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AN UMBRELLA REVIEW ON TREATMENTS AND THERAPEUTIC OPTIONS FOR COVID-19

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Abstract. *Introduction.* As the COVID-19 pandemic continues to pose a significant challenge to global health, effective therapeutic options for preventing and treating the disease have become increasingly important. We aimed to provide an update on current treatments and therapeutic options for COVID-19 patients. *Materials and methods.* The purpose of this umbrella review is to explore the current treatments and therapeutic options for COVID-19 patients. Keywords and their combinations were searched across online databases in Embase, PubMed/MEDLINE, Web of Science, and Scopus spanning from July 1, 2020, through March 3, 2023. Publications were selected for data extraction in two steps based on the study inclusion/exclusion criteria. The study adheres to the PRISMA checklist as well as NIH bias risk and quality assessment tool. *Results.* In this review, 28 relevant articles were selected for the final qualitative synthesis. The majority of included studies had reported on the efficacy of Lopinavir/Ritonavir (n = 4), Ivermectin (n = 3), Baricitinib (n = 2), Tocilizumab (n = 2), Remdesivir (n = 2), ACEI/ARB (n = 2), Vitamin D (n = 2), Molnupiravir (n = 2), Traditional Chinese medicine (TCM) (n = 2), Convalescent plasma transfusion (CPT) (n = 2) and hydroxychloroquine (n = 2) in treating COVID-19. It appeared that Baricitinib, Remdesivir, ACEI/ARB, TCM, and CPT may have beneficial effects on reducing mortality, hospitalization duration, and disease severity in COVID-19 patients. Other interventions, such as Lopinavir/Ritonavir, Ivermectin, Vitamin D, and Hydroxychloroquine did not show clear benefits or had inconclusive results. *Conclusion.* This umbrella review provides a comprehensive overview of the current evidence on the effectiveness and safety of various pharmacological and non-pharmacological interventions for COVID-19. These results provide an updated overview of the current landscape for COVID-19 treatments, highlighting potential avenues for further research and clinical practice. It is crucial to continue monitoring emerging evidence and conducting rigorous studies to guide the development and optimization of therapeutic strategies against COVID-19.

Key words: *COVID-19, SARS-CoV-2, treatments, therapy, medicine, umbrella review.*

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«ЗОНТИЧНЫЙ» ОБЗОР СРЕДСТВ И СТРАТЕГИЙ ЛЕЧЕНИЯ ПРИ COVID-19

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Резюме. *Введение.* Поскольку пандемия COVID-19 продолжает представлять собой серьезную проблему для глобального здравоохранения, все более важными становятся эффективные терапевтические варианты профилактики и лечения этого заболевания. Мы стремились предоставить обновленную информацию о современных средствах и методах лечения для пациентов с COVID-19. *Материалы и методы.* Целью данного обзора являлось изучение современных методов лечения и терапевтических возможностей для пациентов с COVID-19. Поиск ключевых слов и их комбинаций проводился в онлайн-базах данных Embase, PubMed/MEDLINE, Web of Science и Scopus с 1 июля 2020 г. по 3 марта 2023 г. Публикации для извлечения данных отбирались в два этапа на основе критериев включения/исключения. Исследование соответствует контрольному списку PRISMA, а также инструменту оценки риска и качества NIH. *Результаты.* Для окончательного качественного синтеза в настоящем обзоре было отобрано 28 соответствующих статей. В большинстве включенных исследований сообщалось об эффективности лопинавира/ритонавира (n = 4), ивермектина (n = 3), барицитиниба (n = 2), тоцилизумаба (n = 2), ремдесивира (n = 2), ИАПФ/БРА (n = 2), витамина D (n = 2), молнупиравир (n = 2), традиционной китайской медицины (ТКМ) (n = 2), переливания плазмы выздоравливающих (ППВ) (n = 2) и гидроксихлорохина (n = 2) при лечении COVID-19. Оказалось, что прием барицитиниба, ремдесивира, ИАПФ/БРА, ТКМ и ППВ способствуют снижению смертности, укорочению сроков госпитализации и уменьшению тяжести заболевания у пациентов с COVID-19. Результат применения таких препаратов, как лопинавир/ритонавир, ивермектин, витамин D и гидроксихлорохин, был не столь убедителен. *Заключение.* Мы представили всесторонний обзор текущих данных об эффективности и безопасности различных фармакологических и нефармакологических средств терапии COVID-19 и выявили потенциальные направления дальнейших научных и клиническихисследований и клинической практики. Крайне важно продолжать мониторинг новых данных и проводить тщательные исследования для разработки и оптимизации терапевтических стратегий в отношении COVID-19.

Ключевые слова: *COVID-19, SARS-CoV-2, лечение, терапия, медицина, «зонтичный» обзор.*

Introduction

The COVID-19 pandemic has posed a significant challenge to global health, with millions of cases and deaths reported worldwide. The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has become a global public health emergency [30, 40]. As the world continues to grapple with the pandemic, there has been a growing need for effective therapeutic options to prevent and treat COVID-19 [28, 34]. Several potential therapeutic opportunities have emerged, including antiviral drugs, monoclonal antibody therapies, anti-inflammatory drugs, convalescent plasma therapy, and vaccines [7]. In this context, ongoing research and development of treatments and prevention measures have become critical in managing the COVID-19 pandemic [13] and effective therapeutic options for preventing and treating the disease have become increasingly important [24, 25, 28].

The pandemic has highlighted the need to develop treatment guidelines based on current and reliable evidence, rather than relying solely on past experiences and theories. Although various potential therapeutic opportunities have emerged, including antiviral drugs, monoclonal antibody therapies, anti-inflammatory drugs, convalescent plasma therapy, and vaccines, it is essential to frequently review and revise these guidelines due to the rapid pace at which new evidence can emerge during a crisis [4]. The rapidly changing nature of information during a crisis means that guidelines can quickly become outdated, and it is important to stay up-to-date on the latest developments in order to provide the best possible care. By continually revising guidelines, healthcare professionals can ensure that they are providing the most effective and evidence-based treatments to their patients [14, 19].

Against this background, it is crucial to emphasize the importance of ongoing research to fully understand the effectiveness and safety of COVID-19 treatment and prevention options. This review provides a brief overview of some of the potential options for COVID-19, highlighting benefits and the need for ongoing research to fully understand their effectiveness and the safety of current therapeutic options.

Materials and methods

This review investigated currently available treatments and therapeutic options for COVID-19 patients and elaborate on the implications and potential adverse effects. This study adheres to items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The risk of bias for included studies was assessed by the National Institute of Health (NIH) quality and bias risk assessment tool.

Data sources. We performed a comprehensive search on the online database of Embase, PubMed/MEDLINE, Web of Science, and Scopus. Combining the relevant keywords and search queries all the relevant articles published in the English language were browsed and retrieved from July 1st, 2020, to March 3rd, 2023. The comprehensive list of queries in different databases is provided in Supplementary Material 1. Here is an example of a search query in the PubMed/MEDLINE database: ((“COVID-19”[mesh] OR “SARS-CoV-2”[mesh] OR COVID-19[tiab] OR SARS-CoV-2[tiab] OR coronavirus disease 2019[tiab] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019 nCoV [tiab] OR SARS Coronavirus 2[tiab]) AND (“Therapeutics”[mesh] OR Therapeutic [tiab] OR Therapy [tiab] OR Therapies[tiab] OR Treatment[tiab] OR Medicine[tiab] OR Drug[tiab] OR Medication[tiab]) NOT (Vaccine[ti] OR Vaccination[ti])).

Study selection. To ensure the selection of the most appropriate studies, we employed two distinct selection steps. Initially, three research staff screened titles and abstracts of the retrieved articles. In the next step, three other researchers conducted a thorough full-text review of the initially selected articles. Pertinent publications that met the inclusion/exclusion criteria were included for data extraction. The inclusion criteria were as follows: The study had to a systematic review, written in English, peer-reviewed prior to publication, and published in the allocated time period (July 1st 2020 — March 3rd 2023). Studies were excluded if they were original articles, duplicated, non-human research models, ongoing experiments and/or lacking published data, conference abstracts or abstracts without accessible full texts, preprint papers, editorial letters, case reports, or series.

Data extraction. Three researchers extracted the necessary data from the eligible articles. A pre-planned spreadsheet was used to record the detailed information, which is presented in Table 2. Any potential duplicates were removed, and the accuracy of the extracted data was verified by other members of the research team.

Quality and bias risk evaluation. The quality and precision of the studies and reported results were assured by adhering to the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Additionally, the National Institute of Health (NIH) quality and bias risk assessment tool was used to assess and minimize the potential risk of bias in the selected studies. Table 1 presents the results of the quality assessment. The questionnaire at the bottom of the table was used by two researchers to rate the included studies.

Results

In this review, we identified a total of 4717 relevant sources. After an initial check, 805 duplicate articles were excluded, and the remaining 3912 articles were screened based on the relevancy of titles and abstracts through which 3561 resources were excluded. From the remaining 351 articles, 323 were excluded as they have not met the eligibility criteria. These excluded studies were non-English studies (n = 32), enduring studies (n = 53), systematic review protocols (n = 24), non-human studies (n = 85), studies unrelated to treatment and medicine (n = 113), and non-full-text studies (n = 16). Ultimately, 28 articles most relevant to the study objective were selected for the final review.

A total of 28 potential treatment regimens were identified for COVID-19 as shown in Table 2. The majority of included studies reported on the efficacy of Lopinavir/Ritonavir (n = 4), Ivermectin (n = 3), Baricitinib (n = 2), Tocilizumab (n = 2), Remdesivir (n = 2), ACEI/ARB (n = 2), Vitamin D (n = 2), Molnupiravir (n = 2), Traditional Chinese medicine (TCM) (n = 2), Convalescent plasma transfusion (CPT) (n = 2) and hydroxychloroquine (n = 2) in treating COVID-19.

Despite many studies on Lopinavir/Ritonavir, which have shown no specific adverse effects, current research still lacks strong evidence regarding its antiviral effects against COVID-19. Ivermectin shows potential effectiveness in mild-moderate COVID-19 patients. However, further studies are needed. One study indicated that in the absence of antiviral treatments, cautious administration of Ivermectin can be considered. Studies showed that Baricitinib (which is a type of JAK inhibitor) along with Sarilumab, served as a good alternative for COVID-19 treatment and it can lead to a reduction in mortality rate among hospitalized patients with moderate-severe COVID-19. It appeared that Molnupiravir, which is a prodrug for Hydroxycitidine, could reduce the hospitalization and mortality rates in high-risk COVID-19 patients. Some studies have demonstrated the potential of Chinese traditional and herbal medicine as an alternative for the prevention, treatment, and rehabilitation of COVID-19 patients. Furthermore, recent studies have indicated that certain drugs can be beneficial in specific subgroups of COVID-19 patients. For instance, ACE/ARB has shown potential effectiveness in reducing ICU admission and mortality rate among individuals with hypertension who were previously using ACE/ARB. Additionally, Convalescent Plasma Therapy (CPT) has demonstrated effectiveness in patients with hematological malignancies, while Remdesivir has shown posi-

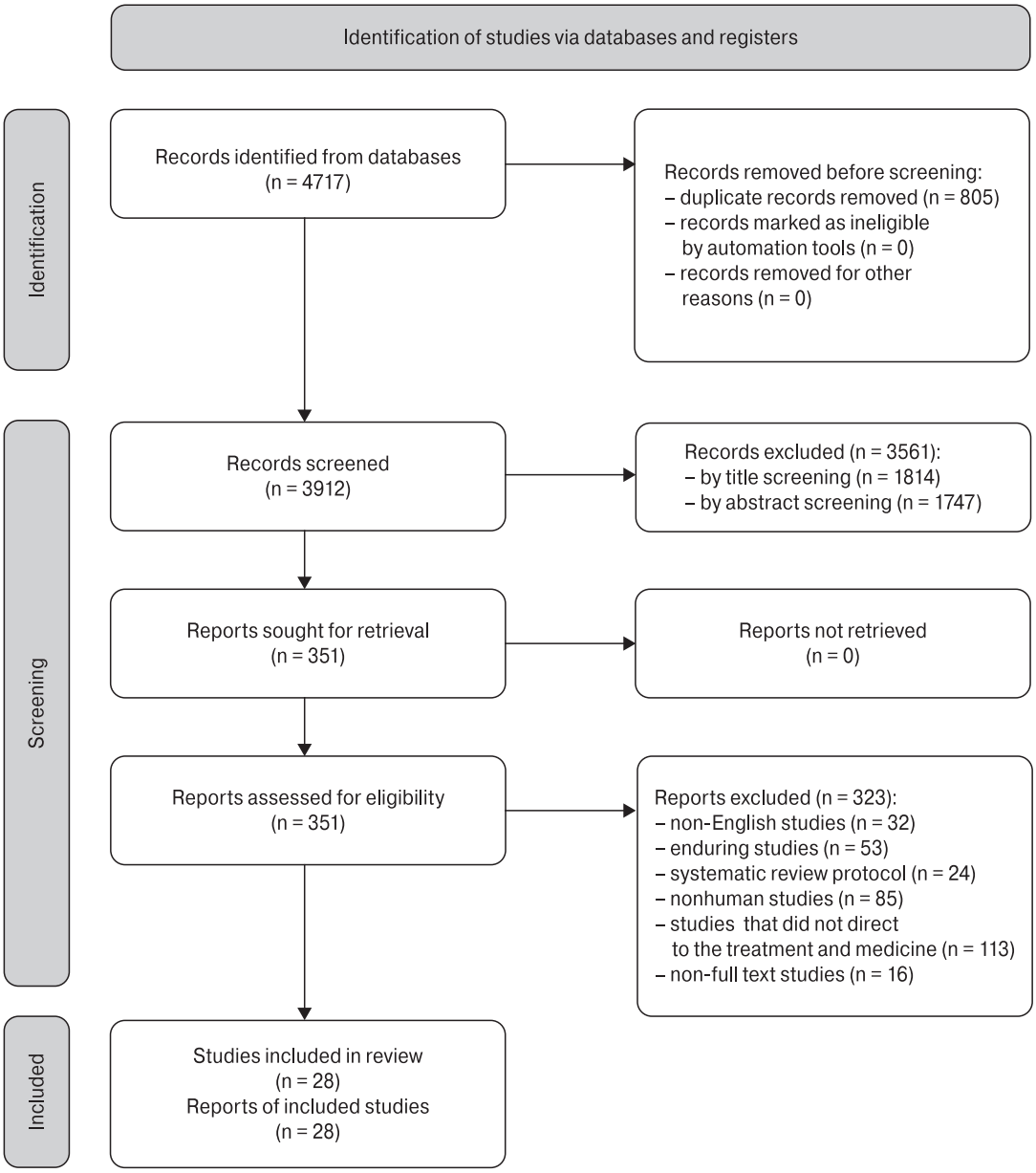

Figure. PRISMA 2020 flow diagram of study retrieval process

tive outcomes in non-ventilated hospitalized patients. Nirmatrelvir/Ritonavir, sold under the name Paxlovid, a combination of the SARS-CoV-2 protease inhibitor nirmatrelvir, and ritonavir, a CYP3A4 inhibitor, is one of the best therapeutic choices for high-risk patients in reducing all-cause mortality and hospital admission. In people without prior or concomitant therapies low- to moderate-certainty evidence revealed that nirmatrelvir/ritonavir can be safe.

Discussion

The main objective of this umbrella review was to evaluate and summarize the existing evidence on the potential treatments and therapeutic options for COVID-19 patients. The review provides a comprehensive overview of the current knowledge in this field. A total of 28 systematic reviews and meta-analyses were included in this review and encompassed a wide range of treatment modalities, including antiviral drugs, immunomodulators, JAK inhibitors, Convalescent plasma transfusion (CPT), Traditional Medicine and Supplementary medicine. The most frequently used therapies in selected studies were Lopinavir/Ritonavir (n = 4), Ivermectin (n = 3), Baricitinib (n = 2), Tocilizumab (n = 2), Remdesivir (n = 2), ACEI/ARB (n = 2), Vitamin D (n = 2), Molnupiravir (n = 2), Traditional Chinese Medicine (TCM) (n = 2), Convalescent plasma transfusion (CPT) (n = 2) and hydroxychloroquine (n = 2).

Lopinavir/Ritonavir is a combination of protease inhibitors that has been used to treat HIV infection and was also effective against SARS-CoV and MERS-CoV *in vitro* and in animal models [35]. Some previous studies reported that there is no significant difference between Lopinavir/Ritonavir and standard care in terms of mortality, viral clearance, or adverse

Table 1. Quality/Bias risk ratings of the included studies according to the NIH Quality Assessment Tool*

Reference	Questions								Rating by reviewers	
	1	2	3	4	5	6	7	8	#1	#2
[1]	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Good	Good
[2]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Good
[6]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Good
[9]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[11]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Fair
[12]	Yes	Yes	Yes	NR	Yes	Yes	Yes	NA	Fair	Good
[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Good
[16]	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Good	Fair
[17]	Yes	Yes	Yes	Yes	No	Yes	No	NA	Fair	Fair
[18]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[20]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[21]	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Fair	Good
[22]	Yes	Yes	Yes	No	No	Yes	No	NA	Fair	Fair
[23]	Yes	Yes	Yes	Yes	NR	Yes	No	NA	Good	Good
[26]	Yes	Yes	Yes	NR	Yes	Yes	No	NA	Fair	Fair
[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Good	Good
[29]	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Good	Good
[31]	Yes	Yes	Yes	Yes	No	Yes	No	NA	Fair	Good
[32]	Yes	Yes	Yes	Yes	No	Yes	NR	No	Fair	Fair
[33]	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	Fair	Fair
[36]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[38]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Fair
[39]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[41]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Fair
[42]	Yes	Yes	Yes	Yes	Yes	Yes	NR	No	Fair	Fair
[43]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
[47]	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Good	Fair

Note. NIH — National Institutes of Health; CD — cannot determine; NR — not reported; NA — not applicable.
*The NIH Quality Assessment Tool for Systematic reviews and Meta-Analysis (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) contains 8 questions: 1 — Is the review based on a focused question?; 2 — Were eligibility criteria for included and excluded studies predefined and specified?; 3 — Did the literature search strategy use a comprehensive, systematic approach?; 4 — Were titles, abstracts and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?; 5 — Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?; 6 — Were the included studies listed along with important characteristics and results of each study?; 7 —Was publication bias assessed?; 8 — Was heterogeneity assessed?

events [37]. In our review, Lopinavir/Ritonavir did not show clear benefits in terms of hospitalization duration and time to negative PCR in mild diseases [27, 29, 32].

Ivermectin is an antiparasitic agent that inhibits the replication of viruses in vitro. The molecular hypothesis of Ivermectin's antiviral mode of action suggests an inhibitory effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in the early stages of infection [36]. One of three studies that evaluated Ivermectin, indicated that it has potential effectiveness in treating mild to moderately ill patients. However, its role as an antiviral drug against COVID-19 in clinical setting is not clear yet as the other two studies were inconclusive [27, 36, 47].

Baricitinib is a Janus kinase (JAK1/JAK2) inhibitor developed to treat patients suffering from rheumatoid arthritis. JAK-STAT signaling is critical to multiple cellular processes, including survival, differentiation, and proliferation [45]. The conclusion of two studies that examined Baricitinib was in line, as they concluded Baricitinib is an alternative to Tocilizumab, which is a recombinant humanized anti-IL-6 receptor monoclonal antibody that has been approved for use in patients with rheumatologic disorders and chimeric antigen receptor T cell-induced cytokine release syndrome [46] for reducing mortality in COVID-19 patients admitted to the hospital and undergoing corticosteroid treatment. Systemic JAK inhibitors reduce all-cause mortality in hospitalized individuals with moderate-severe COVID-19 [1, 16].

Remdesivir is a nucleotide analog that inhibits viral RNA polymerase and has broad-spectrum antiviral activity against several RNA viruses, including SARS-CoV-2 [3]. Studies have shown that in non-ventilated hospitalized patients with COVID-19 who did not require ventilation, Remdesivir can decrease mortality. It is important to note that Remdesivir is associated with specific adverse effects, such as significant bradycardia, so rigorous attention is needed during the administration of this drug in COVID-19 patients [2, 27].

Table 2. Description of the findings reported in the eligible studies

Reference	Country	Method (search date and searched databases)	Number of review studies	Current treatment/ medicine	Therapeutic dose	Clinical considerations	Main findings
[1]	Brazil	Pubmed/EMBASE/Cochrane library/MedRxiv October 7, 2020 — April 30, 2022	27 RCT	Baricitinib Sarilumab Tocilizumab	Not reported	Baricitinib has not been studied in severe renal failure and cannot be given in pregnancy	Baricitinib and Sarilumab are alternatives to Tocilizumab for reducing mortality in COVID-19 patients admitted to the hospital and undergoing corticosteroid treatment
[2]	Switzerland	Pubmed/EMBASE/ Cochrane COVID-19 trial registry/ClinicalTrials.gov/ International Clinical Trial Registry Platform/preprint servers January 1, 2020 — April 11, 2022	9 RCT	Remdesivir	Not reported	Remdesivir has specific side effects (eg, severe bradycardia)	In non-ventilated hospitalized patients with COVID-19 who did not require ventilation, Remdesivir demonstrated a decrease in mortality
[6]	Pakistan	Pubmed/The Cochrane Library/EMBASE Inception — October 5, 2022	6 RCT	Quercetin	Safe up to 500 mg per day	Quercetin is a cheap and easily accessible therapeutic option for COVID-19 patient	The administration of Quercetin, especially in its phytosome formulation can provide benefits for COVID-19 patients by improving its bioavailability
[8]	Germany	Medline/EMBASE/ Clinicaltrial.org/MedRxiv/ WHO International Clinical Trial Registry Platform/CCSR Inception — December 13, 2021	5 RCT	Anakinra	Not reported	Anakinra might be beneficial in hospitalized patients with COVID-19 with low-flow/ high-flow oxygen therapy and suPAR > 6 ng/ml	When compared to placebo or standard care alone, Anakinra does not exhibit any impact on mortality, clinical improvement, worsening or safety outcomes in adult hospitalized patients with COVID-19
[9]	Canada	Medline/EMBASE/Pubmed/ Web of science/CENTRAL/ CINAHL/International pharmaceutial abstracts January 1, 2020 — December 17, 2022	6 RCT 3 Cohort study 1 Case-Control 1 Non-randomized clinical trial	SSRI (Fluvoxamine)	50–100 mg Bid	100 mg bid is more effective than 50 mg bid	Fluvoxamine is a potential therapy in COVID-19 out-patients with medium doses showing more favorable results in comparison with low doses
[11]	Spain	PubMed, Web of Science, the Cochrane COVID-19 Study Register, ClinicalTrials.gov-COVID-19 subset, and the WHO International Clinical Trials Registry Platform (ICTRP) Inception — May 2022	27 RCT	Vitamin D	Not reported	No adverse events were observed in the trials, indicating the safety of Vitamin D supplements within the examined doses	No adverse events were observed in the trials. It can be concluded that Vitamin D supplementation using the doses and preparations examined, is safe

Reference	Country	Method (search date and searched databases)	Number of review studies	Current treatment/ medicine	Therapeutic dose	Clinical considerations	Main findings
[12]	Australia	Medline/EMBASE/Pubmed/ PsycINFO November 2021 — July 7, 2022	8 Retrospective cohort 2 Prospective cohort 3 Cross-sectional study 1 Case-Control 1 Case-Series 3 Retrospective chart review	Clozapine	Not reported	There was a reduction in neutrophil level in COVID-19 positive clozapine users	There is no evidence suggesting that the immune system of Clozapine users put them at risk of COVID-19. It is still crucial to closely monitor these patients
[15]	China	Pubmed/Embase/Cochrane Library January 2000 — May 2022	26 Retrospective cohort 2 Prospective cohort	ACEI/ARB	Not reported	The effect of ACEI/ARB is more obvious in HTN population. The reduction of hospitalization in female is more than male	Use of ACE/ARB among EAST-Asian COVID-19 patients did not show any adverse outcomes and was associated with shorter hospitalization and reduced mortality rates
[16]	Germany	Medline/EMBASE/ ClinicalTrials.gov/WHO International Clinical Trials Registry Platform/medRxiv/ Cochrane Central Register of controlled trials/VA ESP/ WHO COVID-19 Global Literature Inception — February 2022	6 RCT	Janus Kinase Inhibitors: Baricitinib Tofacitinib Ruxolitinib	Not reported	There is no evidence on the efficacy and safety of systemic JAK inhibitors for non-hospitalized individuals	Systemic JAK inhibitors reduce all-cause mortality in hospitalized individuals with moderate-severe COVID-19
[17]	Indonesia	Pubmed/Science direct Inception — October 4, 2021	6 RCT	Anticoagulants in prophylactic vs intermediat/ therapeutic doses	Not reported	The incidence of bleeding at the intermediate/therapeutic doses compared to the prophylactic dose	There was no significant differences in thromboembolic events or all-cause mortality
[18]	China	Campbell Library/Cochrane Library/EMBASE/PubMed/ Web of Science/CBM/CNKI/ CQVIP/WanFang Data Inception — March 23, 2022	76 RCT 50 Systematic Review	TCMs (Tradional Chinese Medicine)	Not reported	XBJ as a TCM was the most common intervention	In terms of treatment, rehabilitation and prevention TCM is a promising alternative
[20]	China	PubMed/the Cochrane Library/Ovid/Embase December 1, 2019 — April 30, 2022	4 RCT 5 Retrospective cohort 1 Prospective cohort 1 Non-experimental comparative study	ACEI/ARB	Not reported	The effects of continuing ACE/ ARB treatment may have been influenced by factors such as male sex and the presence of D.M.	Previous ACEI/ARB treatment was associated with lower hospital mortality, ICU admission, and IMV in patients with COVID-19

Table 2. Description of the findings reported in the eligible studies (continued)

Reference	Country	Method (search date and searched databases)	Number of review studies	Current treatment/ medicine	Therapeutic dose	Clinical considerations	Main findings
[21]	China	CBM/CNKI/Wanfang/ PubMed/Cochrane Library/ EMBASE/preprint platforms Date of database creation — March 31, 2021	51 Systematic Reviews	CHM (Chinese Herbal Medicine)	Not reported	Clinical evidence of the benefits of CHM for acute respiratory infections such as COVID-19, SARS, and H1N1 seems more sufficient than other acute infections	Chinese herbal medicine, used alone or in combination with conventional medicine has benefits in relieving symptoms of patients with acute respiratory infections
[22]	India	LitCOVID/Google Scholar/ Science Direct/EBSCO/ Scopus/Web of Science/ EMBASE Search date not reported	11 RCTs 4 Case reports 1 Case-series 4 Retrospective cohort 3 Non-randomized clinical trial 2 Pilot and prosspective comparative studies	Ayurvedic medicines and formulations: Ayush-64 Guduchi Ghana vati Chyawanprash	Not reported 500 mg BD 500 mg BD 12–24 g BD	Ayurvedic medicines have antiviral, antioxidant, anti-inflammatory, and immunomodulatory properties	Ayurvedic medicines can be combined with standard treatments to aid in early virus detection, accelerate recovery from COVID-19, expedite hospital discharge, and prevent further deterioration
[23]	India	PubMed/MedRxiv/BioRxiv/ FDA/ClinicalTrials.Gov/ctri.nic.in/Google Scholar January 2021 — March 2022	6 RCT: 4 Published 2 Unpublished	Molnupiravir	50–800 mg Bid Or single dose Up to 1600 mg	The drug is well tolerated and safe with no significant adverse events on short-term use	Clinical studies provide evidence that Molnupiravir significantly reduces the risk of hospitalization or death in high-risk mild COVID-19 patients
[26]	Germany	Pubmed/Embase/Scopus/ Google Scholar No time constrain	9 RCTs 9 Retrospective cohorts 2 Prospective cohorts 2 Cross-sectional study 1 Case-control	Vitamin C and D Supplementation	Not reported	Vitamin D modulates the innate immune response Vitamin C has antioxidant, anti-inflammatory, antithrombotic, and immunomodulatory functions	Administration of vitamins C and D in COVID-19 patients doesn't impact disease susceptibility, severity, and progression
[27]	Iran	PubMed/Scopus/Web of Sciences Inception — January1, 2022	46 Reviews	Main intervention: Favipiravir Remdesivir Hydroxychloroqine Ivermectin Lopinavir/ Ritonavir Tocilizumab	Not reported	Not reported	The main limitations observed in the included studies were heterogeneity, sample size, follow-up, treatment variations, study design, definitions, synthesis, quality, and search methodology

Reference	Country	Method (search date and searched databases)	Number of review studies	Current treatment/ medicine	Therapeutic dose	Clinical considerations	Main findings
[29]	Iran	PubMed/Scopus/Web of Sciences/Embase December 2019 — March 2021	266 *in silico* 34 *in vitro* 15 *in vivo*	Main intervention: Saquinavir Ritonavir Lopinavir Herbal medicine	Not reported	Discovering drugs that have multitarget antiviral and anti-inflammatory actions is crucial due to the nature of COVID-19 — Certain herbal medicine exhibit this potential	For antiviral development, the main focus has been on targeting the protease and spike glycoprotein
[31]	Greece	Pubmed/Medline and Embase September 2022	3 RCTs 4 Retrospective cohorts 1 Prospective cohort	N-acetyl cysteine (NAC)	The studies by Mousapour, Taher, and de Alencar used 1 g/12 h, 40 mg/kg/ day, and 21 g (divided into two doses) respectively	Due to the limited certainty of evidence presented in the studies, it is not possible to provide recommendations for clinical practices	In RCTs, the point estimates for hard clinical outcomes tend to be near the null effect line (lack of significant impact). Observational studies show heterogeneity, with certain studies suggesting positive outcomes
[32]	India	Google Scholar January 2020 to May 2020	49 Studies	Hydroxychloroquine, Lopinavir and Ritonavir, Ultra-violet radiation therapy, Convalescent plasma transfusion (CPT) therapy	Not reported	New drugs are in the premature stage of this pandemic. Further research is needed to fully understand the life cycle of n.COV and expedite the development of drugs and vaccines	ICMR and NIH provide guidelines for Hydroxychloroquine and other antiviral drugs. Ongoing research includes natural products, herbs, combination therapy, UV radiation, MD simulations for vaccine development, and CPT
[33]	USA	Google Scholar and PubMed and medRxiv Search date not reported	3 Cohort 1 Case-control 1 RCT 2 Comparative studies	Arbidol, Lopinavir/ Ritonavir	Not reported	Adverse reactions were rarely reported including ECG changes, GI symptoms, bacterial infections, and hepatic and renal dysfunction	Antiviral regimens did not show clear benefits in terms of hospitalization duration and time to negative PCR in mild diseases
[36]	Germany	Cochrane COVID-19 Study Register, Scopus, and WHO COVID-19 Global literature on coronavirus disease database Inception — July 2022	1 RCT 8 Ongoing studies	Nirmatrelvir combined with Ritonavir	Not reported	Ritonavir's role as a CYP3A4 inhibitor, makes Nirmatrelvir/ Ritonavir prone to drug interactions, especially in patients with comorbidities	Low certainty evidence suggests that Nirmatrelvir/Ritonavir reduces the risk of all-cause mortality, and hospital admission/death in high-risk, unvaccinated COVID-19 patients with symptom onset within 5 days. Low-moderate certainty evidence suggests the safety of Nirmatrelvir/Ritonavir in patients without prior-concomitant therapies that rely on CYP3A4

Table 2. Description of the findings reported in the eligible studies (continued)

Reference	Country	Method (search date and searched databases)	Number of review studies	Current treatment/ medicine	Therapeutic dose	Clinical considerations	Main findings
[38]	USA	EMBASE, PubMed, medRxiv, Scopus, Prospero, and Google Scholar inception — February 2021	4 RCTs 2 Retrospective cohorts 2 Case-controls	Colchicine	Not reported	The use of Colchicine for treating COVID-19 is not recommended. Additional high-quality, multicenter RCTs are needed	3 observational studies showed a decrease in all-cause mortality. 1 observational study showed a decrease in the risk of mechanical ventilation. 2 RCTs showed a reduction in hospitalization
[39]	Germany	Cochrane COVID-19 Study Register, Web of Science, medRxiv, and Research Square Inception — May 2021	11 RCTs	IverIvermectinectin	Not reported	The existing reliable evidence does not support the use of Ivermectin as an effective treatment or preventive measure for COVID-19	Evidence for the effectiveness of Ivermectin in treating COVID-19 is currently uncertain for both in-patients and out-patients with limited/ no beneficial effects in different aspects such as viral clearance-clinical improvement and adverse events
[41]	China	PubMed, EMBASE, Cochrane Library, Web of Science databases Inception — October 25, 2022	7 Retrospective cohorts 2 RCTs	Thymosin alpha1 (Ta1)	Not reported	This meta-analysis does not provide support for the utilization of Ta1 in hospitalized adult COVID-19 patients	The meta-analysis results suggest that Ta1 therapy does not have a statistically significant impact on mortality. Subgroup analyses show a beneficial effect on mortality in patients > 60 years with a proportion of females < 40% and with severe COVID-19
[42]	Australia	PubMed, Web of Science, ScienceDirect and Scopus Inception — June 2022	5 Retrospective cohorts 12 Case reports 1 Case series	Convalescent plasma Therapy (CPT)	Not reported	CPT is an effective supportive therapy for COVID-19 patients with hematological malignancies	CPT may lead to improved clinical outcomes, including higher survival rates, enhanced clearance of SARS-CoV-2, presence of anti-SARS-CoV-2 antibodies, shorter hospital discharge time, and better recovery after one month of CPT. The treatment was not associated with adverse events
[43]	India	PubMed, MedRxiv and Google Scholar October 2021 — January 2022	1 RCT 13 Preclinical studies	Molnupiravir	Not reported	Molnupiravir may benefit non-pregnant, unvaccinated adults with COVID-19 who face an elevated risk of severity and hospitalization	Molnupiravir shows promise as a useful agent in reducing death and composite of hospitalization or death in high-risk adult patients with COVID-19. It offers the advantage of being cost-effective
[47]	China	Studies were not restricted by the year of publication, study site, drug dose, or control group	9 RCT	Ivermectin (IVM)	Not reported	In the absence of superior alternatives, clinicians should use IVM with caution in the clinical setting. Self-medication is not recommended for patients	IVM shows potential effectiveness in treating mild to moderately ill patients. Its role as an antiviral drug in COVID-19 is still in the early stages of clinical application

The ACEI/ARB drug class was analyzed in two studies included in this review. The findings of these studies were consistent. The first study examined the use of ACE/ARB among COVID-19 patients of East Asian descent and found no adverse outcomes. Additionally, ACEI/ARB use was associated with shorter hospitalization and reduced mortality rates. The beneficial effects of ACEI/ARB were more pronounced in individuals with hypertension, and the reduction in hospitalization was greater in females compared to males. In the second study, it was concluded that prior ACEI/ARB treatment was linked to lower hospital mortality, ICU admission, and the need for Intermittent Mandatory Ventilation (IMV) in COVID-19 patients [15, 20].

Two studies investigating the effects of vitamin D supplementation, with one study combining it with vitamin C, were included in this review. Vitamin D plays a role in modulating the innate immune response, while vitamin C possesses antioxidant, anti-inflammatory, antithrombotic, and immunomodulatory functions. Administration of vitamins C and D to COVID-19 patients did not demonstrate any influence on disease susceptibility, severity, or progression. Importantly, no adverse events were observed in the trials, indicating the safety of vitamin D supplements at the examined doses [11, 26].

Molnupiravir is an antiviral drug similar to Remdesivir, targeting the RNA-dependent RNA polymerase (RdRp) enzyme utilized by the coronavirus for transcription and replication of its viral RNA genome [44]. Two reviews encompassing a total of 7 randomized controlled trials (RCTs) provide evidence that Molnupiravir shows promise as a valuable agent, significantly reducing the risk of hospitalization or death in high-risk/mild COVID-19 patients. Additionally, it may benefit non-pregnant, unvaccinated adults with COVID-19 who face an elevated risk of severity and hospitalization. Another advantageous feature of Molnupiravir is its cost-effectiveness. The drug has demonstrated good tolerance and safety with no significant adverse events reported in short-term use at doses ranging from 50–800 mg BID or a single dose up to 1600 mg [23, 43, 44].

Traditional Chinese Medicine (TCM) is a holistic approach that uses herbal formulas, acupuncture, moxibustion, and other modalities to treat various diseases based on the principles of yin-yang balance, qi circulation, and organ function. TCM has been widely used in China to prevent and treat COVID-19 patients with different disease stages and syndromes. Two comprehensive reviews, comprising a total of 76 randomized controlled trials (RCTs) and 101 reviews, have reached a consensus that TCM shows promise as an alternative approach for treatment, rehabilitation, and prevention. Furthermore, when used alone or in conjunction with conventional medicine, TCM has demonstrated benefits in alleviating symptoms among patients with acute respiratory infections. Notably, one intervention that emerged as commonly utilized was Xuebijing (XBJ) injection [18, 21].

Convalescent plasma therapy (CPT) involves the use of plasma collected from individuals who have recovered from COVID-19. This plasma contains neutralizing antibodies against the SARS-CoV-2 virus. CPT has been utilized as a passive immunotherapy for COVID-19 patients, aiming to transfer immunity from donors to recipients [10]. One study has demonstrated that CPT can serve as an effective supportive therapy for COVID-19 patients with hematological malignancies. The findings indicate that CPT may lead to improved clinical outcomes, including higher survival rates, enhanced clearance of SARS-CoV-2, presence of anti-SARS-CoV-2 antibodies, shorter hospital discharge time, and better recovery after one month of CPT. Importantly, the treatment did not show any association with adverse events [31, 42]. Data on the effectiveness of Hydroxychloroquine as an antimalarial used for treating COVID-19 patients were inconclusive [27, 31]. While there has been an umbrella study on the effects of Hydroxychloroquine and chloroquine therapy in COVID-19 [5], no umbrella review has compared different classes of therapeutic options.

In addition to the above-mentioned treatments, this umbrella review discussed other therapeutic options for COVID-19 patients. These include Thymosin alpha1 (Ta1), anticoagulants, other antivirals (such as Nirmatrelvir, Saquinavir, Favipiravir), Ultra-violet radiation therapy, Colchicine, Arbidol, N-acetyl cysteine (NAC), Ayurvedic medicines, JAK inhibitors (such as Tofacitinib, Ruxolitinib, Sarilumab), SSRI (Fluvoxamine), Clozapine, Quercetin and Anakinra (immunomodulator). Among these treatment options, Ayurvedic medicines, JAK inhibitors (such as Tofacitinib, Ruxolitinib, Sarilumab), SSRI (Fluvoxamine), colchicine, and Quercetin have shown to be beneficial in treating COVID-19 [6, 9, 16, 22, 39]. On the other hand, NAC, anticoagulants, Clozapine, and Anakinra were non-beneficial [8, 12, 17, 33]. In the case of Thymosin alpha1 (Ta1), the findings suggest that Ta1 therapy does not have a statistically significant impact on mortality. However, subgroup analyses indicated a beneficial effect on mortality in patients over 60 years of age, with a proportion of females less than 40%, and with severe COVID-19 [41].

The main limitations of this systematic review are the heterogeneity of the included studies in terms of design, population, intervention, comparator, outcome, and quality; the lack of meta-analysis due to the scarcity and diversity of data; and the possibility of publication bias due to the rapid emergence and dissemination of COVID-19 literature. Therefore, the results of this review should be interpreted with caution and updated regularly. Despite the extensive research conducted on treatments for COVID-19, there are still gaps and areas of uncertainty in the existing evidence. For example, there is limited evidence on the effectiveness of certain antiviral drugs or immunomodulatory therapies. Additionally, the long-term effects of these treatments and their impact on specific patient populations, such

as pregnant women or individuals with comorbidities, require further investigation. Therefore, more high-quality RCTs are needed to evaluate the efficacy and safety of these treatments and to identify the optimal dose, duration, timing, and combination of interventions for different subgroups of COVID-19 patients.

Conclusion

In conclusion, this umbrella review offers a comprehensive overview of the current evidence on the effectiveness and safety of various pharmacological and non-pharmacological interventions for COVID-19. Based on the included studies, we found that some interventions, such as Baricitinib, Remdesivir, ACEI/ARB, TCM, and CPT may have beneficial effects on reducing mortality, hospitalization duration, and disease severity in COVID-19 patients. However, the results should be interpreted with caution due to the heterogeneity and potential bias of the studies. Other interventions, such as Lopinavir/Ritonavir, Ivermectin, Vitamin D, and Hydroxychloroquine did not demonstrate clear benefits or provided inconclusive results. Therefore, additional high-quality randomized controlled trials are needed to confirm the efficacy and safety of these interventions, while also investigating optimal dosage, duration, and timing. Furthermore, future research should also consider the potential interactions, adverse events, and cost-effectiveness of the interventions, as well as the individual characteristics and preferences of the patients. The results of this study can be useful for clinicians and physicians who need evidence to choose the best treatment in a critical situation such as COVID-19.

Additional information

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Consent to publication. Not applicable.

Availability of data and material. The authors stated that all information provided in this article could be shared.

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