (long CV) and to outline key areas to consider for clinical application and for further research.

Methods: This paper is part of a six-part umbrella review which progresses from a living review. This review incorporates systematic reviews and narrative reviews as they relate to nutraceuticals. A live literature search occurred monthly in PubMed and Google Scholar from May 2022 to May 2023. Assessing the Methodological Quality of Systematic Reviews Version 2 (AMSTAR-2) scoring assessed systematic review quality, while the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines evaluated narrative reviews. Only those studies that were relevant to the nutraceuticals outlined above and that addressed COVID-19 prevention and/or treatment of CV and/or long CV were extracted from each review.

Results: Fifteen narrative reviews and 16 systematic reviews were included in this umbrella review. Studies indicate that nutraceuticals may be beneficial in improving the rate of recovery from various COVID-19 symptoms, rate of conversion parameters such as rate or duration of hospital stay and risk of intensive care unit (ICU) admission, and an improvement in various laboratory tests.

Conclusion/Summary: The broad antioxidant, anti-inflammatory, antiviral, and immune modulatory characteristics make the nutraceuticals included in this review reasonable choices for further research. Of the nutraceuticals discussed above, probiotics, melatonin, NAC, and quercetin indicate the greatest potential for benefit in the prevention and treatment of COVID-19 and long CV.

Key Words Anti-viral, anti-oxidant, anti-inflammatory, complementary therapies, immune system, naturopathic medicine, nutritional medicine, respiratory syndrome, SARS-CoV-2 vitamins, minerals

INTRODUCTION

The first cases of atypical pneumonia were reported in December of 2019 and quickly spread to all areas of the globe. Within 1 year of those first cases, COVID-19 was declared a pandemic by the World Health Organization (WHO; see Appendix 1 for a glossary of terms and acronyms used in this manuscript).¹ The development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, was a prominent focus during the pandemic,² with the aim of reducing the death rate and the number and severity of new cases of COVID-19.² Yet 3 years later, there remains a serious public health concern and the need for treatment and prevention is as great as ever, as even fully vaccinated individuals are not completely immune to infection.³ Early on in the pandemic,

many varied conventional and natural therapies were suggested as potential agents to reduce the risk of infection and improve the prognosis of the disease.⁴ In this umbrella review, a team of naturopathic researchers supported by the World Naturopathic Federation (WNF) examine the available literature of common natural health products used by patients that are available over the counter or prescribed by naturopathic practitioners and other traditional, complementary and integrative healthcare (TCIH) practitioners for the prevention and/or treatment of COVID-19 and long COVID (long CV). Nutraceuticals included in this review are melatonin, poly-unsaturated fatty acids (PUFAs), probiotics, quercetin, N-acetyl cysteine (NAC), and propolis.

The nutraceuticals are worth considering for respiratory infections based on their historic use. The understanding of their biochemical properties—defined as nutritionally-based natural

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health products that are not commonly classified as vitamins or minerals—justify the need to consider their value in the prevention and treatment of viral infections. For instance, NAC is established as a mucolytic nutrient with antioxidant properties and has been found to improve outcomes for acute respiratory distress syndrome and acute lung injury patients.⁵ Quercetin, a flavonoid found in fruits such as grapes, apples, strawberries, cloudberry, and raspberries and in vegetables such as onions, tomatoes, lettuce, and green beans,^{6–7} has demonstrated *in vitro* effects of increasing neutrophil chemotaxis, natural killer (NK) cell lytic activity, and inhibition of influenza A.⁸ *In vitro*, *in vivo*, and clinical studies have highlighted the broad spectrum of antiviral properties of propolis.⁹ Some common actions of these nutraceuticals include anti-inflammatory, antioxidative, immune-modulating, and antiviral mechanisms.^{5–10} Melatonin is regarded as a positive regulator of immune responses and a negative regulator of inflammation.¹¹ Lower melatonin levels are common in the elderly and, as there is a correlation between age and severity of COVID-19, there is value in considering the role of melatonin in COVID-19 prevention and treatment.¹² PUFAs have demonstrated effectiveness in preventing respiratory tract infections,¹³ and broad evidence indicates that intestinal immune cells interact with consumed probiotics, and this interaction improves host immune homeostasis and immune function. Furthermore, the meta-analyses investigating probiotic clinical interventions on respiratory tract infections (RTIs) indicates that probiotic use is associated with a lower incidence and duration of mild RTIs, in both children and adults.¹⁴

The aim of this paper is to review the available literature on probiotics, melatonin, PUFAs, quercetin, NAC, and propolis with the goal of describing the published peer review literature and identifying key areas to consider for research and clinical application in the treatment of COVID-19.

METHODS

Design

This umbrella review began as a high-level live review monitoring of all narrative and systematic reviews on nutraceuticals and natural treatments for the prevention and symptomatic management of COVID-19 and its sequelae.¹⁵ The umbrella review is part of a six-part review in which this paper focuses on a group of nutraceuticals that are likely of value for the treatment of COVID-19 but do not fit neatly into other categories, such as herbal medicines, vitamins, or minerals. While narrative reviews are not typically included in an umbrella review, this paper included those that met specific criteria in order to provide context to the rationale for considering nutraceuticals in the prevention and/or treatment of COVID-19 and long CV.

Search Strategy

Over the course of 1 year (May 2022–May 2023), monthly literature searches were performed to collect the current and emerging data on natural prevention or treatment of COVID-19. Searches followed Cochrane Guidelines for a live systematic review.¹⁶ PubMed and Google Scholar were searched using the following terms:

“natur*,” “herb*,” “nutraceutical,” “botanical,” “medicinal plant,” “fish oil,” “quercetin,” “melatonin,” “vitamin,” “mineral,” combined with “prevention,” “prophylaxis,” “deficiency,” “treatment,” “management,” and “*COVID*,” “Coronavirus,” “SARS-CoV-2.” Individual names of nutraceuticals, compounds, vitamins, minerals and other health protocols were also searched. These papers were then classified as systematic reviews, narrative reviews, meta-analyses, or other based on their description in the abstract.

Inclusion/Exclusion Analysis

Narrative reviews and systematic reviews from the live review were eligible for inclusion in this paper if they were related to the use of the nutraceuticals for the prevention or treatment of COVID-19. Both review types were appraised by at least two blinded reviewers, systematic reviews based on the Assessing the Methodological Quality of Systematic Reviews Version 2 (AMSTAR-2) guidelines¹⁷ and narrative reviews according to the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines.¹⁸ Systematic reviews were included if the review authors, at least partially, accounted for risk of bias (RoB) in individual studies and used a satisfactory technique for assessing the RoB. Narrative reviews were included if the scientific reasoning score was 1 or 2 and the overall total sum >5. Nutraceuticals that appeared in more than three systematic reviews after AMSTAR-2 assessment were included.

PICO eligibility criteria requirements for study inclusion were as follows:

Population: Clinical/observational (humans of any age/gender, any setting), *in vivo* (including animals), *in vitro*, or *in silico* studies.

Intervention: probiotics, melatonin, PUFAs, quercetin, N-acetyl cysteine (NAC), and propolis.

Comparison: No comparator limitation.

Outcome: Symptoms, biological markers, diagnostic criteria, or viral traits related to severe acute respiratory syndrome, viral respiratory tract infections, or COVID-19.

Excluded were secondary analyses, literature reviews, editorial discussions, best practice guidelines, and book chapters. To ensure that results were not overstated, researchers utilized a citation overlap analysis to track the duplication of papers. Due to the diverse topics covered in this umbrella review, a sub-analysis of overlap was also conducted focusing on each of the nutraceuticals covered. The overlap was categorised as “slight” (0%–5%), “moderate” (6%–10%), “high” (11%–15%), or “very high” (>15%) (see Table S1 in the supplemental material for full details of the overlap analysis).

Data Extraction

Data extraction for the systematic and narrative reviews was completed using separate shared, online spreadsheets. Some reviews covered topics that spanned multiple categories of the umbrella review, but only outcomes related to nutraceuticals were extracted for this paper.

Narrative reviews were included to highlight the therapeutic considerations and known mechanism of action of each criterion. The data extracted from the narrative reviews included study number, study identification, citation in American Medical Association (AMA) style, author(s), date, journal, country/world region, review objective, details of any search conducted, area of focus (prevention, treatment, long CV), and therapeutic considerations, including properties (anti-inflammatory, antiviral, etc.), based on the therapeutic properties outlined on https://www.ndhealthfacts.org/wiki/Action_of_Herbs and associations to other vitamins, minerals, or pathways.

The data extracted from the systematic reviews included study number, study identification, citation in AMA style, author(s), date, journal, country/world region, area of focus (prevention, treatment, long CV), review objective, review type (narrative, systematic, or meta-analysis), search date, search databases, study designs included, countries included in the studies, publication date range, tools for assessment of risk of bias and methods of synthesis/analysis. The study results data extracted included the intervention or exposure assessed, the outcomes measured, the number of studies included in the synthesis, the number of participants included in the studies, the age of the participants, the sex of the participants, the results or findings and results of heterogeneity analysis (if applicable). An overview of the umbrella review process is presented in Figure 1.

RESULTS

Narrative Reviews

Given that the role of nutraceuticals in the prevention and treatment of COVID-19 is relatively new, narrative reviews were included as they provide an overview of the biochemical properties, and potential therapeutic considerations and they complement the details of the systematic reviews. Of the 93 narrative reviews included in the live review, 16 were originally identified for the nutraceuticals section and 15 were included (see Table 1).¹⁹⁻³³ Of those, 6 were from the region of the Americas (Brazil,^{19,20} Argentina,²¹ Canada,²² Mexico,²³ USA²⁴), 5 from the European region (Italy,^{25,26} Denmark,²⁷ Romania,²⁸ Russia²⁹), 2 from the South-East Asia region (India,³⁰ Korea³¹), and one each from the Western Pacific region (Australia³²) and Eastern Mediterranean region (Iran³³). The individual nutraceuticals covered by these reviews included melatonin,^{20,21,25,26,28,29,31,33} quercetin,^{23,26,27,30,31} PUFAs,^{22,24,27,32} probiotics,^{19,24,32} and NAC.²⁸

Systematic Reviews

The live review included 308 systematic reviews, of which 43 were initially identified as containing reporting about nutraceuticals; 15 were included (see Table 2).³⁴⁻⁴⁸ The included systematic reviews were conducted in the Western Pacific region (WPR),³⁴⁻³⁹ European region (EUR),^{40,41,42} region of the Americas (AMR),⁴²⁻⁴⁵ South-East

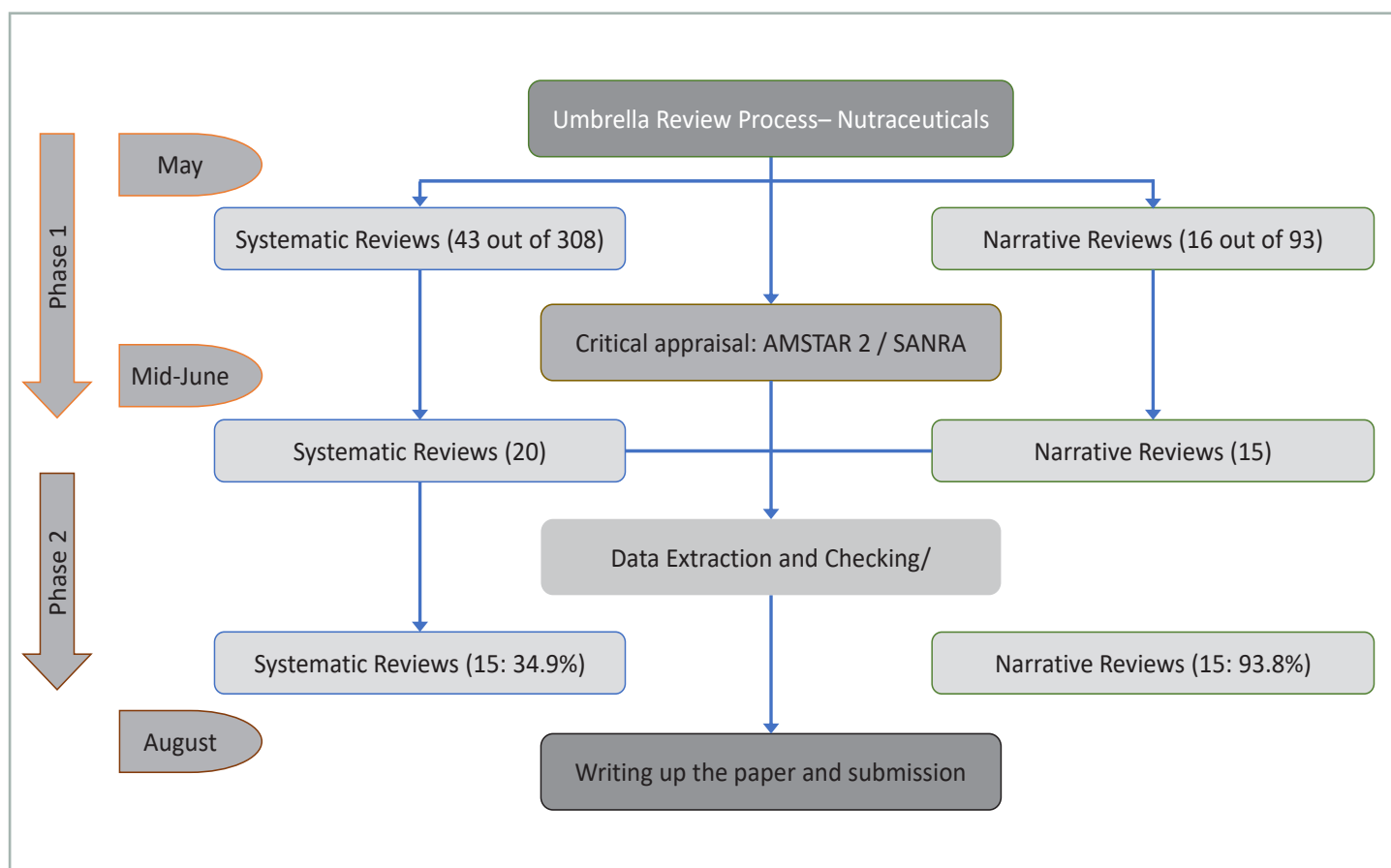


FIGURE 1 Umbrella review process — nutraceuticals

TABLE 1 (Part 1 of 2) Narrative Reviews – Nutraceuticals

First Author, Publication year (study #)	Area of Focus	WHO Region / Country	SANRA Score / Search details (Y or N)	Therapies Investigated	Properties / Association (if listed in paper)	Therapeutic Considerations
Bader-Larsen KS et al., 2021 ²⁷ (125)	Treatment	EUR / Denmark	11 / N	PUFAs (P)	P: anti-inflammatory, immune modulating	P: may play a role in decreasing the severity of CV infection by inhibiting cellular viral entry, suppressing the production of pro-inflammatory cytokines, and increasing the phagocytic capacity of the innate immune system.
Choe K et al., 2022 ³¹ (22)	Treatment	SEA / Korea	7 / Y	Melatonin (M)	M: Anti-inflammatory, neuroprotective, immunoregulation / regulating effects against neurodegenerative diseases associated with oxidative stress, neuroinflammation, and mitochondrial dysfunction.	M: may reduce CV-associated complications, as has been suggested to block the nuclear translocation of NF-κB, expression of c-Fos, and suppression of matrix metalloproteinases-3 (MMP-3), which are responsible for pro-fibrotic and pro-inflammatory cytokine production. Has shown promising regulating effects against neurodegenerative diseases associated with oxidative stress, neuroinflammation, and mitochondrial dysfunction.
Cardinali DP et al., 2022 ²¹ (279)	Long CV	AMR / Argentina	9.5 / Y	Melatonin (M)	M: antioxidant, anti-inflammatory, immunomodulatory	M: may reduce delirium and restore circadian imbalance seen in ICU CV patients; aids in the prevention of comorbidities, including diabetes, metabolic syndrome, and ischemic and non-ischemic CVD; neuroprotective and may help to control cognitive deterioration.
Gareau MG et al., 2023 ²⁴ (353)	Long CV	AMR / USA	7 / N	Probiotics (Pr) PUFAs (P)	Pr / P: anti-inflammatory, supportive role in gut microbiome / microbiota–gut–brain axis (MGB), gut–lung axis	Pr / P: improved MGB which may decrease long CV symptoms and decrease brain fog and neurological impairments, decrease in chronic dysbiosis, improved gut–lung axis.
Hosseini A et al., 2022 ³³ (299)	Prevention, Treatment	EMR / Iran	11.5 / Y	Melatonin (M)	M: antioxidant, anti-inflammatory; increases antioxidant enzymes (e.g., superoxide dismutase), decreasing preoxidative enzymes (e.g., nitric oxide synthase) and as a free radical scavenger	M: adjuvant and a potential alternative for the better management of SARS-CoV-2 infection in high-risk populations.
Inchingolo AD et al., 2021 ²⁵ (347)	Long CV	EUR / Italy	7 / N	Melatonin (M)	M: anti-inflammatory, antioxidant	M: may assist long haulers affected by chronic symptoms (chest and heart pain, intestinal disorders, headache, difficulty concentrating, memory loss, and tachycardia)
Notarbartolo V et al., 2022 ²⁶ (260)	Prevention, Treatment	EUR / Italy	12 / Y	Melatonin (M) Quercetin (Q)	M: immune modulating, anti-inflammatory. Q: antiviral, viricidal; inhibits activation of NF-κB, modulation of the acid sphingomyelinase / ceramide system, increase in neutrophil chemotaxis, NK-cells' activity and macrophages' phagocytosis. Increase in lymphocyte proliferation and regulation of IFN-γ secretion; inhibit SARS-CoV-2 proteins 3CL and PLpro.	M: Inhibits viral replication so theoretically it may inhibit SARS-CoV-2. Significant improvement in respiratory symptoms (cough, dyspnea) and fatigue, as well as a significant reduction in CRP serum levels and an improvement in the chest X-ray. Inhibits the expression of inflammasome genes, the inflammasome activation and the translocation and expression of NF-κB. Q: expected to reduce viral replication and support adaptive immunity for faster clearance of the virus.
Paudel KR et al., 2022 ³² (331)	Prevention, Treatment	WPR / Australia	7 / Y	Probiotics (Pr) PUFAs (P)	Pr / P: immune-modulating, anti-inflammatory	Pr / P: modulate local immunity (by maintaining the well-being of the gut microbiome and boosting gut health) and systemic immunity (by stimulating specific/non-specific immune response).

TABLE 1 (Part 2 of 2) Narrative Reviews – Nutraceuticals

First Author, Publication year (study #)	Area of Focus	WHO Region / Country	SANRA Score / Search details (Y or N)	Therapies Investigated	Properties / Association (if listed in paper)	Therapeutic Considerations
Pisoschi AM et al., 2022 ²⁸ (262)	Prevention, Treatment	EUR / Romania	6 / N	NAC (N), Melatonin (M)	N: mucolytic, antioxidant, anti-inflammatory, immunomodulatory M: antioxidant, anti-inflammatory, immunomodulatory, antiviral	N: Oral and intravenous glutathione, as well as precursors like NAC and alpha lipoic acid, constitute therapeutic alternatives to block NF-κB, hamper cytokine storm, and alleviate respiratory symptoms in CV pneumonia Q: may assist in regulating platelet aggregation, blood coagulation, fibrinolysis, and NO production due to their action on multiple receptors and enzymes
Quintal Martínez JP et al., 2022 ²³ (325)	Treatment	AMR / Mexico	11.5 / Y	Quercetin (Q)	Q: antiplatelet, anticoagulant, fibrinolytic, and nitric oxide regulating effects	
Savant S et al., 2021 ³⁰ (108)	Treatment	SEA / India	8 / N	Quercetin (Q) Probiotics (Pr) PUFA (P)	Q: antiviral, antioxidant, hypolipidemic / inhibitor of SARS-CoV-2 3CL, affects ACE2 expression, inhibits NF-κB pathway, reduces expression of pro-inflammatory cytokines (IL-6) Pr: anti-inflammatory / gut-brain axis P: anti-inflammatory / hypolipidemic, regulates fat oxidation by enhancing β-oxidation, improves insulin sensitivity, anti-hyperglycemic function	Q: broad antiviral properties which may be beneficial in the treatment of CV. Pr: may decrease the spread of infection and decrease duration P: may be beneficial in the management of CV.
Shchetinin E et al., 2022 ²⁹ (78)	Treatment	EUR / Russia	7.5 / N	Melatonin (M)	M: antioxidant, anti-inflammatory, antifibrotic, psychotropic, antiviral / decreases the levels of IL-2, IL-4, and IFN-γ. Improves sleep.	M: ROC: may decrease mortality, may improve survival of intubated patients and may reduce the risk of delirium in ICU patients. Reduces the risk of thrombosis and sepsis. Labs: may result in a decrease in positive PCR-test for SARS-CoV-2, decrease in CRP levels, and improved CT lung scan.
Trivedi P et al., 2022 ²² (237)	Treatment	AMR / Canada	7 / N	PUFAs (P)	P: Anti-inflammatory	P: likely to be beneficial in reducing systemic inflammation in CV patients.
Xavier-Santos D et al., 2022 ¹⁹ (715)	Treatment	AMR / Brazil	7 / Y	Probiotics (Pr)	Pr: antiviral, immunomodulatory, anti-inflammatory, inhibition of microbial adherence, enhancement of the gut barrier function	Pr: may contribute to reducing the duration of the disease and the severity of symptoms such as fatigue, olfactory dysfunction and breathlessness, nausea and vomiting and other gastrointestinal symptoms. Caution: Not recommended for immunocompromised patients on corticosteroid therapy
Xerfan E et al., 2022 ²⁰ (297)	Prevention / Treatment	AMR / Brazil	8 / Y	Melatonin (M)	M: anti-inflammatory, antioxidant / Role in circadian rhythmic balance, participates in immunomodulatory, metabolic and endocrinological processes	M: Possible direct role of SARS-CoV-2 in the pineal gland/hypothalamus-pituitary axis, and in melatonin receptors in the olfactory bulb. Circadian rhythm dysregulation leads to sleep disturbance which impacts immune function. Melatonin helps regulate circadian rhythms.

3CL = 3C-like proteinase; ACE2 = angiotensin-converting enzyme 2; AMR = region of the Americas; CRP = C-reactive protein; CT = computed tomography; CV = COVID-19; CVD = cardio-vascular disease; EMR = Eastern Mediterranean region; EUR = European region; ICU = intensive care unit; IFN = interferon; IL = interleukin; long CV = long COVID; M = melatonin; MGB = microbiota-gut-brain axis; MMP-3 = matrix metalloproteinase-3; N = no; NAC = N-acetyl cysteine; NF = nuclear factor; NK = natural killer; NO = nitric oxide; P = PUFAs; PCR = polymerase chain reaction; PLpro = papain-like protease; Pr = probiotics; PUFA = poly-unsaturated fatty acids; Q = quercetin; ROC = rate of conversion; SANRA = Scale for the Assessment of Narrative Review Articles; SARS-CoV-2 = severe acute respiratory syndrome caused by Coronavirus 2; SEA = Southeast Asian region; USA = United States of America; WHO = World Health Organization; Y = yes.

TABLE 2 (Part 1 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Search Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Aldhafiri FK et al., 2022 ⁴⁶ (714)	Treatment / SEA / Saudi Arabia	8 / RCTs, prospective cohorts, varied / 2019–2022 / PubMed, Embase, Cochrane library, CNKI / PRISMA	PUFAs (P) various dosages Probiotics (Pr) P and Pr compared to CWM and placebo.	P 2013, Pr 1111 / NS / NS	Efficacy ROC : duration ROR : gastrointestinal Labs/Imaging : inflammation, renal, respiratory QoE : CI and RR determined for each intervention.	Improved ROR : P and Pr may shorten duration of COVID-19. Improved ROR : Pr direct effect on GI symptoms, P decreased inflammation, P improved levels of several respiratory and renal functions in critically ill COVID-19 patients.
Arentz S et al., 2021 ³⁴ (675)	Treatment / WPR / Brazil	1 / RCT / 29 April – 15 August 2020 / PubMed, Embase, Central, AMED, Alt Health Watch, medRxiv, bioRxiv, clinicaltrials.gov, ISRCTN, WHO ICTRP / Cochrane RoB-2	Propolis (B) 400 mg to 800 mg QD compared with CWM.	124 / adults mean 50 (± 12.8) / all genders	ROC : duration, severity, ROR, ICU admissions, oxygen dependency, AR QoE : low due to small number of studies and differences in study designs.	Impr ROC : decreased duration of hospital admissions; reduced risk of shock, respiratory failure and kidney injury. No ROC impr : duration of oxygen therapy, risks of ICU admission
Cheema HA et al., 2023 ⁴⁷ (761)	Treatment / SEA / Pakistan	6 / RCT, MA / database inception until 5 October 2022 / PubMed, Cochrane Library, Embase	Quercetin (Q) 260 to 1000 mg QD compared with CWM.	951 / all ages / all genders	ROC : risk of ICU admission, incidence of hospitalization, mortality QoE : low risk of bias, yet some concerns with randomisation	Improved ROC : decreased the risk of ICU admission (OR=0.31, 95% CI: 0.10–0.99, $I^2=0\%$) and the incidence of hospitalisation (OR=0.25, CI: 0.10–0.62, $I^2=0\%$). No ROC improvement : no decrease in risk of all-cause mortality.
Chen CH et al., 2023 ³⁵ (763)	Treatment / WPR / Taiwan	4 / RCTs (3) and observational study / inception to 14 May 2022 / Cochrane Library, PubMed, Embase, Web of Science, and SCOPUS / Cochrane RoB-2	NAC (N) compared to CWM and control	355 / 58.4 $\pm$ 4.9 / NS /	ROC : intubation rate, duration of hospital and ICU, mortality QoE : very low due to small number of patients included in the RCTs.	Non-sig ROC : RCTs negative for all primary and secondary outcomes; non-randomized studies were mixed with high degrees of heterogeneity regarding in-hospital mortality; respiratory outcome, duration of ICU stay, and hospital stay.
Dilokthornsakul W et al., 2022 ³⁶ (673)	Treatment / WPR / Brazil, Turkey, Egypt, Pakistan, Iran	15 / RCT, case reports / series / database inception to April 2021 / PubMed, Scopus, ScienceDirect, Cochrane Library / Cochrane RoB	Propolis (B) (various dosages and strains) lab changes, 3 RCT compared with CWM.	569 / 18–65, avg female 52, avg male 38 / all genders	ROR : clinical symptoms Binding affinity : SARS-CoV-2 ACE2, protease enzyme, RNA polymerase as the target enzyme, spike protein subunit. QoE : ranged from low to high	Improved ROR : fever, dry cough, shortness of breath, sore throat, chest pain, headache, muscular pain, diarrhea, runny nose, sore larynx, fatigue, nausea, vomiting, dizziness. May help with prevention High binding affinity : to SARS-CoV-2 ACE2, to main protease enzyme, to spike protein subunit 1.

TABLE 2 (Part 2 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Faridzadeh A et al., 2022 ⁴⁸ (733)	Treatment / EMR / Iran	10 / RCTs (5), CTs (3), ORC (2) / Oct 2021 – Jan 2022 / Web of Science, PubMed / MEDLINE, Cochrane Library, SCOPUS / Cochrane RoB tool	Melatonin (M) adjunctive tx	665 / 18 ± 72 / 93 females, 130 males	ROR : platelet aggregation ROC : recovery time, mortality, incubation Labs : inflammatory markers QoE : low due to small number of studies and differences in study designs.	Improved ROR : thrombosis and sepsis in severe cases Improved ROC : recovery time, mortality rate, incubation outcomes Improved labs : decreased inflammatory markers, expression of some genes, including the STAT4, STAT6, T-bet, GATA binding protein 3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1 (CASP1).
Lan SH et al., 2022 ³⁷ (678)	Treatment / WPR / China	3 / RCTs, MA / April – Aug 2020 / PubMed, Web of Science, Cochrane Library, Ovid MEDLINE, clinicaltrials.gov / Cochrane RoB	Melatonin (M) – 3 to 6 mg dosage, 7- to 14-day duration compared with CWM and control	86 / NS / NS	ROC : ROR, risk of ICU admission, mortality. QoE : low due to small number of studies and differences in study designs.	Improved ROC : clinical recovery rates were higher (OR 3.67; 95% CI: 1.21 – 11.12; $I^2=0\%$, $p=0.02$). Risk of ICU admission (8.3% vs. 17.6%; OR 0.45; 95% CI: 0.16 – 1.25; $I^2=0\%$, $p=0.13$). Risk of mortality lower (1.4% [1/72] vs. 4.4% [3/68], OR 0.32; 95% CI: 0.03 – 3.18; $I^2=0\%$, $p=0.33$).
Neris AVS et al., 2022 ⁴² (737)	Treatment / AMR / Turkey, Italy, Mexico, China, Russia	9 / clinical trials, cohort studies / inception through 16 March 2022 / PubMed, Embase, Scopus, Web of Science, ICTRP, BioRxiv / Cochrane RoB 2 and ROBINS	Probiotics (Pr) (various strains) along with CWM	1410 / 18–77 / 6 studies both genders, 3 only males	ROR : overall symptoms, cough, headaches, diarrhea ROC : hospital stay, blood oxygenation, ICU admissions, invasive mechanical ventilation Labs : inflammatory markers, CBC, albumin, IgM, IgG QoE : low due to lack of homogeneity between studies and strains of probiotics.	Sig Improved ROR : symptoms 51% reduction (RR 0.49, 95% CI 0.40–0.61), cough (RR 0.56, 95% CI 0.37–0.83), headaches (RR 0.17, 95% CI 0.05–0.65), and diarrhea (RR 0.33, 95% CI 0.12–0.96). Improved ROC : decreased hospital stay, decreased secondary infection, decreased ICU admissions and invasive mechanical ventilation, increased blood oxygenation. Improved labs : CRP, IgM, IgG, ESR, albumin, LYM, PLT, LEU, NK, IL-6

TABLE 2 (Part 3 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Paraskevas T et al., 2023 ⁴⁰ (755)	Treatment / EUR / Italy and others not specified	8 / RCT, retrospective observational study, pros cohort, MA / database inception to Sept 2022 / PubMed, Medline, Embase / Cochrane RoB	NAC (N) along with CWM	21141 / >18 years / any sex / Italy plus others not stated	ROR: dyspnea, walking distance ROC: necessity for mechanical and non-invasive ventilation, rate of endotracheal intubation, ICU admissions, mortality, supplemental oxygen, rate of respiratory failure Labs: liver function Imaging: chest computed tomography scan QoE: low due to small number of studies and differences in study designs.	Non-sig ROR: RCTs negative for all primary and secondary outcomes; non-randomized studies were mixed with high degrees of heterogeneity regarding in-hospital mortality. Improved ROR: Observational studies suggest favorable results yet have a high degree of heterogeneity.
Pechilvanidou E et al., 2022 ⁴¹ (610)	Treatment / EUR / Mexico	1 / CT / PubMed, CINAHL, Cochrane, database inception to April 2021 / NS	NAC (N) and melatonin (M) along with other NHPs – treatment every 12 h for 5 days	110 / avg 58 / all	ROC: survival rates Labs: inflammation markers, PCT QoE: low due to small number of studies and differences in study designs.	Improved ROR: survival scores Labs: IL-6 decreased (N), CRP decreased (N and M), in NAC and melatonin; PCT decreased (N)
Sobrinho RCS et al., 2022 ⁴³ (692)	Treatment / AMR / Turkey, Canada, Egypt, Indonesia, India, Brazil, Iran	13 / RCT and others / December 2021 to April 2021 / Central, PubMed, Scielo, Scholar Goggle, SCOPUS, Web of Science / Cochrane RoB	Propolis (various strains) compared with CWM	105 / NS / all genders	ROC: efficacy, length of hospitalization, clinical outcome Binding affinity: SARS-CoV-2 ACE2, protease enzyme, RNA polymerase as the target enzyme, spike protein subunit. QoE: low due to small number of studies and differences in study designs.	Potentially improved ROR: varied results, but some studies indicated decreased hospitalization and improved clinical outcomes. Varied results re: binding affinity: interaction with main protease less than remdesivir, but greater than hydroxychloroquine. B has potential to inhibit binding of virus to ACE2.
Wang XC et al., 2022 ³⁸ (736)	Treatment / WPR / Iran	6 / RCT / Dec 2019 – June 2022 / PubMed, Embase, Web of Science, Cochrane library, clinicaltrials.gov / NS	Melatonin in combination with CWM + control group.	338 / 18-65 / all / Iran	ROR: clinical recovery rate Labs: CRP, SaO2, WBC QoE: low due to small number of studies and differences in study designs.	Improved ROR: improvement in symptoms, improves quality of life when combined with CWM Improved ROR: clinical recovery rate (OR 3.05, 95% CI: 1.47–6.31; $p=.003$). No sig difference in labs. Reduced adverse reactions
Xavier-Santos D et al., 2022 ⁴⁴ (690)	Treatment / AMR / Austria, Romania, Japan + 34 other countries	84 / clinical studies, other studies / Scopus	Probiotics (Pr) (various strains) compared with CWM + Pr	4423 / 1–99 / NS	ROR: gastrointestinal and microbiota, general symptoms ROC: efficacy, prevention Labs: viral entry QoE: low due to small number of studies and differences in study designs.	May decrease risk of infection. Improved ROR: decrease symptoms due to inflammation, decrease diarrhea. Improved ROR: decrease cytokine storm, improved intestinal microbiota, improved immune response, decrease secondary infection, improved gut-brain and gut-lung barriers. Improved labs: NK cells, block viral entry by binding with RdRp, RBD and ACE2, decreased IL-6, increased IL-10

TABLE 2 (Part 4 of 4) Systematic Reviews – Nutraceuticals

First Author, Publication Date (study #)	Area of Focus / WHO Region / Countries in Study	Number of Studies / Design Method / Search Date / Search Databases / Risk of Bias	Intervention	Participants: Number / Age / Sex	Review Objectives and Measurements	Findings
Yao J et al., 2022 ³⁹ (677)	Treatment / WPR / NS	5 / RCTs, MA / database inception until 16 September 2021 / PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, clinicaltrials.gov / Cochrane RoB	Propolis (P) and quercetin (Q) compared with CWM + flavonoids (B and Q), compared with controls	1060 / no restriction / all genders	ROR : symptoms ROC : necessity for oxygen, hospitalization duration, rate requiring mechanical ventilation, ICU rates, mortality Labs : IL-6, IL-8, TNF-alpha, RT-PCR clearance QoE : low due to small number of studies and differences in study designs.	Sign improved ROR : decreased time for alleviation of symptoms (WMD=-4.92, 95% CI: -7.46 to -2.37, $p<.001$) Sig improved ROC : decreased number patients needing oxygen, hospitalization and mechanical ventilation, decreased ICU days and mortality. Improved labs : decreased time for RT-PCR clearance vs control (WMD: -4.11, 95% CI: -4.54 to -3.68, $p<0.001$) No adverse effects reported
Zhu J et al., 2023 ⁴⁵ (767)	Treatment / AMR / USA, Italy, Russia, Mexico, Spain, India	8 / RCTs, MA / database inception until 31 July 2022 / PubMed, Cochrane Library, Embase, CINAHL, clinicaltrials.gov, Cochrane Central Register of Controlled Trials, PROSPERO / Cochrane RoB	Probiotics (various strains) compared to CWM + Pr	1027 / any age / 49.2% male, 50.8% female	ROR : cough, dyspnea, diarrhea, gastrointestinal symptoms, respiratory symptoms ROC : mortality, rate of recovery Labs : CRP QoE : heterogeneity assessed	Improved ROR : improved cough and dyspnea (RR 0.37 [0.19 to 0.73]), diarrhea (RR 0.61 [0.43 to 0.87]) Improved ROC : larger effect in hospitalized patients (RR 0.13 [95% CI 0.05 to 0.39]) Uncertain change in labs : CRP Reduced adverse events

ACE2= angiotensin-converting enzyme 2; AMED=Allied and Complementary Medicine Database; AMR=region of the Americas; AP=adverse reactions; B=propolis; CBC=complete blood count; CI=confidence interval; CINAHL=Cumulated Index to Nursing and Allied Health Literature; CNKI=China National Knowledge Infrastructure; CRP=C-reactive protein; CT=clinical trials; CWM=conventional western medicine; EMR=Eastern Mediterranean region; EUR=European region; GI=gastrointestinal; ICU=intensive care unit; IgG=immunoglobulin G; IgM=immunoglobulin M; IL6=interleukin-6; ISRCTN=International Standard Randomised Controlled Trial Number; M=melatonin; MA=meta-analysis; NAC=N-acetyl cysteine; NK=natural killer; NS=not stated; OR=odds ratio; ORC=observational retrospective cohorts; PCT=procalcitonin; Pr=probiotics; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO=International Prospective Register of Systematic Reviews; PUFA=polyunsaturated fatty acid; Q=quercetin; QD=every day; QoE=quality of evidence; RBD=receptor binding domain; RCT=randomized controlled trial; RdRp=RNA-dependent RNA polymerase; ROC=rate of conversion; ROR=rate of response; RR=relative risk; RT-PCR=reverse transcriptase polymerase chain reaction; SaO2=arterial oxygen saturation; SARS-CoV-2= severe acute respiratory syndrome caused by Coronavirus 2; SEA=South-East Asian region; Sig=significant; TNF=tumour necrosis factor; WBC=white blood cell; WHO ICTRP=World Health Organization International Clinical Trials Registry Platform; WHO=World Health Organization; WMD=weighted mean difference; WPR=Western Pacific region.

Asia region (SEA)^{46,47} and Eastern Mediterranean region (EMR)⁴⁸ and covered the following nutraceuticals: melatonin,^{37,38,41,48} probiotics,^{42,44–46} NAC,^{35,40,41} propolis,^{34,36,39,43} quercetin^{39,47} and PUFAs.⁴⁶ The overlap analysis of the included systematic reviews found 2.6% overlap, which is classified as a “slight” overlap. Sub-analyses by nutraceutical category found “very high” for the reviews covering flavonoids (20%), PUFAs (24.2%), propolis (25%), and NAC (25%). “Slight” overlap was found for probiotics (1.3%). Melatonin was only covered in one systematic review and as such the overlap was nil.

Five papers included multiple nutraceuticals and although specific nutraceuticals were listed as being included in the review, those that did not provide adequate details were excluded. Reviews were excluded if they did not refer to COVID-19. Only individual nutraceuticals that had at least three reviews were included.

Melatonin

Eight narrative reviews addressed the clinical and biochemical properties of melatonin as it relates to COVID-19 treatment and/or prevention. The anti-oxidant ($n = 3$), anti-inflammatory ($n = 6$), and immune modulating ($n = 4$) properties were the main focus of the narrative reviews on melatonin.^{20,21,26,28,29,30,33} Several of the reviews suggested that the actions of melatonin may be valuable for reducing complications from COVID-19 via suppression of the cytokine storm as well as improving long-term outcomes via neuroprotective effects,^{26,29,31} and sleep regulation.^{20,21,29} The benefits of melatonin in high-risk, aging populations and in those with long CV was also covered.^{25,29,33}

Four systematic reviews included melatonin as an intervention. These focused mainly on antioxidant and immunomodulatory properties of melatonin clinical outcomes, including changes in laboratory biomarkers indicating a decrease in inflammation,^{41,48} and three reported on improved rates of recovery.^{37,38,48} Lan et al. (2022)³⁷ included a meta-analysis of three small studies, only one of which was double-blinded, which showed a statistically significant improvement in clinical recovery rate (odds ratio [OR]: 3.67; 95% confidence interval [CI]: 1.21–11.12; $P = 0\%$, $p = .02$) for patients with COVID-19 treated with melatonin compared with those treated with placebo, but no significant difference in the risk of intensive care unit (ICU) admission (OR: 0.45; 95% CI: 0.16–1.25; $P = 0\%$, $p = .13$), mortality (OR: 0.32; 95% CI: 0.03–3.18; $P = 0\%$, $p = .33$), the rate of CRP (C-reactive Protein; an inflammatory marker) normalization (OR: 1.14; 95% CI: 0.34–3.89; $P = 0\%$, $p = .83$), or values of follow-up CRP (mean difference [MD], -1.03 ; 95% CI: -3.47 to 1.42 ; $P = 0\%$, $p = .41$). Wang et al. (2022)³⁸ reported better total effective rate among patients with COVID-19, 18 years of age and older, who were treated with melatonin plus conventional treatments compared with conventional treatments alone (OR = 3.05, 95% CI: 1.47–6.31; $p = .003$) in a meta-analysis of six small studies. Again, no significant difference was found for the biomarkers CRP (weighted mean difference [WMD] = -0.36 , 95% CI: -3.65 to 2.92 , $p = .83$), arterial saturated oxygen (SaO_2) (WMD = 1, 95% CI: -1.21 to 3.22 , $p = .37$), or white blood cell (WBC) count (WMD = -1.07 , 95% CI: -2.44 to 0.30 , $p = .13$).

Probiotics

The four narrative reviews discussing probiotics focused on their potential for prevention through the beneficial manipulation of the gut microbiome.^{19,24,30,32} Probiotics were ascribed actions such as antiviral^{19,30} and anti-inflammatory,^{19,30,32} mostly in the context of maintaining a functional gut lining and attenuating local and systemic immunity³² and limiting downstream gut–lung mucosal immune responses.²⁴ Through the microbiome–gut–brain axis and the gut–lung axis, probiotics were argued to have the potential to reduce the risk of COVID-19 incidence as well as long CV symptoms.²⁴

The four systematic reviews that included studies investigating probiotics all suggested to some degree that the immune modulatory effects of probiotics, likely due to improvement of mucosal barriers of the gut and lung and associated immune monitoring, may be protective against SARS-CoV-2 infection.^{40,42,44,46} Three of the studies emphasized the benefits of probiotics for gastrointestinal symptoms due to COVID-19.^{40,42,44} Neris et al. (2022) indicated that probiotics were associated with a significant 51% reduction in symptoms reported by COVID-19 patients (relative risk [RR] 0.49, 95% CI: 0.40–0.61). There was a significant improvement in cough (RR 0.56, 95% CI: 0.37–0.83), headaches (RR 0.17, 95% CI: 0.05–0.65), and diarrhea (RR 0.33, 95% CI: 0.12–0.96) of patients on probiotic therapy. These findings suggest that probiotic supplementation is effective in improving symptoms of COVID-19.⁴²

N-Acetyl Cysteine

The one narrative review exploring the value of NAC highlighted its antioxidant, mucolytic, anti-inflammatory, and immune modulating properties and indicated that NAC can alleviate oxidative stress and dampen the cytokine storm, thus having a protective effect on organ damage.²⁸ It described the NAC as able to reduce inflammation by blocking the nuclear factor kappa B (NF-kappa B) pathway, as a precursor to glutathione, and as a free radical scavenger.²⁸

Three systematic reviews included NAC, of which two reported on studies focused on NAC alone^{35,40} and one synthesized study involving NAC alongside other nutraceuticals.⁴¹ While one systematic review did find that NAC can reduce inflammatory markers interleukin-6 (IL-6), CRP, and procalcitonin (PCT),⁴¹ none of the systematic reviews found a relation between NAC treatment and reduced hospital stays, ICU admissions, or mortality.^{35,40}

Quercetin

Two of the three narrative reviews describing research related to quercetin emphasized its antiviral, antioxidant, and hyperlipidemic properties.^{26,30} Savant et al. (2021) stated quercetin has broad antiviral properties and is specifically an inhibitor of SARS-CoV-2,³⁰ while Quintal Martinez et al. (2022) highlighted quercetin's antiplatelet, anticoagulant, fibrinolytic, and nitric oxide (NO) regulating effects.²³ The reviews suggest that, due to its antiviral activity and other targets of action, quercetin could play a role in prevention and to help reduce recovery time from COVID-19.

The two systematic reviews on quercetin focused on the treatment benefits of supplementation, and both reported similar

findings.^{39,47} The two reviews were in general agreement and their conclusions were summarized nicely by Cheema et al. (2023), who concluded that “quercetin decreased the risk of intensive care unit admission (OR = 0.31; 95% CI: 0.10–0.99) and the incidence of hospitalisation (OR = 0.25; 95% CI 0.10–0.62) but did not decrease the risk of all-cause mortality and the rate of no recovery and that quercetin may be of benefit in COVID-19 patients but large-scale RCTs [randomized controlled trials] are needed to confirm these findings.”^{39,47}

Propolis

No narrative reviews on propolis met the inclusion criteria. However, four systematic reviews were included. Three of the reviews looked mostly at clinical outcomes of COVID-19, including symptom severity, duration of illness, duration of hospitalization, and duration of respiratory support.^{34,36,39} The rate of recovery results reported by Sobrinho et al. (2022) were not as positive as the other three papers, but the focus of this paper was more on the biochemical actions of propolis, which were stated to be anti-inflammatory, immunoregulatory, and anti-COVID19 effects, including protein kinase-1 (PAK-1) inhibition and binding to angiotensin-converting enzyme 2 (ACE2), one of the main routes of infection for SARS-CoV-2.⁴³ All systematic reviews were in agreement that propolis may be useful but further research into the efficacy for the treatment of COVID-19 is needed to confirm.

Polyunsaturated Fatty Acids (PUFAs)

The five narrative reviews that included PUFAs highlight their anti-inflammatory,^{22,24,27,30,32} antioxidant,³⁰ and immune modulating properties.^{27,32} Paudel et al. (2022)³² and Gareau et al. (2023)²⁴ focused on the ability of PUFAs to modulate immune system functions through alterations in the gut microbiome. Although each of these reviews provides some analysis of PUFAs and their effect on COVID-19, they are relatively inconsistent with regard to the form of PUFA assessed and the outcomes measured. For instance, Bader-Larsen et al. (2021) cautioned against the supplementation of omega-3 fatty acids in cancer patients (despite also suggesting it may be beneficial for COVID-19 symptoms) and barely mentions PUFAs other than to mention that short chain fatty acids (SCFAs) may be helpful for relieving gastrointestinal symptoms associated with SARS-CoV-2 pathology.²⁷

The systematic review by Aldhafiri et al. (2022) was the only review focused on PUFAs included. It indicated that PUFAs together with probiotics may shorten the duration of COVID-19 and may have a direct effect on decreasing inflammation and gastrointestinal symptoms.⁴⁶

DISCUSSION

COVID-19 is a highly communicable disease caused by SARS-CoV-2 infection leading to a wide range of clinical manifestations, from mild forms, such as fever, cough, and myalgia, to moderate forms requiring hospitalization (pneumonia and localized inflammation), to severe/critical forms with fatal outcomes.⁴⁹ As vaccine efficacy can be jeopardised by the rapid emergence

and spread of SARS-CoV-2 variants,⁵⁰ there remains a need for therapies to reduce the severity and duration of COVID-19 as well as long COVID.⁵¹ Three key areas where nutraceuticals may provide benefit relate to prevention, immune modulation, and anti-inflammatory support and supporting aging and high-risk populations.

Prevention

A focus on prevention reduces the likelihood of contracting COVID-19 and reduces the risk of long CV. Of the nutraceuticals discussed, probiotics may have a unique role to play in reducing the risk of contracting COVID-19 as well as the risk or severity of long CV symptoms. The interaction of the gut microbiome with the immune system and the subsequent effects on inflammation, mental health, and a host of other health outcomes is no longer a novel concept.⁵² While tailoring the microbiome to precise parameters is not yet (and may never be) a possibility, we are aware of measures that may be taken to alter the gut microbiome to a state of eubiosis or a composition that is beneficial for human hosts.⁵³ It is generally believed that certain beneficial bacteria generate certain SCFAs, such as butyrate, propionate, and acetate, that appear to be key mediators of the beneficial effects elicited by the gut microbiome. Microbial SCFA production is essential for gut integrity by regulating the luminal pH and mucus production, providing fuel for epithelial cells, and procuring beneficial effects on mucosal immune function. SCFAs also directly modulate host metabolic health through a range of tissue-specific mechanisms related to appetite regulation, energy expenditure, glucose homeostasis and immunomodulation, leading the immune system to better recognize infectious agents and to suppress the unnecessary activation of the innate inflammatory response. Therefore, increased microbial SCFA production can be considered a health benefit.⁵⁴ Given this potential, further studies of probiotics (as well as synbiotics, prebiotics, and postbiotics) are warranted to determine how much benefit they can provide, the expected time frame to show effects, dosing, and the most effective species to prevent and treat COVID-19.

Immune Modulating and Anti-Inflammatory Support

Many of the nutraceuticals in this paper are anti-inflammatory or immune modulating. NAC, for instance, is a precursor molecule to glutathione,⁵⁵ the most important low-molecular-weight antioxidant synthesized in cells.⁵⁶ COVID-19 leads to an immune response resulting in what is known as a cytokine storm.⁵⁷ Long CV may develop via mechanisms involving neuroinflammation owing to unique signaling pathways and blood–brain barrier dysfunction, persistent inflammation related to an altered homeostatic milieu and organs, persistence of proinflammatory cells, altered cytokine production, and altered immune metabolic pathways in the lingering inflammatory response of the SARS-CoV-2 infection COVID-19.⁵⁸ Anti-inflammatory and immune modulation would seemingly be the ideal properties needed to combat these effects of SARS-CoV-2. Although the nutraceuticals breadth of research in this field is limited, of the nutraceuticals covered in this review, NAC and quercetin seem to have the potential for the

greatest benefit, NAC given its particular role as a precursor to one of the most important antioxidants in the body, and quercetin as it seems to be a potent inhibitor of the interaction between spike glycoproteins of SARS-CoV-2 and the ACE2 receptor.⁵⁹ In addition, active compounds in propolis and honey have anti-inflammatory properties. Galangin, an active compound in propolis, has been shown to inhibit tumor necrosis factor- α and interleukin-8, leading to a decrease in tissue inflammation and clinical symptoms. PUFAs' primary role is anti-inflammatory, reducing systemic inflammation and infections.

Aging and High-Risk Populations

Older adults and those with comorbidities are at greater risk for developing COVID-19 and have worse outcomes. Many of the nutraceuticals studied in this paper may be beneficial indirectly as they are associated with decreasing the risk of comorbidities such as diabetes, cardiovascular disease, gastrointestinal diseases, and others.^{21,23,31} Melatonin warrants further consideration and research as it is well known that melatonin levels are often significantly lower in the elderly and are associated with decreased immune function.^{11,12} Melatonin protects against cellular damage induced by reactive oxidative species due to its anti-inflammatory and antioxidant effects, and promotes an adaptive immune activity.

Limitations

Although the results of many nutraceuticals are promising, there are not nearly enough quality studies available to truly understand the significance of any of the above-mentioned nutraceuticals in their therapeutic role for COVID-19 or long CV treatment and prevention. Further studies are warranted to understand optimal effectiveness, dosing, and delivery methods for any of the nutraceuticals considered above. When interpreting the results, it is important to note that there was great heterogeneity between studies within most of the reviews and much more so between systematic reviews. Many of the studies included in the reviews also had small sample sizes, which limits the statistical power and generalizability of the findings. It is also important to note that there was very high overlap across systematic reviews for some of the nutraceuticals studied. This has implications for this umbrella review as it is important not to overemphasise findings arising from different systematic reviews if the reviews themselves draw upon the same original research articles. However, the high level of overlap is also an important finding for the wider research community investigating natural health products as it suggests significant duplication in research efforts have occurred during the COVID-19 pandemic, and that greater coordination is needed to avoid such duplication in the future.

CONCLUSION

The need for COVID-19 treatments remains significant, even after the development of effective vaccines. The antioxidant, anti-inflammatory, antiviral and immune modulatory characteristics make the nutraceuticals included in this review reasonable choices for further research. Additional high-quality randomized

controlled trials with large sample sizes are required to fully determine their efficacy, with the inclusion of recommendations on dosing and administration. Of the nutraceuticals discussed above, probiotics, melatonin, NAC, and quercetin appear to have the greatest potential for benefit in the prevention and treatment of COVID-19 and long COVID.

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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.165>:

- Table S1: Citation overlap: Umbrella review other NHPs

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APPENDIX 1: GLOSSARY OF TERMS

ACE2 = angiotensin-converting enzyme 2
AMA = American Medical Association
AMR = region of the Americas
AMSTAR-2 = Assessing the Methodological Quality of Systematic Reviews Version 2
CI = confidence interval
CV = COVID-19
EMR = Eastern Mediterranean region
EUR = European region
ICU = intensive care unit
IL-6 = interleukin-6
long CV = long COVID
NAC = N-acetyl cysteine
NF = nuclear factor
NK = natural killer
NO = nitric oxide
OR = odds ratio
PAK1 = protein kinase-1
PCT = procalcitonin
PUFA = polyunsaturated fatty acid
RCT = randomized controlled trial
RoB = risk of bias
RR = relative risk
RTI = respiratory tract infection
SANRA = Scale for the Assessment of Narrative Review Articles
SARS-CoV-2 = severe acute respiratory syndrome caused by Coronavirus 2
SCFA = short chain fatty acid
SEA = Southeast Asian region
TCIH = traditional, complementary and integrative healthcare
WBC = white blood cell
WHO = World Health Organization
WMD = weighted mean difference
WNF = World Naturopathic Federation
WPR = Western Pacific region

Diet and Nutritional Factors in the Prevention and Treatment of COVID-19: An Umbrella Review



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ABSTRACT

Background: There is growing interest in the use of natural therapies for the prevention and treatment of COVID-19 and related illnesses. The aim of this review was to identify and examine the systematic and narrative reviews reporting on the relationship between diet or nutritional status and COVID-19.

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

Results: Seven narrative reviews and four systematic reviews were included. The reviews included evidence suggesting that dietary patterns and nutritional status are important modifiable risk factors relevant to the prevention and treatment of COVID-19. Three systematic reviews reported an association between poor nutritional status and greater COVID-19 severity or death. Narrative reviews suggested a possible benefit of the Mediterranean diet, fibre-rich diets, and antioxidant-rich fruits and vegetables.

Conclusion: The research suggests that nutrition status is a significant factor in the progression of COVID-19 infection. While more clinical and interventional evidence is needed to precisely understand the impact of diet, dietary constituents, and nutritional status on modifying COVID-19 risk, the findings of this review highlight the importance of following existing dietary guidelines to support healthy immune function.

Key Words COVID-19, SARS-CoV-2, nutrition, diet, naturopathic medicine, anti-inflammatory, immune

INTRODUCTION

Coronavirus-19 disease (COVID-19; see Appendix 1 for a list of terms and acronyms used in this article) is an infectious disease caused by the novel severe acute respiratory syndrome of the coronavirus-2 (SARS-CoV-2) which emerged in late 2019. Prevention strategies such as hygiene measures, mask wearing, and vaccines played a role in mitigating spread and disease severity.¹ Medical treatment strategies for the treatment of COVID-19 were limited in availability and efficacy.² The lack of successful treatment strategies led to significant worldwide morbidity and mortality,^{3,4} as well as high prevalence of post-viral syndrome, referred to as long COVID.⁵ In an effort to find effective solutions to prevent or treat COVID-19, many patients and health providers pursued alternative therapies, including herbal supplements, vitamin supplements, and natural health products.⁶

Nutrition is at the core of optimal health and a key component of naturopathic medicine and many traditional systems of

medicine globally. Dietary patterns and diet constituents are known to be important modifiable risk factors in a range of acute and chronic illnesses and in overall mortality.⁷ Diet is a source of essential macronutrients and micronutrients that support maintenance of a healthy immune response. The Mediterranean diet,⁸ high-fibre diets, and intermittent fasting (IF)/time-restricted eating (TRE)⁹ have demonstrated clinical benefit in the mitigation of disease factors such as increased inflammation¹⁰ and high blood glucose.^{11,12} Diets which are high in omega-3 and omega-9 fatty acids, fruit, vegetables, herbs and spices and fibre are also linked to reduced systemic inflammation and support lower blood glucose levels.¹³ An additional benefit of diets that include (1) fresh fruits and vegetables,¹⁴ (2) sufficient fibre intake,¹⁵ and (3) plant-based or whole foods with healthy fats, is a healthy gut microbiome, which provides a barrier to potential pathogens. Multiple studies verify a relationship between diminished gut health and increased risk for viral infection, especially respiratory diseases similar to COVID-19.¹⁶ The anti-inflammatory, anti-viral, and anti-oxidant effects of these diets and diet constituents suggest these nutritional

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interventions may be effective in helping with prevention and symptoms of COVID-19.¹⁰

Insufficient and improper diet selection can lead to malnutrition,¹⁷ which is associated with an increased risk of mortality as a result of sarcopenia, frailty, insulin resistance, and overall inflammation.¹⁸ Malnutrition has been identified as a highly important factor in immune health and a critical modifiable risk factor for severe infectious disease outcomes. In addition to concerns about the effects of undernutrition on COVID-19 prevention and treatment, overnutrition is also a concern. Obesity disrupts metabolic function in a way that dramatically increases COVID-19 severity, recovery time, intensive care unit admission, and death.¹⁹ Obesity is associated with an increase in inflammatory cytokines which has been identified as a predictor of COVID-19 severity and mortality.²⁰

The aim of this review was to identify and evaluate the systematic and narrative reviews reporting on the relationship between dietary patterns or nutritional status and the prevention and treatment of COVID-19 and long COVID. An additional goal was to identify areas of opportunity for further research and clinical application on topics related to diets, dietary constituents, and nutritional status.

METHODS

Design

This review 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 recently completed.²¹ The live review took place between May 2022 and May 2023 and involved monthly literature searches for relevant publications. This review reported on the narrative reviews and systematic reviews related to diet and nutrition. While narrative reviews are not typically included in an umbrella review, this study team included those that met specific criteria as the narrative reviews provided insights on topics that are not yet broad enough to be covered in systematic reviews.

Search Strategy

Over the course of one year (May 2022 – May 2023), researchers performed monthly literature searches. These searches followed Cochrane Guidelines for a live systematic review. Monthly meetings served to review and collate collected literature and to ensure that it met inclusion criteria. These searches helped to collect all current and emerging data on natural prevention or treatment of COVID-19.

Databases used included PubMed and Google Scholar. Examples of search terms used in the full umbrella review include: “natur*,” “herb*,” “nutraceutical,” “botanical,” “medicinal plant,” “Ayurvedic,” “Chinese medicine,” “herbal patent formula,” “vitamin,” “mineral,” combined with “prevention,” “prophylaxis,” “deficiency,” “treatment,” “management,” and “*COVID*,” “Coronavirus,” “SARS-CoV-2.” Individual herb names, compounds, vitamins, minerals and other health protocols were also searched. These articles were grouped, and the tally for each type of natural

therapy as well as location (i.e., world region) of research were updated monthly. Articles with a primary focus on diet, dietary constituents or nutrition status were included in this review and grouped as a systematic review, narrative review, meta-analysis, or other based on their description in the abstract. While the live review provided a continually updated summary of the evidence that captured the evolving nature of this topic, this review now serves as a synthesis of the included papers.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they were related to the use of diet, dietary constituents, or nutrition status for the prevention or treatment of COVID-19 and were identified in the live review. Articles primarily focused on other topics within the umbrella review, including vitamins, minerals, natural health products, or herbal supplements were excluded.

Systematic reviews were assessed by two independent reviewers using a measurement tool to assess systematic reviews (AMSTAR). In order to be eligible for inclusion, studies needed to have a response of “Yes” or “Partially Yes” to Questions 9 and “Yes” to Question 13. Reviewers were blind to the AMSTAR score required for eligibility while completing the assessment. Narrative reviews were reviewed by two reviewers and the quality of the review was evaluated using the scale for the assessment of narrative review articles (SANRA).²² Articles were included if they had a scientific reasoning score of 1 or 2 AND an overall total sum >5. Individuals providing data extraction were blind to the quality assessment criteria for inclusion/exclusion.

Any discrepancies found in the inclusion questions were verified by a separate reviewer. The data in the studies had to be statistically significant to be included. Only outcomes related to natural health products and therapies were extracted. Some reviews covered topics that spanned multiple categories of the umbrella review; researchers used a reference overlap analysis to track these papers.

Data Extraction

Data extraction for the systematic and narrative reviews took place using separate shared, online spreadsheets. Narrative reviews were collated and data in each of the following categories was extracted: study number, study identification, citation in American Medical Association (AMA) style, author(s), date, journal, country/world region, review objective, details of any search conducted, area of focus, single/mixed category, doses, therapeutic considerations, associations with other vitamins/minerals/pathways, therapeutic considerations, and additional clinical notes. For the systematic reviews, the following data was extracted: study number, study identification, citation in AMA style, author(s), date, journal, country/world region, area of focus (prevention, treatment, post-COVID), review objective, review type (narrative, systematic, or meta-analysis), search date, search databases, study designs included, countries included in the studies, publication date range, tools for assessment of risk of bias and methods of synthesis/analysis. The study results data extracted included the intervention or

exposure assessed, the outcomes measured, the number of studies included in the synthesis, the number of participants included in the studies, the age of the participants, the sex of the participants, the results or findings and results of heterogeneity analysis (if applicable).

RESULTS

On the topic of “nutrition,” “food,” or “diet,” 13 narrative reviews were captured in the original search and 7 of these met qualifications for inclusion (see Table 1). The narrative reviews were completed by researchers from Canada ($n = 1$), India ($n = 1$), Brazil ($n = 2$) and the USA ($n = 3$). Some reviews addressed multiple diet and nutrition topics included in this analysis: the role of fibre and

the gut microbiome ($n = 3$), plant-based and Mediterranean diets ($n = 3$), fruit and vegetable intake ($n = 2$), IF/TRE ($n = 1$), and a ketogenic diet ($n = 1$).

Four systematic reviews related to nutrition were identified (see Table 2). The systematic reviews were completed in Taiwan, China, Israel, and the United Kingdom. All of the reviews related to the prevention of COVID-19 and severe COVID-19 outcomes. Of these reviews, three aimed to examine the relationship between malnutrition and COVID-19 hospitalization, severity and/or mortality. The fourth review synthesized research on the effects of a fibre-dense, hypocaloric Mediterranean diet on body mass index (BMI) and inflammatory markers among participants whose BMI was in the overweight or obese ranges and who were at risk of developing severe outcomes following COVID-19 infection.

TABLE 1 Summary of the Included Narrative Reviews

Article	WHO Region	Review Type/ Study Design	Intervention	Properties Referenced	Associations/ Mechanisms Referenced	Findings
Enichen et al., 2023 ²³	AMR	Narrative review/ included designs not disclosed	Fiber-rich foods, fruits and vegetables	Anti-inflammatory, anti-viral	Gut microbiome composition impacts expression of ACE2 receptor (COVID-19 cellular entry point).	Fruits, vegetables and fibre-rich foods support butyrate-producing gut microbiome that reduces ACE2 receptor expression and promotes healthy immune system.
Trivedi et al., 2022 ²⁴	AMR	Narrative review/ in vivo, in vitro, and clinical trial studies	Fiber-rich foods, plant compounds	Anti-inflammatory	Fibres (in diet or as prebiotics) help modulate inflammation and support healthy gut immune responses.	In-silico studies confirm efficacy of fibre and plant compounds in modifying the gut microbiome production of SCFA.
Dos Santos et al., 2022 ²⁵	AMR	Narrative review/ literature related to nutrition, immune system, COVID-19	Fiber-rich foods, gut microbiome	Anti-viral, anti-inflammatory, anti-oxidation, immune health	Fibre-rich diet fosters gut microbiome producing SCFA, tryptophan metabolites and secondary bile acids supporting health gut immune function.	Healthy diet aids in maintaining healthy immune system preventing and lessening symptoms of COVID-19.
Bell et al., 2023 ²⁶	AMR	Narrative review/ included designs not disclosed	Plant-based diet, Mediterranean diet	Anti-inflammatory, anti-oxidation, immune health	Plant-based diet had a 73% lower OR of moderate-to- severe COVID-19 and Mediterranean diet lowers risk of COVID-19 infection	Lessened risk of infection and severity of symptoms with a well- balanced diet.
Chatterjee et al., 2022 ²⁷	SEA	Narrative review/ articles linking viral infections (esp. COVID-19), micronutrients and the immune system	Plant-based diet, fresh fruits and vegetables	Anti-oxidation, immune health	Under-nutrition and lack of antioxidants linked with greater risk of COVID-19 and viral infection.	Whole foods diet, consisting of fresh fruits and vegetables, improves gut health and reduces risk of viral infection.
Manica-Cattani et al., 2022 ²⁸	AMR	Narrative review, qualitative analysis/ experimental, epidemiological and clinical	Amazonian fruits	Anti-viral, anti-inflammatory, anti-oxidation, geno-protective	Acai may limit activity of COVID-19 ACE2 receptor spike protein and INF- γ , antioxidants limit ROS and resulting tissue damage	Amazonian fruits may be beneficial in prevention of COVID-19 and lessening severity of symptoms.
Ezzati et al., 2022 ²⁹	AMR	Narrative Review/ peer-reviewed RCT, observational and clinical data published between Jan. 2017 and March 2022	Intermittent fasting	Anti-inflammatory, anti-oxidation	IF/TRE reduce inflammatory and stress markers in the immune system (IL-1 β , IL-6, IL- 8, INF- γ , 8-isoprostane)	IF/TRE in combination with micronutrient supplementation may help reduce COVID-19 severity

ACE2=angiotensin-converting enzyme 2; AMR=region of the Americas; IF=intermittent fasting; IL=interleukin; INF- γ =interferon gamma; OR=odds ratio; RCT=randomized controlled trial; ROS=reactive oxygen species; SCFA=short chain fatty acids; SEA=South-East Asian region; TRE=time-restricted eating; WHO=World Health Organization.

TABLE 2 Summary of the Included Systematic Reviews

Article	WHO Region	Review Type/ Include Study Designs	# of Studies, Sample Size Range, Total Sample Size	Intervention/ Exposure	Outcomes Reported	Findings
Boaz et al., 2023 ³⁰	EMR	Meta-analysis/ observational studies: prospective, retrospective, cross-sectional	12, 75–343,188, 354,332	Malnutrition as measured by a range of tools	In-hospital death among COVID-19 patients	Malnutrition or increased risk of malnutrition increased the risk of death (OR 3.43, 95% CI [2.549, 4.60])
Hung et al., 2022 ³¹	WPR	Meta-analysis/ observational studies: retrospective	13, 111–748, 4204	Malnutrition as measured by PNI	COVID-19 mortality and disease severity	Lower PNI associated with increased severity (mean difference –5.19, $p < .001$) and increased mortality (mean difference –8.65, $p < .001$). An increase in PNI per point was associated with reduced mortality (OR=0.84, 95% CI [0.77, 0.9]) and severity (OR=0.84, 95% CI [0.77, 0.92])
Feng et al., 2022 ³²	WPR	Meta-analysis/ observational studies: cohort and cross-sectional	53, 27–760, 3614	Malnutrition as measured by NRS-2002	ICU hospitalization	High malnutrition among COVID-19 patients hospitalized in the ICU (92.2%, 95% CI [85.9, 96.8%]) compared with those in the general ward (70.7% 95% CI 56.4–83.2%)
Moore et al., 2022 ³³	EUR	Systematic review/ intervention studies: RCTs, controlled intervention, crossover RCT, cohort study involving an intervention	6, 36–225, 582	Intervention: Mediterranean diet	BMI and inflammatory markers	Significant reduction in BMI and inflammatory markers

BMI=body mass index; CI=confidence interval; EMR=Eastern Mediterranean region; EUR=European region; ICU=intensive care unit; NRS=nutrition risk score; OR=odds ratio; PNI=prognostic nutritional index; RCT=randomized controlled trial; WHO=World Health Organization; WPR=Western Pacific region.

Narrative Reviews

High-Fibre Diet

Three narrative reviews synthesized the evidence for the role of a high-fibre diet in maintaining a healthy digestive system and of the gut microbiome as part of a healthy immune response for the prevention and treatment of respiratory diseases, including COVID-19.^{23–25} Two of these did not clearly outline the types of studies included,^{23,25} while one stated inclusion of in vivo, in vitro, and clinical studies.²⁴ These reviews discussed the role of fibre in cultivating a gut microbiome that produces short-chain fatty acids (SCFA), such as butyrate, that are anti-inflammatory and anti-viral. One of the reviews discussed the role of butyrate in minimizing angiotensin-converting enzyme 2 (ACE2) receptor expression, limiting the ability of COVID-19 to enter host cells.²³ While the ability of a high-fibre diet to reduce the ACE2 receptor expression has been documented, no clinical trials have measured its impact in modifying the progression or symptom severity of COVID-19.

Mediterranean and Plant-Based Diets

Three narrative reviews investigated the impact of a plant-based diet, including but not limited to Mediterranean diet, on reducing the risk of acquiring and limiting the symptom severity of COVID-19 infection.^{23,26,27} All three reviews described the benefit of a plant-based or Mediterranean diet in establishing a healthy immune system to prevent COVID-19.^{23,26,27} One paper cited a

73% lower odds ratio (OR) of moderate-to-severe COVID-19 in individuals consuming a plant-based diet in a population case study.²⁶ The other two studies stated, without specific figures, the greater risk of acquiring COVID-19 associated with low antioxidant consumption.^{23,27} Together, these studies suggest a possible benefit from consuming a plant-based or Mediterranean diet in improving immune health. This may aid in prevention and treatment of COVID-19; however, limited clinical data exists to date.

Fresh Fruits and Vegetables

Two narrative reviews discussed the impact of including fresh fruits and vegetables on specific inflammatory factors related to respiratory diseases and COVID-19.^{27,28} Both reviews completed systematic literature searches on key terms. One included experimental, epidemiological, and clinical data and the other did not specify data type. One study cited a reduction in plasma levels of interferon-gamma (IFN- γ) with regular consumption of Acai juice in subjects with metabolic syndrome.²⁸ Both of these reviews suggested the relationship between antioxidant content in Amazonian fruits²⁸ and fresh fruits and vegetables²⁷ and improving immune system function. However, neither study provided data directly related to COVID-19 risk or severity of symptoms.

Intermittent Fasting

One narrative review investigated the role of food intake timing with the consideration of TRE or IF.²⁹ This study completed a systematic literature search on key terms. It included randomized

controlled trials (RCTs), clinical interventions and observational data. The review summarizes the impact of IF and TRE on reducing markers of immune stress including interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), interleukin 8 (IL-8), IFN- γ , and 8-isoprostane. This data confirms reduction of inflammation with IF/TRE diet patterns; however, no direct data is available investigating TRE or IF with COVID-19.

Systematic Reviews

Malnutrition

Three systematic reviews highlighted the impact of malnutrition in increasing the risk of COVID-19 hospitalization, disease severity, or mortality.³⁰⁻³² All three completed a meta-analysis to combine the data identified. All three reviews included studies that used observational design. The first one included prospective, retrospective, and cross-sectional studies,³⁰ while a second included retrospective studies,³¹ and the third included cohort and cross-sectional studies.³² Each review assessed the quality of the included studies; the tools used included the Quality in Prognostic Studies (QUIPS) tool,³¹ the Newcastle-Ottawa Scale,³² and the 14-question Quality Assessment Tool for Studies with Diverse Designs (QATSDD).³⁰ The exposure of interest was malnutrition, as measured by the Prognostic Nutritional Index (PNI)³¹ in one meta-analysis and the Nutrition Risk Score (NRS-2002)³² in a second. The third meta-analysis included studies using a wide range of malnutrition measures.³⁰ The outcomes of the observational studies included COVID-19 prevalence, disease severity, intensive care unit (ICU) hospitalization, and COVID-19 mortality. The number of studies included in each review was 12,³⁰ 13,³¹ and 53³² with a total sample size of $n = 354,332$, $n = 4204$, and $n = 3614$, respectively.

All the meta-analyses found an association between poor nutritional status and worse COVID-19 outcomes. In one, a significant association was found between lower PNI and both increased mortality (mean difference [MD]: -8.65 , $p < .001$) and increased severity (MD: -5.19 , $p < .001$).³¹ This association was found when PNI was analyzed as both a continuous (range) and binary (high versus low) parameter. In the second review, it was found that the risk of malnutrition among patients hospitalized in the ICU with COVID-19 (92.2% 95% confidence interval [CI] [85.9, 96.8%]) was significantly higher than among COVID-19 patients hospitalized in the general ward (70.7%, 95% CI [56.4%, 83.2%]) ($p = .002$).³² In a sub-analysis, which categorized the studies based on the country's income level, no difference was identified between high, upper-middle, and lower-middle countries. In the third meta-analysis, it was found that malnutrition, or increased risk of malnutrition, increased the risk of death in hospital among adults diagnosed with COVID-19 by greater than three-fold (OR 3.43, 95% CI [2.549, 4.60], $p < .001$).³⁰

Mediterranean Diet

One systematic review aimed to evaluate the effects of a hypocaloric, fibre-dense Mediterranean diet on BMI and inflammatory markers among adults who were overweight or obese, and thus

at increased risk of severe COVID-19 outcomes.³³ The review identified and combined six intervention studies that delivered a Mediterranean diet intervention to overweight/obese adults 18 years of age or older. The number of participants in the six studies ranged from 36 to 225, with a total of 582. The individual studies reported on changes in BMI and inflammatory markers.³³ Study quality was assessed using the criteria from the Academy of Nutrition and Dietetics Evidence Analysis Manual. The researchers found that most of the studies reported a reduction in BMI and the inflammatory cytokines tumour necrosis factor (TNF)- α , IL-6 and high-sensitivity C-reactive protein (hs-CRP); the majority of these reductions were considered statistically significant.³³ None of the included studies assessed outcomes related to COVID-19 incidence, severity, or mortality.

DISCUSSION

There is significant evidence suggesting that dietary patterns, dietary constituents, and nutritional status are important modifiable risk factors relevant to the prevention and treatment of COVID-19. Important factors highlighted in this review include the deleterious effects of malnutrition as well as the possible benefits of the Mediterranean diet, fibre-rich diets, IF/TRE, and antioxidant-rich foods. Clinically significant findings were limited from the data reviewed, and many areas of opportunity for future research were detected.

Malnutrition Is a Risk Factor

This review identified evidence suggesting that malnutrition is a significant risk factor for COVID-19 outcomes such as higher disease severity, ICU hospitalization, and death. This finding is in line with other research on the effects of malnutrition on immune function, acute infection,³⁴ and the risk of death.³⁵ The papers reviewed in this study suggested potential mechanisms to explain the relationship between malnutrition and diminished immune function including impairment of gut-barrier function, decreased secretion of protective exocrine substances, decreased levels of plasma complement, atrophy of lymphatic tissues such as the thymus, decreased antibody production in response to vaccination, and cytokine patterns favouring a Th2-response.

The changes in immune function may be associated with deficiency of a range of dietary constituents, including protein, energy, vitamins C and E, selenium, iron, copper, folic acid, and zinc.³⁶ These are all areas of opportunity for further study related to COVID-19. Another area of opportunity for future research is the impact of treatment of malnutrition in improving COVID-19 symptoms and severity. While studies assessing the impact of correcting malnutrition in the prevention or treatment of COVID-19 were not identified, such studies exist for other infectious diseases. A meta-analysis of RCTs providing protein-energy-fortified macronutrient supplementation to patients with HIV found significant improvement in one immune parameter (CD4 count).^{37,38} The effects of nutritional supplementation for prevention of COVID-19 and treatment of long COVID is an opportunity for further research.

Mediterranean Diet and Diets Containing Fresh Fruits and Vegetables May Be Beneficial

The evidence for the benefit of the Mediterranean diet or fresh fruits and vegetables related to COVID-19 outcomes is minimal and of moderate quality. Further study is needed to make clear connections between diets containing fresh fruits and vegetables and COVID-19. One emerging strategy in COVID-19 prevention is reduction in inflammation, which is cited as a positive outcome of consuming the Mediterranean diet.³⁹ Many diseased states are initiated, worsened, or progressed as a result of unchecked inflammation and oxidation.⁴⁰ Plant-based diets containing high amounts of fruits and vegetables have demonstrated similar effectiveness in reducing inflammation. Fruits and vegetables have antiviral properties which may be of benefit in the prevention and treatment of COVID-19.⁴¹ Acai and similar fruits discussed in this review have compounds that may reduce the level of inflammatory markers and proteins related to ACE2 receptor expression which are the cellular entry point of COVID-19. Despite the current lack of conclusive evidence related to COVID-19, this is a definite area of opportunity for future research.

Lack of Evidence Related to IF/TRE and COVID-19

This review did not find conclusive evidence linking IF/TRE diets to COVID-19 symptom and severity reduction. However, the ability of IF/TRE diets to improve glycemic control, decrease insulin resistance,⁴² reduce inflammation,⁴³ and limit cytokine secretion⁴⁴ may make it a beneficial strategy related to COVID-19. This diet seems to be a successful intervention for conditions such as metabolic syndrome and type 2 diabetes,^{45,46} both comorbidities that increase the likelihood of severe COVID-19 outcomes.⁴⁷ More interventional data to test the efficacy and treatment strategies related to IF/TRE and COVID-19 is warranted.

A High-Fibre Diet may be Preventive

Data from studies in this review articulated the beneficial effects of the production of SCFA and the reduction of ACE2 resulting from a high-fibre diet. More clinical data is needed to assess the impact of a high-fibre diet and modification of the gut microbiome on the severity and progression of COVID-19. There is sufficient evidence that beneficial changes in the gut microbiome can reduce expression of the ACE2 receptor, limiting potential entry points for the SARS family of viruses.^{48,49} There is also a suggested link between gut and lung health; through the gut–lung axis, diet impacts the health of respiratory defenses.⁵⁰ A high-fibre diet fosters microbial production of SCFA and serotonin in the intestinal cells, which directly strengthens respiratory immune responses and membranes.⁵¹ Though data on this topic is still very limited, the suggested relationship between a high-fibre diet and reduction of COVID-19 risk is a promising area for more clinical and interventional study.

Limitations

This review includes a relatively high proportion of narrative reviews and a limited body of clinical and interventional data within these reviews. While some of the reviews evaluated

included data from clinical or in vitro studies, others did not specify or included mainly observational data. Several of the included reviews presented evidence on the impact of dietary factors on COVID-19 risk or on the risk of developing other infections, or highlighted mechanisms by which dietary constituents may theoretically improve COVID-19 outcomes. Authors made every effort to base conclusions about COVID-19 and dietary patterns or nutritional status primarily on clinical and interventional data. While these studies provide useful information about therapeutic approaches that warrant further investigation, they cannot be used to make definitive clinical recommendations. More interventional data is needed to establish the impact of a healthy diet, metabolic health, and a healthy gut microbiome on COVID-19 prevention and treatment.

CONCLUSION

It is evident that nutrition is a significant factor impacting the incidence and severity of COVID-19 infection. Under- and over-nutrition are risk factors that can be reduced through dietary intervention; however, studies assessing the impact of modulating these risk factors on COVID-19 outcomes are lacking. Diets and dietary components that are anti-viral, anti-inflammatory and antioxidant may lower the risk and severity of symptoms and illness associated with COVID-19. While more clinical and interventional evidence is needed to precisely understand the impact of diet changes on COVID-19 risk, the findings of this review support the importance of following existing dietary guidelines such as consuming a diet that is calorically appropriate, rich in fruits and vegetables, healthy fats, and fibre to support healthy immune function.

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

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APPENDIX 1: GLOSSARY OF TERMS

ACE2	angiotensin-converting enzyme
AMA	American Medical Association
BMI	body mass index
CI	confidence interval
COVID-19	Coronavirus-19 disease
hs-CRP	high-sensitivity C-reactive protein
ICU	intensive care unit
IF	intermittent fasting
IFN- γ	interferon-gamma
IL	interleukin
MD	mean difference
NRS-2002	Nutrition Risk Score
OR	odd ratio
PNI	Prognostic Nutritional Index
QATSDD	Quality Assessment Tool for Studies with Diverse Designs
QUIPS	Quality in Prognostic Studies
RCT	randomized controlled trial
RCTs	randomized controlled trials
SARS-CoV-2	severe acute respiratory syndrome of the coronavirus-2
SCFA	short-chain fatty acids
TNF	tumour necrosis factor
TRE	time-restricted eating

Corrigendum: The Critical Role of Diet in the Prevention and Treatment of Mental Disorders: An Opportunity for the Naturopathic Profession to Positively Impact the Burden of Illness Using a Recently Developed Clinical Tool



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In the article “The Critical Role of Diet in the Prevention and Treatment of Mental Disorders: An Opportunity for the

Naturopathic Profession to Positively Impact the Burden of Illness Using a Recently Developed Clinical Tool,” the English version of the patient worksheet (Appendix 1) contained French text in the plate portion guide labels on the second page, in error. The article has been updated to correct this error.

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