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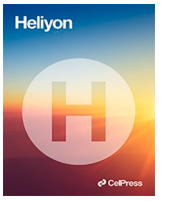

Curcumin as an antiviral agent and immune-inflammatory modulator in COVID-19: A scientometric analysis

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ABSTRACT

Background: Reports regarding the antiviral activity of curcumin have surfaced. However, to date there has been no scientometric analysis of the relationship between curcumin and Coronavirus Disease 2019 (COVID-19). To comprehensively understand the studies involving curcumin in the context of COVID-19, we conducted a scientometric analysis to provide an exhaustive review of these studies.

Methods: We systematically searched the Web of Science core collection database for bibliographic data indexed from January 1, 2020, to December 31, 2022, using keywords such as 'curcumin', 'COVID-19', and their synonyms. To clarify the research content and trends related to curcumin in COVID-19, we utilized VOSviewer, Origin 2023, and Charticulator for analysis, supplemented by external data.

Results: The final count of publications included in this study was 252. These publications originated from 63 countries or territories, with India contributing the highest number of publications. They were published across 170 journals. Notably, the Egyptian Knowledge Bank (EKB) emerged as the most important institution that carried out this study. The most cited publication had been referenced 166 times. The main elements involved in the keyword analysis were reflected in the antiviral activity of curcumin and the immuno-inflammatory modulation of the inflammatory cytokine storm. Furthermore, the pharmacological mechanisms of curcumin for treating COVID-19 emerged as a prominent area of research. Simultaneously, there exists direct evidence of clinical usage of curcumin to enhance COVID-19 outcomes.

Conclusions: The scientometric analysis underscores the burgeoning professional domain of curcumin-based treatment for COVID-19. Ongoing studies have focused on the antiviral activity of curcumin and its immunomodulatory effects on inflammatory cytokine storms. On the other hand, the pharmacological mechanism of curcumin in the treatment of COVID-19 is a hot spot in the research field at present, which may become the main research trend in this field in the future. While maintaining a focus on foundational research, the clinical application of curcumin in COVID-19 infection is developing in parallel, highlighting its obvious guiding value in clinical practice. These insights offer researchers a snapshot of the present state of curcumin treatment for COVID-19 and guide further mechanistic validation efforts in the future.

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1. Introduction

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of April 4th, 2023, there have been over 700 million confirmed cases worldwide, resulting in 6 million deaths [1]. The angiotensin-converting enzyme 2 (ACE2) acts as the gateway for SARS-CoV-2 to invade cells. It is highly expressed in numerous organs and tissues, including the lungs, heart, liver, kidneys, intestines, and vascular endothelium [2]. The immune and inflammatory response induced by SARS-CoV-2 infection plays a central role in the pathogenesis of COVID-19, and the immunopathological damage caused by this immune response is linked to the progression of the disease [3,4]. The pathophysiology of COVID-19 involves several aspects. It includes a severe inflammatory response, coagulopathy, endothelial injury, and cytokine storm [4]. Studies have shown that levels of pro-inflammatory cytokines are notably elevated in severe COVID-19 cases, correlating with intricate complications, poor prognosis, and cytokine storms [5,6]. Various methods have been developed to treat SARS-CoV-2 to reduce the occurrence of severe outcomes, including antiviral drugs, monoclonal antibodies, interleukin (IL)-1 and IL-14 inhibitors, mechanical ventilation and corticosteroids, and immunotherapy [7,8]. Antiviral drugs and vaccines are being used to treat SARS-CoV-2 infection. Nonetheless, the COVID-19 pandemic continues to have lasting effects on humanity persist.

Increasing evidence suggests that medicinal plants possess antiviral properties [9]. Ethnomedical reports emphasize the attention given to phytochemistry due to its effectiveness and safety [10]. Curcumin, the primary constituent of Curcuma longa, is a natural phytochemical with broad pharmacological activity, extensively studied in pharmacological investigations and clinical trials [11,12]. Approved by the U.S. Food and Drug Administration (FDA), it is considered to be well tolerated and safe. Apart from turmeric, curcumin is present in various traditional herbs (Table 1). Curcumin demonstrates efficacy against both RNA and DNA viruses, including Human Immunodeficiency Virus (HIV), Influenza A Virus, Human Adenovirus, Herpes Simplex Virus 2 (HSV-2), and Cytomegalovirus [13]. Furthermore, curcumin exhibits anti-inflammatory, anticoagulant, antiplatelet, and cytoprotective effects, that may help prevent the progression of inflammatory diseases [14]. Consequently, curcumin is being considered as a potential treatment option for COVID-19 [10]. Studies propose multiple ways in which curcumin might combat SARS-CoV-2. For example, it can simultaneously inhibit the SARS-CoV-2 S protein and the ACE2 receptor, as well as inhibit SARS-CoV-2 proteases including papain-like protease and main protease [15–17]. Systematic reviews suggest that supplementing with curcumin could significantly reduce the duration of common symptoms, hospital stays, and mortality among COVID-19 patients, thereby enhancing their prognosis [18–20]. Moreover, curcumin can significantly reduce the levels of inflammatory cytokines and activate anti-inflammatory pathways, thereby increasing anti-inflammatory cytokines and partially rebalancing pro-inflammatory and anti-inflammatory substances in COVID-19 patients, which could potentially regulate the COVID-19-related cytokine storm [18,21–23].

Scientometric analysis is mainly reflected in both bibliometric and manual analysis, incorporating multiple data sources. Bibliometric analysis is a quantitative research method based on retrieved literature and can reveal the correlation between literature and research trends [24]. Despite notable studies on curcumin and COVID-19, there has been no scientometric analysis conducted on this subject to date. To gain a comprehensive understanding of curcumin's role in COVID-19 studies, we conducted an exhaustive scientific analysis. This study aims to provide a holistic perspective on this subject, contributing to the current understanding and providing a reference for researchers seeking further exploration in this domain.

2. Materials and methods

2.1. Literature search and screening

For this study, literature data indexed from January 1, 2020, to December 31, 2022, were systematically searched in the Web of Science (WOS) core collection database using "curcumin", "COVID-19", and their synonyms as topics (search formula ((TS=(COVID 19

Table 1
Common herbs containing curcumin.

Herb pinyin name[a]	Herb Latin name[b]
JIANG HUANG	*Curcuma Longa* L.
CAO GUO	*Amomum tsao-ko Crevost & Lemarié*
DA ZAO	*Ziziphus jujuba Mill.*
DANG GUI	*Angelica sinensis (Oliv.) Diels*
E ZHU	*Curcuma zedoaria*
GAO LIANG JIANG	*Alpinia officinarum Hance*
GUANG XI E SHU	*Curcuma kwangsiensis S.G.Lee & C.F.Liang*
HE TAO REN	*Juglans regia* L.
LUO HAN GUO	*Siraitia grosvenorii (Swingle) C.Jeffrey ex A.M.Lu & Zhi Y.Zhang*
PIAN JIANG HUANG	*Curcuma wenyujin Y.H.Chen & C.Ling*
SHAN ZHU YU	*Cornus officinalis Siebold & Zucc.*
SUO LUO ZI	*Aesculus chinensis Bunge*
YU JIN	*Curcuma aromatica Salisb.*

[a] Source: Related herbs were collected from multiple TCM databases, including TCMSP (https://old.tcmsp-e.com/), SymMap (http://www.symmap.org/), and HERB (http://herb.ac.cn/).
[b] Plant Latin name has been checked with http://www.theplantlist.org.

or SARS-CoV-2 or 2019 Novel Coronavirus or Coronavirus Disease 19 or Severe Acute Respiratory Syndrome Coronavirus 2 or SARS Coronavirus 2 or Wuhan Coronavirus or Coronavirus Disease 2019 Virus or 2019 nCoV or Wuhan Seafood Market Pneumonia Virus)) AND TS=(Curcumin or Turmeric Yellow or Yellow, Turmeric or Diferuloylmethane or Mervia))). Original articles and reviews were used for the scientometric analysis. Letters, books, and editorials were excluded. The WOS has more scientific publications than databases such as Scopus, Derwent, and the China Knowledge Network (CNKI), making it the most commonly used database in scientometric research. Two investigators (Ke Liu and Yi Zhu) independently reviewed the identified literature data, and disagreements were resolved by a third investigator (Xiyu Cao).

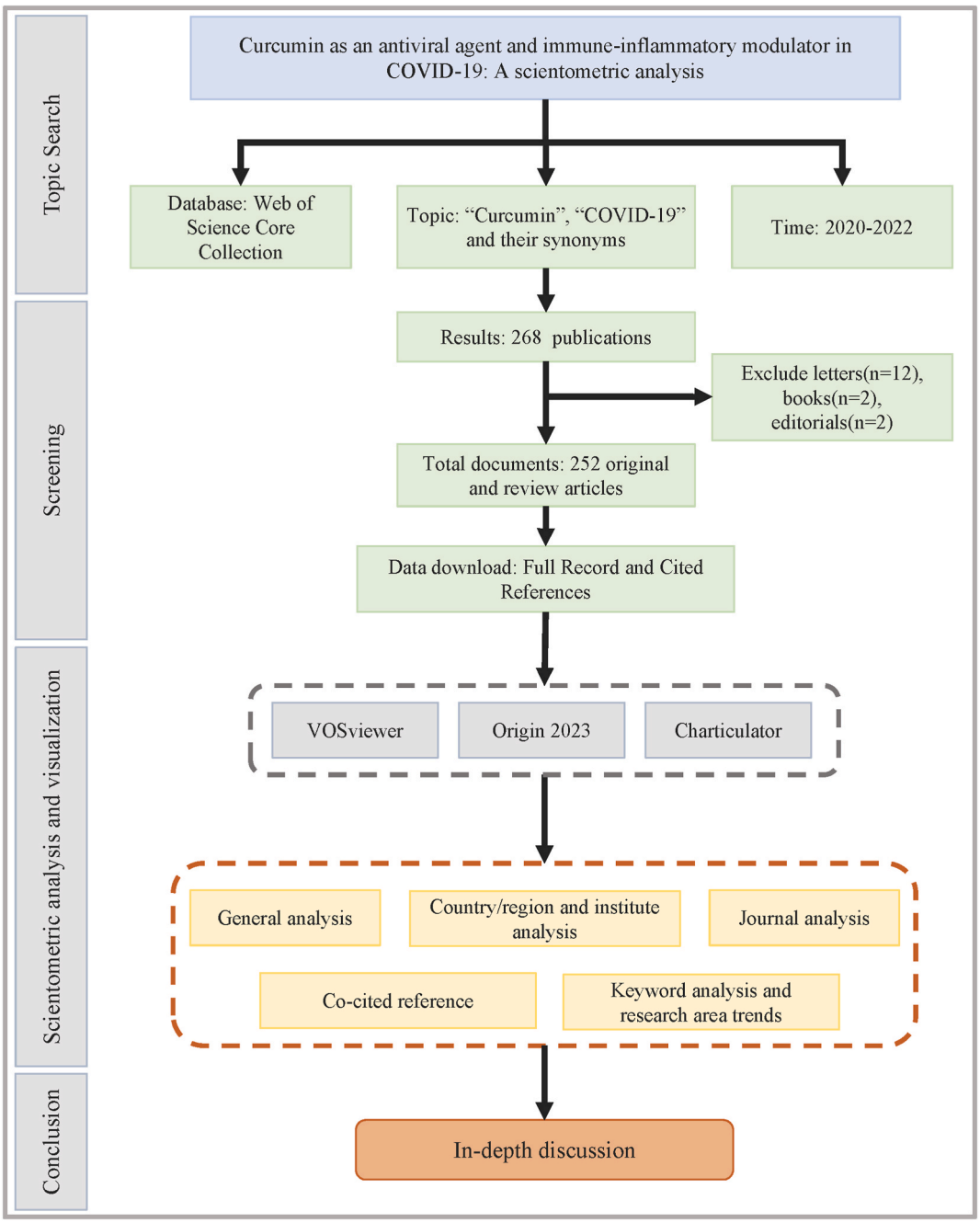

Fig. 1. Study flow chart.

2.2. Data analyses and visualization

Once the target literature was identified, we downloaded the relevant literature data from the WOS Core Collection database. VOSviewer (version 1.6.19) and the WOS Core Collection database were used to extract data for bibliometric analysis, including country or region, institution, author, keywords, journal, research area, co-cited reference, etc. Origin 2023 (https://www.originlab.com/) and Charticulator (https://charticulator.com/) were used to visualize the data. To ensure consistency in naming countries/regions, keywords, and institutions, we looked up the results and explained whether they were consistent. ClinicalTrials.gov (www.clinicaltrials.gov) served as the global database for COVID-19 clinical studies involving curcumin. Common herbs containing curcumin were collected from various Traditional Chinese Medicine databases, including TCMSP (https://old.tcmsp-e.com/), SymMap (http://www.symmap.org/), and HERB (http://herb.ac.cn/).

Total citations, impact factor (IF), and H-index are widely used methods to evaluate the quality of articles and journals [25], so they are included in our statistical results to show their impact and scientific validity. Fig. 1 illustrates the flowchart depicting the study process.

Ethical statement

This study was a scientometric analysis of published data or literature from databases only and did not involve human subjects or animal experimentation.

3. Results

3.1. General analysis

A total of 252 original and review articles related to the research topic were retrieved from the WOS Core Collection database. These publications exhibited varying citation frequencies, and the top ten most cited articles are listed in Table 2. The number of citations a publication receives is a crucial criterion used to assess its scientific merit. Notably, the most cited article in this study, with a frequency of 166, focused on the therapeutic potential of curcumin for treating COVID-19. It explored curcumin's role in inhibiting viral entry, hindering viral protease packaging, and regulating cellular signaling pathways [10]. Interestingly, while the majority of articles were published in 2021 (n = 109), the top ten most influential articles (Table 2) emerged in 2020, with only three articles published in 2021, a phenomenon possibly reflecting the emergence of the COVID-19 outbreak in late 2019. The COVID-19 outbreak

Table 2
The top 10 cited articles related to curcumin and COVID-19.

Ranking[a]	Cited Number	Year	The Title of Article	Journal[b]		
				Name	Country /Region	Impact Factor (2021)
1	166	2020	Potential effects of curcumin in the treatment of COVID-19 infection	Phytotherapy Research	England	6.388
2	119	2020	Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19	Frontiers in Immunology	Switzerland	8.787
3	105	2020	Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients	International Immunopharmacology	Netherlands	5.714
4	99	2020	Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review	Phytotherapy Research	England	6.388
5	81	2020	In silico drug discovery of major metabolites from spices as SARS-CoV-2 main protease inhibitors	Computers in Biology and Medicine	USA	6.698
6	67	2021	In silico Screening of Natural Compounds as Potential Inhibitors of SARS-CoV-2 Main Protease and Spike RBD: Targets for COVID-19	Frontiers in Molecular Biosciences	Switzerland	6.113
7	67	2020	The Inhibitory Effect of Curcumin on Virus-Induced Cytokine Storm and Its Potential Use in the Associated Severe Pneumonia	Frontiers in Cell And Developmental Biology	Switzerland	6.081
8	59	2021	Oral Curcumin With Piperine as Adjuvant Therapy for the Treatment of COVID-19: A Randomized Clinical Trial	Frontiers in Pharmacology	Switzerland	5.988
9	54	2021	Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication	Phytomedicine	Germany (FED REP GER)	6.656
10	54	2020	Curcumin, a traditional spice component, can hold the promise against COVID-19?	European Journal of Pharmacology	Netherlands	5.195

Corona Virus Disease 2019, COVID-19; Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2; USA, United States.

[a] When the number of citations is the same, the articles are sorted by the first word of the title in alphabetical order.

[b] Source: 2021 Journal Citation Reports released by Clarivate Analytics (https://jcr.clarivate.com/jcr/home).

sparked global research attention, and early findings of the outbreak formed the basis for impactful research in this field. With time, in an effort to eradicate the human impact of COVID-19, research institutions worldwide have increased their investments in COVID-19 projects, leading to a proliferation of related publications.

3.2. Country/region and institute analysis

A total of 63 countries or regions contributed scientific publications on curcumin's potential in treating COVID-19. The top 30 countries or regions in number of publications are shown in Fig. 2A. H-indexes are credible indicators when measuring scientific results, and they are complemented by the presentation of the results [26]. Among them, India published the most articles (85, 33.730 %). This is followed by United States (USA) (42, 16.667 %), Iran (33, 13.095 %), China (28, 11.111 %), Brazil (18, 7.143 %), Italy (16, 6.349 %), United Kingdom (15, 5.952 %), Egypt (13, 5.159 %) and Germany (10, 3.968 %). India had the largest share of total publications, which can be attributed to its significant COVID-19 burden. As of April 4, 2023, official statistics released by World

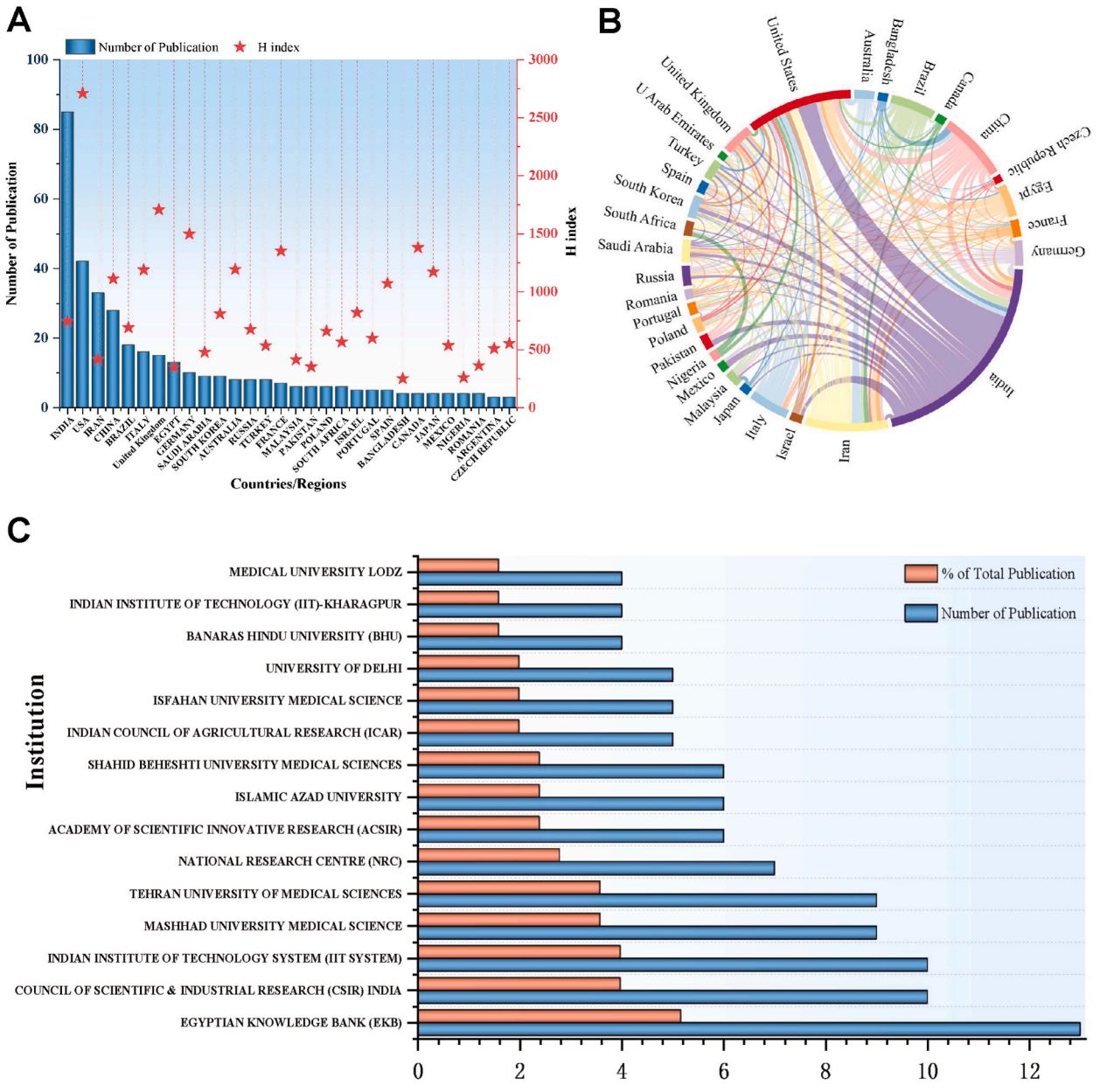

Fig. 2. Analysis by country or region and by institution. (A) The top 30 countries or regions by number of publications. (B) The collaborations of the country or region. (C) The top 15 institutions by number of publications.

Health Organization (WHO) data showed that India has 44,707,525 confirmed cases and 530,841 deaths, ranking it among the top three worldwide for both confirmed cases and deaths, likely motivating increased research investments [1]. On the other hand, spices and herbs are used to treat various chronic diseases, especially in India and other Asian countries [27].

In response to the widespread COVID-19 pandemic, countries forged collaborative partnerships to tackle this global challenge. This close collaboration is demonstrated by partnerships between countries or regions and is a trend that is driving the development of in-depth research. Different countries or regions are indicated by different colors, and the size of the color area represents the intensity of cooperation (Fig. 2B). India displayed extensive collaboration with the USA. In terms of institutional ranking (Fig. 2C), the Egyptian Knowledge Bank (EKB) stood out with the highest publications (13, 5.159 %), making significant contributions to the research on curcumin and COVID-19. Their research confirmed that curcumin has a high affinity for the SARS-CoV-2 target proteins and antiviral properties [28,29].

3.3. Journal analysis

These publications were published in 170 journals. The top 10 journals in terms of the number of publications related to curcumin and COVID-19 are listed in Table 3. The top 3 included Frontiers in Pharmacology (9, 3.571 %), Journal of Biomolecular Structure and Dynamics (9, 3.571 %) and Phytotherapy Research (9, 3.571 %). Following these were Computers in Biology and Medicine (6,2.381 %) and Molecules (5,1.984 %). The average IF of the top 10 journals was 5.431, with the highest IF coming from Frontiers in Immunology (IF 8.787) and the lowest from Molecules (IF 4.927). It is interesting to note that four of the journals are from Switzerland. These data suggest that there is still great research potential in this area. Fig. 3A shows the relationship between the top 10 journals in terms of number of publications and research fields. “Pharmacology Pharmacy” was the most researched area, and this result suggests that most of the current research is exploring the pharmacological properties of curcumin interventions in COVID-19.

3.4. Co-cited references

Co-cited references signify instances where one or more references are cited together in one or more publications, forming the research base of the field [30]. Table 4 presents the top 10 co-cited references in curcumin-COVID-19 studies. A density visualization of the cited references is shown in Fig. 3B. The weight of the density size depends on the number of citations to be determined, and the higher the number of citations, the higher the weight. As seen in Tables 4 and it can be seen that all the co-cited references in the top 10 have a frequency of more than 20 times, with the highest number of co-citations being 49. These articles formed the basis for research on curcumin in COVID-19 and offered influential insights guiding subsequent studies. Importantly, these findings reported meaningful results, including the antiviral, antibacterial, and antifungal mechanisms of curcumin [9,31–34], modulation of COVID-19 inflammatory cytokines [22], and an overview of the potential utility of curcumin in the prevention of COVID-19 [10]. These findings demonstrate the essential role of curcumin in combatting COVID-19.

3.5. Keyword analysis and research area trends

Keywords are a condensed form of research content that reflects the prevalent topics and trends in the field of study [35]. In this study, the keyword analysis was color mapped by taking the score values based on the average year to analyze the changing research trends and co-occurrence relationships in the field (Fig. 4A). Based on the frequency of keywords, we show the top 15 most frequently

Table 3
The top 10 journals related to curcumin and COVID-19.

Ranking[a]	Number of Publication	% of Total Publication	Journal				
			Name	Country/ Region[b]	Total Citations[b]	Impact Factor[b] (2021)	H-Index[c]
1	9	3.571	Frontiers in Pharmacology	Switzerland	51,910	5.988	104
2	9	3.571	Journal of Biomolecular Structure and Dynamics	USA	12,828	5.235	73
3	9	3.571	Phytotherapy Research	England	22,172	6.388	140
4	6	2.381	Computers in Biology and Medicine	USA	14,531	6.698	102
5	5	1.984	Molecules	Switzerland	128,386	4.927	171
6	4	1.587	Biointerface Research in Applied Chemistry	Romania	1969	/	15
7	4	1.587	Biomedicine and Pharmacotherapy	France	52,615	7.419	109
8	3	1.190	Current Pharmaceutical Design	U Arab Emirates	23,736	3.310	166
9	3	1.190	Foods	Switzerland	20,947	5.561	53
10	3	1.190	Frontiers in Immunology	Switzerland	127,486	8.787	155

USA, United States; U Arab Emirates, United Arab Emirates.

[a] When the number of publications is the same, the journal’s name is sorted by the first initial of the word.

[b] Source: 2021 Journal Citation Reports released by Clarivate Analytics (https://jcr.clarivate.com/jcr/home).

[c] Source: SCImago Journal & Country Rank (https://www.scimagojr.com/).

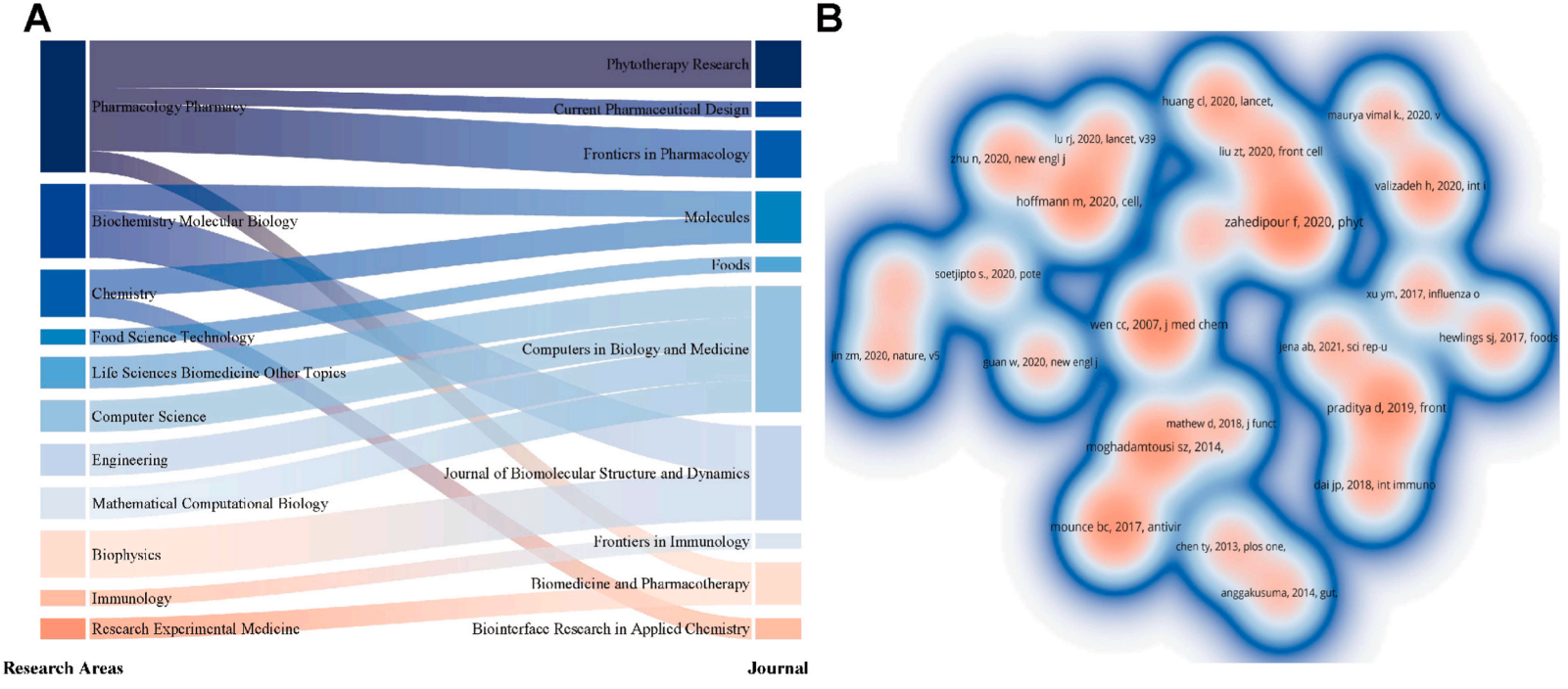

Fig. 3. Analysis of journals and co-cited references. (A) Relationship between the top 10 journals in terms of number of publications and their research fields. (B) Density visualization of co-cited references.

Table 4
The top 10 co-cited references for curcumin and COVID-19 studies.

Ranking	Cited Number	Year	The Title of Article	Journal[a]		
				Name	Country/ Region	Impact Factor (2021)
1	49	2020	Potential effects of curcumin in the treatment of COVID-19 infection	Phytotherapy Research	England	6.388
2	44	2007	Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus	Journal of Medicinal Chemistry	USA	8.039
3	40	2017	Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding	Antiviral Research	Netherlands	10.103
4	39	2019	Anti-infective Properties of the Golden Spice Curcumin	Frontiers in Microbiology	Switzerland	6.064
5	37	2014	A Review on Antibacterial, Antiviral, and Antifungal Activity of Curcumin	Biomed Research International	USA	3.246
6	36	2020	SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor	Cell	USA	66.85
7	31	2020	Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients	International Immunopharmacology	Netherlands	5.714
8	28	2020	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	Lancet	England	202.731
9	27	2020	A Novel Coronavirus from Patients with Pneumonia in China, 2019	New England Journal of Medicine	USA	176.082
10	25	2018	Inhibition of curcumin on influenza A virus infection and influenzal pneumonia via oxidative stress, TLR2/4, p38/JNK MAPK and NF-kappa B pathways	International Immunopharmacology	Netherlands	5.714

Corona Virus Disease 2019, COVID-19; Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2; USA, United States.
[a] Source: 2021 Journal Citation Reports released by Clarivate Analytics (https://jcr.clarivate.com/jcr/home).

occurring keywords (Fig. 4B). The top three keywords are COVID-19, SARS-CoV-2 and curcumin, but they are related to our research topic, so we will not discuss them. Notably, in addition to the top three keywords related to the topic, the main elements addressed in the other keywords in the top 15 are reflected in the antiviral activity of curcumin and the immune-inflammatory modulatory effects on inflammatory factor storm. Therefore, our discussion will focus more on the potential impact of curcumin on COVID-19 in these aspects.

In addition, the research area analysis provides further insight into the trending themes of curcumin in COVID-19. Our exploration utilized the WOS Core Collection database. Fig. 5 shows the top 15 research areas related to curcumin and COVID-19, with "pharmacology pharmacology" currently being the most involved area, followed by "chemistry" and "biochemistry molecular biology".

4. Discussion

Reviewing the past three years of curcumin and COVID-19 research poses both a challenge and a rewarding opportunity, particularly given the ongoing global pandemic of COVID-19. Databases serve as consolidated repositories of research results that effectively standardize information about studies. However, the information often remains fragmented and lacks systematic presentation in a unified manner. To ascertain the potential role of curcumin in treating COVID-19 and to identify prevailing research trends, we conducted an analysis. Through keyword analysis, it becomes apparent that the effect of curcumin on COVID-19 primarily centers on its antiviral activity and its role in regulating the immuno-inflammatory mechanisms associated with the inflammatory factor storm. Thus, our discussion will focus on these aspects to comprehensively grasp their mechanisms of action and provide insights for future research directions. In addition, curcumin has indeed been employed as a clinical intervention to ameliorate COVID-19 effects (Table 5). In light of these clinical trials demonstrating curcumin's effective intervention in COVID-19, we also delve into a discussion of these trials to emphasize potential future strategies involving curcumin.

4.1. Antiviral activity of curcumin as an antiviral drug

The antiviral properties of curcumin were proposed in the 1990s, and since then, it has gradually attracted attention and research. Curcumin exhibits a broad spectrum of antiviral effects, including its activity against human immunodeficiency virus, hepatitis C virus, hepatitis B virus, herpes simplex viruses, and coronavirus [36]. The antiviral effect of curcumin is achieved through multiple pathways, including virus attachment, virus entry, protein replication, and direct virus killing [13]. Clearly, curcumin's antiviral mechanism spans the entire course of viral invasion and proliferation, with considerable direct antiviral impact. For example, curcumin at 50 μM has significant anti-Zika virus activity [37], curcumin at 30 μM can inhibit Human Parainfluenza Virus Type 3 replication [38].

Moreover, curcumin has demonstrated remarkable efficacy against coronaviruses. It inhibits SARS-CoV replication and 3CL protease in Vero E6 cells [32]. Curcumin modifies the surface protein of the porcine epidemic diarrhea virus (a model coronavirus), thereby obstructing viral entry. Additionally, curcumin also suppresses the synthesis of negative-strand RNA of the virus, thereby

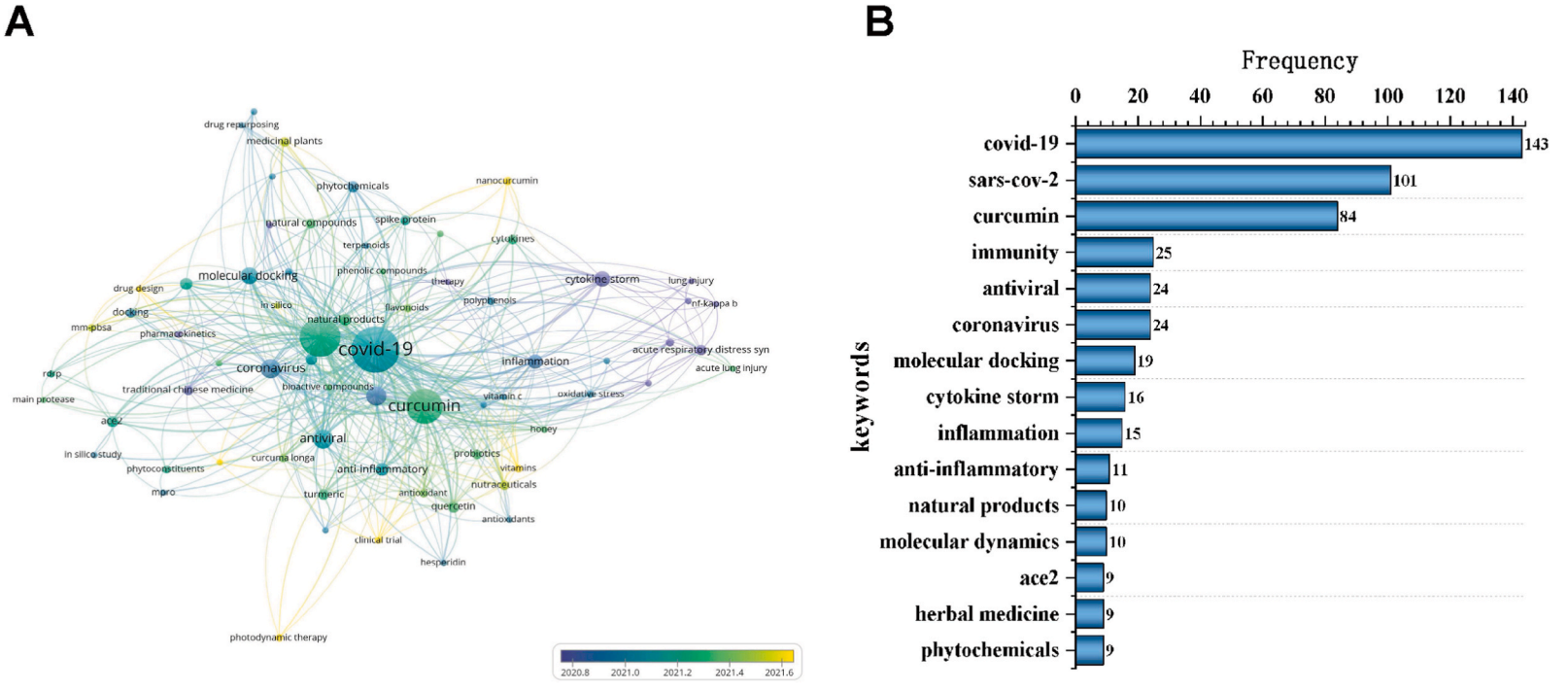

Fig. 4. Keyword analysis. (A) Keyword co-occurrence network. (B) The top 15 most frequent keywords.

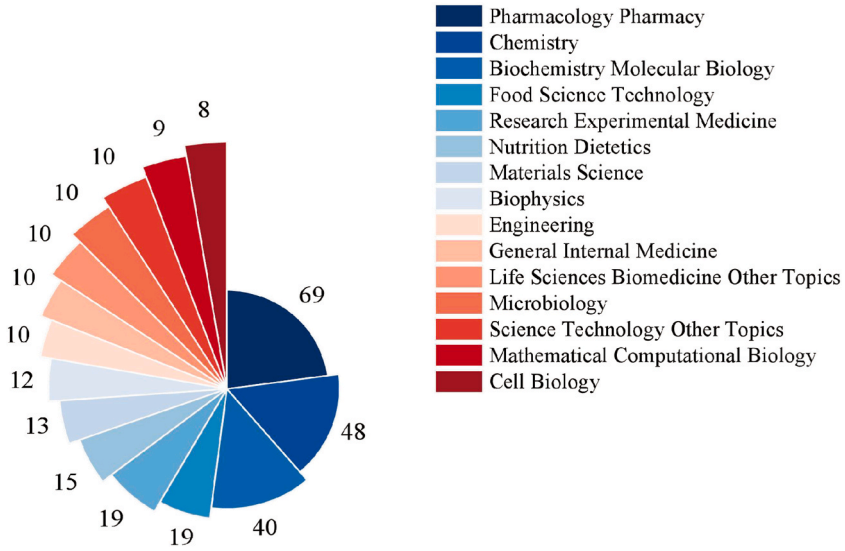

Fig. 5. The top 15 research areas in number of studies.

inhibiting viral replication [39]. Another similar study showed that curcumin can inhibit porcine delta coronavirus replication in LLC-PK1 cells [40]. Moreover, curcumin also inhibits transmissible gastroenteritis virus (an alpha-coronavirus model) proliferation and viral protein in porcine kidney cells [41]. Therefore, curcumin has been recommended as a potential anti-SARS-CoV-2 drug and the current study supports this hypothesis.

Curcumin inhibits the binding of SARS-CoV-2 spike protein and ACE2 according to in silico studies demonstrating its high affinity for SARS-CoV-2 spike protein and ACE2 [42–44]. This binding ability was validated in A549 cells in vitro. Curcumin also suppresses the activity of transmembrane serine protease 2 (TMPRSS2) [45], implying its potential to obstruct SARS-CoV-2 attachment and entry.

In addition, in silico studies have also demonstrated the ability of curcumin to bind to the major protease of SARS-CoV-2, thereby inhibiting protease activity [46–50]. For instance, curcumin impedes SARS-CoV-2 3CLpro main protease in vitro (with IC50 values of 11.9 μM) [51]. Meanwhile, curcumin also showed the binding potential to RNA-dependent RNA polymerase [29]. In vitro experiments illustrate curcumin's ability to significantly reduce SARS-CoV-2 RNA levels in Vero E6 and human Calu-3 cell culture supernatants [52]. Notably, a concentration of 10 μM curcumin inhibited SARS-CoV-2 replication (reduction >99 %) in Vero E6 cells, which may be related to disruption of the structure of the virus [53]. Hence, curcumin's role in inhibiting SARS-CoV-2 replication assumes significance.

Overall, experimental evidence underscores curcumin's potential to combat SARS-CoV-2, involving inhibition of viral attachment, viral entry, and replication of the major protein (Fig. 6). Nevertheless, the mechanisms underlying this anti-SARS-CoV-2 effect necessitate further investigation.

4.2. Immune-inflammatory mechanisms of curcumin in response to cytokine storm

Curcumin exhibits significant anti-inflammatory activity, modulating cytokine cascades and cytokine storms caused by excessive inflammatory cytokines. It mitigates cytokine storms by reducing pro-inflammatory cytokines and stimulating anti-inflammatory signals [9,21,34,54–57]. While the precise pathogenesis of COVID-19 remains uncertain, mounting evidence suggests that SARS-CoV-2 causes an imbalance in the host's immune and inflammatory responses, leading to a phenomenon known as "cytokine storm." This storm involves a rapid systemic inflammatory reaction characterized by hyperactivated immune cells, pro-inflammatory responses, and abnormal cytokine production and release [58]. Immune effector cells release substantial amounts of pro-inflammatory cytokines (IL-6, IL-18, tumor necrosis factor-α) and chemokines (CXCL10, CXCL8, IP10, MCP1) during SARS-CoV infection, exacerbating the overall inflammatory response [59–62].

Studies have confirmed that the severity of COVID-19 correlates with cytokine storms, where heightened cytokine storm levels lead to more severe disease progression [63,64]. Intervening in this cytokine storm presents a novel approach to treating COVID-19 and alleviate its adverse effects resulting from cytokine overproduction. Studies reveal that COVID-19 patients exhibit significantly elevated mRNA expression and release of IL-1β, IL-6, tumor necrosis factor (TNF)-α, and IL-18, along with increased proinflammatory cytokine levels compared to healthy individuals [22,65]. Notably, curcumin effectively inhibits the production and secretion of pro-inflammatory cytokines (such as IL-1, IL-6, IL-8, and TNF) to a significant degree [66,67]. Accordingly, Valizadeh et al. [22] observed that the expression and release of IL6 and IL1β were significantly reduced in the serum and supernatant of COVID-19 patients treated with nanocurcumin. In vitro studies demonstrate that curcumin inhibited the SARS-CoV-2-induced release of pro-inflammatory cytokines (IL-1, IL-6, and IL-8) from peripheral blood mononuclear cells (PBMCs) [68]. Meanwhile, Vivek K. Sharma et al. [69] observed that curcumin significantly inhibited intracellular levels of IL-6 and IL-8 when applied to SARS-CoV-2 spike protein-induced

Table 5
Clinical trials related to curcumin and COVID-19 (www.clinicaltrials.gov).

Study Title	Condition or disease	Intervention/treatment	Sample size	Status	Clinical Trial Identifier
The Effect of Micellized Food Supplements on Health-related Quality of Life in Patients With Post-acute COVID-19 Syndrome	Post-acute COVID-19 Syndrome	Dietary Supplement: Curcumin/ Boswellia Serrata/Ascorbic acid mixture	32	Not yet recruiting	NCT05150782
Nutritional Supplementation of Flavonoids Quercetin and Curcumin for Early Mild Symptoms of COVID-19	COVID-19	Drug: Standard of care Dietary Supplement: Investigational treatment	50	Completed	NCT05130671
Oral Curcumin, Quercetin and Vitamin D3 Supplements for Mild to Moderate Symptoms of COVID-19	COVID-19	Dietary Supplement: Complementary therapy Drug: Standard of care	50	Completed	NCT04603690
Effect of Palmitoylethanolamide on Proinflammatory Markers in Adults Recently Diagnosed With COVID-19	Inflammation COVID-19	Dietary Supplement: palmitoylethanolamide Dietary Supplement: Placebo Dietary Supplement: Curcumin Dietary Supplement: Control (microcrystalline cellulose)	115	Completed	NCT04912921
Clinical Study Designed to Evaluate the Effect of CimetrA[a] in Patients Diagnosed With COVID-19	Corona Virus Infection COVID-19 SARS-CoV Infection	Drug: Placebo administration/ CimetrA-1/CimetrA-2	252	Active, not recruiting	NCT04802382
A Phase II, Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC[b] in Patients Diagnosed With COVID-19	COVID-19 Corona Virus Infection SARS-CoV-2 Coronavirus Coronavirus Infection	Drug: ArtemiC Drug: Placebo	50	Completed	NCT04382040
Study Designed to Evaluate the Effect of CimetrA in Patients Diagnosed With COVID-19	COVID-19 Corona Virus Infection	Drug: Treatment administration	240	Completed	NCT05037162
Oral Nutritional Supplements in Treatment of Elderly Mild-to-Moderate COVID-19	Nutrition, Healthy	Dietary Supplement: Oral Nutritional Supplements	150	Not yet recruiting	NCT05629975
Covid-19, Hospitalized, PatIents, Nasafytol	Coronavirus Infection	Dietary Supplement: NASAFYTOL®[c] Dietary Supplement: FULTIUM® -D3 800 Drug: Strandard of care treatment	51	Completed	NCT04844658

Corona Virus Disease 2019, COVID-19; Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2.
[a] A nanoparticular formulation consisting of artemisinin, curcumin, boswellia and vitamin C.
[b] A micellar formulation spray consisting of artemisinin, curcumin, frankincense and vitamin C.
[c] The supplement contains a bioactive mixture of turmeric extract or curcumin, natural quercetin from Sophora japonica and vitamin D3.

hepatic Huh7.5 and pulmonary A549 epithelial cells with nanocurcumin. Moreover, curcumin has been observed to effectively modulate cytokines, chemokines, and growth factors induced by the SARS-CoV-2 spike protein, subsequently alleviating the inflammatory response and associated organ damage in COVID-19 patients.

We know that after SARS-CoV-2 enters host cells through ACE2, the level of ACE2 receptors on the cell surface decreases. With the down-regulation of ACE2, the expression level of angiotensin II (AngII) increases, resulting in modifications to the renin angiotensin system (RAS) and contributing to the conversion of the RAS to the Ang II/angiotensin II type 1 receptor (AT1R) axis. The overstimulation of AT1R by Ang II mediates subsequent signaling, leading to uncontrolled production and release of pro-inflammatory cytokines [58,70–72]. AT1R can induce monocyte chemoattractant protein-1 (MCP-1) by activating RhoA/RhoA-kinase, which promotes inflammatory responses [73]. Studies have shown that curcumin can reduce MCP-1 expression by targeting various molecular pathways and mechanisms of action [74,75]. Pro-inflammatory factors produced by immune cells and the Ang II/AT1R axis act through activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT), and nuclear factor kappa-B (NF-κB) pathways [76]. Curcumin is believed to inhibit STAT3, preventing its activation and mitigating cytokine storms [77,78].

On the other hand, AngII can also activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and thus NF-κB [79]. Meanwhile, various pattern recognition receptors (PRRs) allow the innate immune system to detect the presence of viruses [80]. These PRRs initiate a series of signaling cascades by binding to pathogen-associated molecular patterns (PAMPs) structures and damage-associated molecular patterns (DAMPs) on pathogens, producing cytokines and chemokines and promoting innate immune responses [81]. Among them, toll-like receptors (TLR) are key pattern recognition receptors that bind to PAMPs to activate NF-κB, thereby promoting transcriptional activation of inflammatory cytokines and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), which perform a key function in the SARS-CoV-2-induced cytokine storm [82]. The mechanisms by which curcumin regulates inflammation have been extensively studied, with TLR and NF-κB playing pivotal roles. It has been shown that curcumin inhibits the NF-κB signaling pathway by targeting IKKβ activation [83], preventing IκBα degradation [84,85], and blocking the nuclear

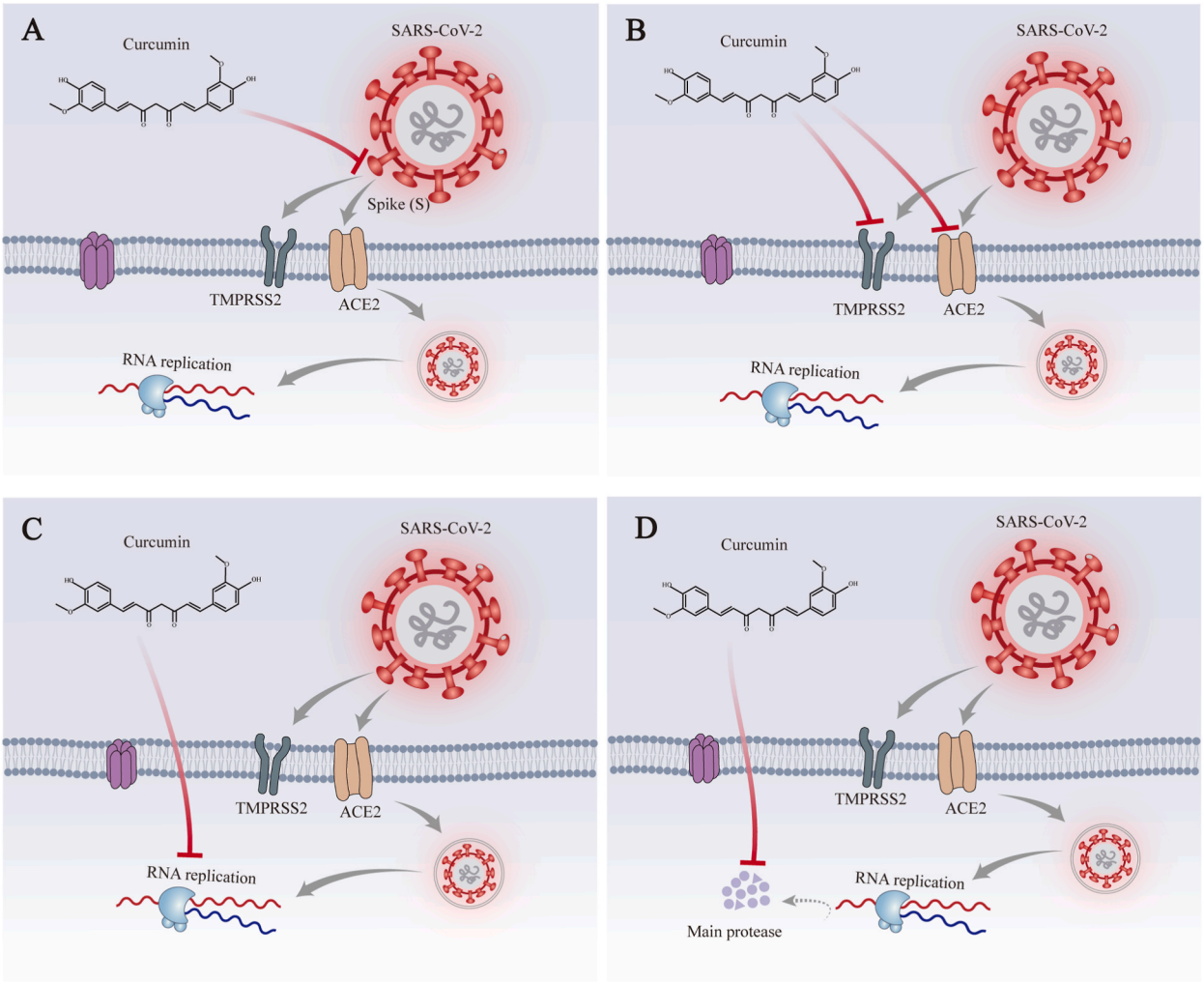

Fig. 6. Potential targets of curcumin in anti-SARS-CoV-2. (A) Curcumin has high affinity for SARS-CoV-2 spike protein, thereby interfering with the binding of SARS-CoV-2 spike protein and ACE2. (B) Curcumin binds better to ACE2 and TMPRSS2 receptors and inhibits the attachment and entry of SARS-CoV-2 virus. (C) Curcumin inhibits viral replication. (D) Curcumin inhibits the main protease SARS-CoV-2.

translocation of NF-κB and p65 [85]. In addition to its effects on the NF-κB pathway, curcumin also downregulates TLR and inhibits virus-induced NLRP3 activation, effectively reducing the inflammatory response [34,86–88]. In conclusion, curcumin has the potential to improve the cytokine storm status by modulating multiple inflammatory pathways (Fig. 7) and has great potential to suppress excessive inflammation in SARS-CoV-2 infection.

In contrast to inhibiting pro-inflammatory factors, curcumin elevates anti-inflammatory cytokines like IL-10 [89]. IL-10, known for its anti-inflammatory properties, mitigates inflammation-induced responses via various pathways [90]. Safa Tahmasebi et al. [23] showed that nanocurcumin significantly upregulated serum Treg cell counts, Treg transcription factor forkhead box P3 (FoxP3) and anti-inflammatory cytokines (IL-10, IL-35 and TGF-β) in patients with mild and severe COVID-19. Consistent with previous findings, Yu-Sen Chai et al. [89] found in a mouse model of acute lung injury that curcumin not only decreased pro-inflammatory cytokines, but also increased Treg cell differentiation and IL-10 cytokine expression, exerting an anti-inflammatory cytokine effect. Thus, under a cytokine storm, curcumin can act as a bidirectional regulator, inhibiting pro-inflammatory factors and upregulating anti-inflammatory factors.

4.3. Clinical application of curcumin in COVID-19

Interestingly, our study also observed clinical trials in which curcumin was used to treat COVID-19. Table 5 shows the registered clinical trials in various countries on this subject. To enhance its bioavailability, curcumin analogues and various formulations such as nanoparticles, micelles, and liposomes have been employed [78]. Hamed Valizadeh et al. [22] administered nanocurcumin to COVID-19 patients and demonstrated that it could modulate inflammatory cytokines, leading to improved clinical outcomes and

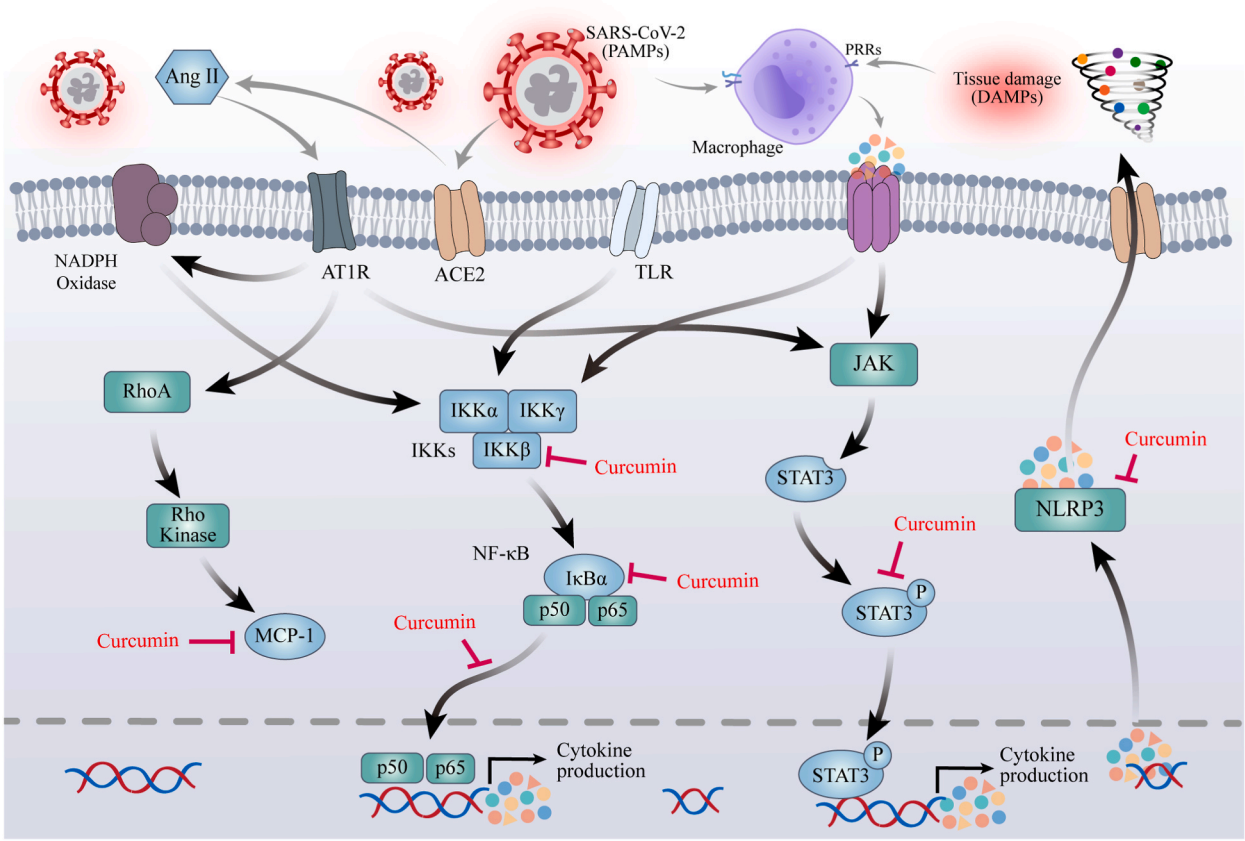

Fig. 7. Inhibition of COVID-19 cytokine storm by curcumin. Curcumin inhibits the cytokine cascade and cytokine storm caused by excessive inflammatory cytokines. Curcumin inhibits NF-κB, JAK-STAT signaling and downstream activation of MCP-1 and NLRP3.

physical recovery. Similarly, two other randomized controlled trials indicated that nanocurcumin, functioning as an anti-inflammatory agent, suppressed the inflammatory response of symptoms in patients with COVID-19 [91,92]. On the contrary, studies have also highlighted the ability of nanomicelles containing curcumin to expedite recovery from acute inflammation by regulating the immunoinflammatory response during the inflammatory phase of COVID-19 [93]. In addition, the combination of curcumin and piperine as a supplement significantly reduced weakness in patients with COVID-19 [94]. Overall, these studies collectively underscore that curcumin can effectively enhance COVID-19 outcomes and holds significant potential in the clinical improvement of the condition.

4.4. Future trends

Fig. 4A depicts the temporal progression of keywords, offering insights into potential future research avenues, including "drug design," "nanocurcumin," "vitamins," "photodynamic therapy," and "clinical trial." As mentioned above, curcumin is widely found in food and is a safe drug, so it has broad prospects for drug design. In drug development, oral formulation is still the most common way to take curcumin [95,96], among them, nanocurcumin is a successful practice, it has higher bioavailability than curcumin and can better exert the pharmacological activity of curcumin [97]. Several randomized controlled trials have evidenced that nanocurcumin can inhibit natural killer cells and T helper 17 cells, thereby reducing the release of inflammatory factors such as IL-1β, IL-6, and TNF-α. Moreover, since nanocurcumin can effectively increase O_2 saturation and reduce the severity of symptoms in COVID-19 patients, it may be used as a supplement to accelerate the recovery of patients, thereby improving the symptoms and shortening the recovery period of COVID-19 patients [22,91,98,99]. However, most of these studies were single-center studies with small populations and different oral doses of nanocurcumin. In the future, more long-term, multi-center and large-sample studies are recommended.

Additionally, the combination of curcumin with natural products or vitamins continues to demonstrate promising therapeutic effects against COVID-19. A system biology analysis showed that the combination of curcumin, vitamin C, and glycyrrhizic acid could regulate immune and inflammatory responses associated with coronavirus infections [100]. Another randomized controlled trial confirmed the superiority of this drug combination; oral supplementation with curcumin, quercetin, and vitamin D3 expedited SARS-CoV-2 RT-PCR test negativization, improved symptoms, reduced excessive inflammatory responses, and exhibited good tolerance and safety [101]. Furthermore, curcumin's potential extends to acting as a photosensitizer for combating SARS-CoV-2 in vitro [102,103].

4.5. Limitations and advantages

The data for this study are sourced from the WOS Core Collection dataset, which is considered to provide high-quality research outcomes, containing a substantial volume of data to substantiate the study, and is ideal for econometric analysis [104]. Thus, the results we have obtained are both credible and scientifically grounded. Our findings elucidate the trend of curcumin research in the context of COVID-19 and comprehensively summarize the current findings. However, our study does exhibit certain limitations. First, we used the WOS Core Collection dataset for our study, and the results may have been different if other databases had been used. Second, despite conducting a thorough search, it is possible that some recent articles might not have been adequately indexed by WOS within the timeframe, thereby potentially not being fully accounted for in our analysis.

5. Conclusions

This study systematically analyzed literature and data employing scientometric methods, thereby revealing the focal points and research trends surrounding curcumin's role in COVID-19 over the past three years. Our study summarizes curcumin's function in antiviral activity and immune inflammatory modulation of inflammatory factor storms. Beyond fundamental research, there is concurrent advancement in clinical trials involving curcumin for COVID-19 infection, underscoring its pronounced guiding significance in clinical practice. As COVID-19 is gradually recognized worldwide, combating the pandemic remains a pivotal step for future development. Our study not only delineates current research focal points and trends but also exposes the limitations within current curcumin research. However, curcumin continues to captivate researchers' interest for its potential in COVID-19 prevention, and its research and innovation within the field of COVID-19 are poised for substantial and sustained advancement in the future.

Author contributions

Ke Liu, Yi Zhu: conceived and designed the experiments, performed the experiments, analyzed and interpreted the data, and wrote the paper. Xiyu Cao, Yufei Liu and Rongtao Ying: analyzed and interpreted the data. Qingsong Huang and Peiyang Gao: contributed reagents, materials, analysis tools or data. Chuantao Zhang: contributed reagents, materials, analysis tools or data, and wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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