Worldwide research trends on chloroquine: a bibliometric analysis from 2012 to 2021

Lei Xu1, Qi-Han Zhu2, Yang Zhao3, Ming Xiong2, Si He1, Yao-Na Xu1, Chen-Xi Liu4**, Xiao-Fei Hu5**

1School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing 102488, China. 2Department of Basic Medicine, Third Military Medical University (Army Medical University), Chongqing 400038, China. 3Development Research Center of TCM, China Academy of Chinese Medical Sciences, Beijing 100700, China. 4Department of Nuclear Medicine, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing 400038, China.

*These authors contributed equally to this work and are co-first authors for this paper.

**Corresponding to: Chen-Xi Liu, Development Research Center of TCM, China Academy of Chinese Medical Sciences, No. 16 Dongzhimen Inner South Street, Beijing 100700, China. E-mail: lyj_20080819@126.com; Xiao-Fei Hu, Department of Nuclear Medicine, Southwest Hospital, Third Military Medical University (Army Medical University), No. 30 Gaotanyan Street, Shapingba District, Chongqing 400038, China. E-mail: harryzonetmmu@163.com.

Author contributions
Xu L, Zhu QH and Zhao Y collected and analyzed the data, wrote the paper. Xiong M, He S, and Xu YN performed the data curation. Hu XF and Liu CX conceived and designed this study, analyzed the data, wrote the paper. Hu XF revised the paper. Xu L, Zhu QH, and Zhao Y contributed equally to this work. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
CQ, chloroquine; WoSCC, Web of Science Core Collection; NC, number of non-self-citations; NP, number of publications; HCO, hydroxochloroquine; SLE, systemic lupus erythematosus.

Citation

Abstract
Background: Chloroquine (CQ) is an antimalarial drug that was first synthesized by Hans Andersag, a German scientist, in 1934. Chloroquine has been widely researched and used over the years. The rapid development in the fields of modern science and technology has also contributed to the increase in interest in chloroquine. Hence, it is necessary to comprehensively summarize the research trends to understand the breakthroughs made in the field. Methods: The required data was compiled by analyzing the Web of Science Core Collection (WoSCC) database. The search period for studying global research trends in chloroquine research was set from 2012 to 2021 to ensure a comprehensive analysis over an extended timeframe. Data retrieval was performed on April 4, 2022, focusing on articles and reviews published in English. The retrieval words were: (TS = (chloroquine)) OR (TS = (aralen)). A total of 1,091 reviews and 7,259 articles were retrieved and analyzed. The data obtained from WoSCC was captured and analyzed using VOS viewer (version 1.6.16) and Citespace (version 5.8.R5). Results: The number of literature reports on chloroquine published in the past 10 years has shown an annual increase. Among the countries, the United States has contributed the highest number of papers and ranks first in terms of both H-index and citation count. The League of European Research Universities is one of the largest research-focused university networks, and Malaria Journal stands out as a prominent journal publishing articles relevant to the field of study. A paper authored by Gautret and Philippe in 2020 achieved the highest citation score globally. The biosynthesis of chloroquine, mechanisms of drug resistance, and drug combinations are receiving growing attention. Conclusion: The research area of chloroquine has been significantly influenced by the American and China. The progress of chloroquine research is further propelled by fruitful collaborations among various countries. Researchers have extensively studied the anti-malarial effect, drug resistance mechanism, and autophagy of chloroquine for the development of a treatment method for COVID-19 based on chloroquine. Bibliometric analysis can be employed to identify hotspots, new directions, and frontiers in the field of chloroquine research.

Keywords: bibliometrics; chloroquine; vosviewer; citespace; network; hotspot
Collection (WoSCC) database. The search period for studying global research trends in chloroquine research was set from 2012 to 2021 to ensure a comprehensive analysis over an extended timeframe. Data retrieval was performed on April 4, 2022, focusing on articles and reviews published in English. The retrieval words were: (TS = chloroquine) OR (TS = aralen)). Various related publications, including previously published papers, letters, book reviews, bibliographical entries, conference abstracts, book chapters, reprints, editorial materials, news items, corrections, data files, early visits, and bibliographies, were considered. A total of 1,091 reviews and 7,259 articles were retrieved and analyzed (Figure 1A).

Bibliometric analysis
The data obtained from WoSCC was captured and analyzed using VOS viewer (version 1.6.16) and Citeseer (version 5.8.R5). Bibliometric indicators, including the number of non-self-citations (NC) and the number of publications (NP), were extracted from the obtained data. Hirch J E introduced the concept of H-index in 2005, revolutionizing the study of science. According to the original definition, a researcher's scientific output can be measured by the H-index if they have published H papers, each of which has been cited at least H times. The study of the H-index is expected to become one of the most important areas of focus in scientometrics over the next 10 years. The introduction of the H-index concept is considered the most significant breakthrough in the field of scientometrics since the 21st century. Additionally, a co-occurrence keyword network was constructed to display research hotspots related to chloroquine. The burst of references and keywords is frequently used to identify new research trends in this field [8].

Results
Citations and influence for chloroquine
The retrieval strategy described earlier was employed to gather 8,350 reviews and articles on chloroquine published between 2012 and 2021. A total of 102,859 citations were obtained from all the articles, resulting in an average of 21.48 citations per article. The H-index for all publications reached 134.

Annual trend (NP)
A polynomial fitting curve (Figure 1B) was used to analyze the data on the annual trend. The annual NP showed a significant association with the year of publication. Despite the volatility observed over the past decade, the NP increased from 593 in 2012 to 1,361 in 2021, with the peak occurring in 2020.

National characteristics
The influence of a country/region in a research field and the importance the country/region pays to a certain research field can be understood to some extent by analyzing the papers published by a country/region. A total of 156 countries/regions published articles on chloroquine in the period 2012–2021 (Figure 2A). The top 10 contributors are depicted in Figure 2B. In 2020 and 2021, the number of publications from all countries or regions significantly increased. Overall, these results indicate that chloroquine is being extensively researched and that the field has entered a stage of rapid development. Table 1 reveals that the United States reported the highest number of research articles on chloroquine (2,135), followed by China (1,762) and India (853). American, China and England ranked first, second and third, respectively, in terms of citation counts, with 41,139, 28,731 and 13,082 citations. Additionally, the United States reported the highest H-index (102), which was twice that of India (51). American, China and England ranked first, second and third, respectively, in terms of citation counts, with 41,139, 28,731 and 13,082 citations. High quality publications were from France and Italy, which had high average per publication. On the other hand, India and Japan need to improve their publication quality. Figure 2C portrays the international collaboration network, demonstrating the close cooperation among countries. Initial research in the field was...
AIGA conducted by the USA, England, Thailand, and Kenya (Figure 2).

**Performance of affiliates and authors**

Table 2 presents the top 10 affiliates with the highest number of chloroquine-related papers. The League of European Research Universities achieved the highest NC (14,568), NP (434), and H-index

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**Figure 1** The search strategy and the growth trend of publications. (A) The search strategy with a frame chart. (B) The growth trend of publications from 2012 to 2021. WOS, Web of Science.

**Figure 2** Countries/regions in artemisinin research. (A) Annual output trend of the top 10 productive countries/regions. (B) Visual cluster analysis of cooperation among countries/regions. (C) Timeline visualization of cooperation among countries/regions.

**Table 1** Publications in the top 10 productive countries

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country/Region</th>
<th>Np</th>
<th>%of(8,350)</th>
<th>Nc</th>
<th>H-index</th>
<th>Average per item</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>2135</td>
<td>25.57</td>
<td>41139</td>
<td>102</td>
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<tr>
<td>2</td>
<td>PEOPLES R CHINA</td>
<td>1762</td>
<td>21.10</td>
<td>28731</td>
<td>71</td>
<td>21.13</td>
</tr>
<tr>
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<td>INDIA</td>
<td>853</td>
<td>10.21</td>
<td>10788</td>
<td>51</td>
<td>16.91</td>
</tr>
<tr>
<td>4</td>
<td>ENGLAND</td>
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<td>7.84</td>
<td>13082</td>
<td>66</td>
<td>30.61</td>
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<tr>
<td>5</td>
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<td>6</td>
<td>BRAZIL</td>
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<tr>
<td>7</td>
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<td>6942</td>
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<td>JAPAN</td>
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<td>5426</td>
<td>38</td>
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<tr>
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<td>ITALY</td>
<td>333</td>
<td>3.99</td>
<td>10100</td>
<td>50</td>
<td>34.29</td>
</tr>
</tbody>
</table>
Journal performance and co-citation analysis

An analysis of the data indicates that the Malaria Journal (IF: 2.979) has published most papers on chloroquine (498 publications). PLOS ONE (IF: 3.24) ranks second with 230 papers, followed by Antimicrobial Agents and Chemotherapy (IF: 5.191) with 178 publications (Table 4). Among these top 10 journals, Autophagy (IF: 16.016), European Journal of Medicinal Chemistry (IF: 6.514), Cell Death & Disease (IF: 8.469), Frontiers in Pharmacology (IF: 5.811), and Antimicrobial Agents and Chemotherapy (IF: 5.191) had higher impact factors, while the remaining journals had lower impact factors (below 5.000). These findings underscore the necessity for enhancing the quality of research and conducting more comprehensive studies. It is worth noting that Autophagy exhibited the highest H-index and average per item among the journals analyzed.

Figure 4A illustrates the co-occurrence network, with PLOS ONE, Malaria Journal, and Autophagy being the journals with the highest citation frequency. A co-citation relationship is formed when two articles are simultaneously cited in a third publication [9]. The minimum number of co-citations for a paper was set at 90 references. Figure 4C presents comprehensive data, indicating that a total of 149 references were utilized for co-citation analysis. Supplementary Table S1 presents the top 10 most cited papers. In 2020, the paper reported by Wang ML was cited 636 times, ranking first. It was followed by the paper reported by Dondorp, AM in 2009, and the paper reported by Trager, W in 1976, which came in third.

Group 1 (red) consisted of 54 articles primarily focused on the efficacy and clinical trials of hydroxychloroquine against COVID-19. Group 2 (green) primarily focused on drug resistance and drug resistance research of falciparum malaria. Group 3 (blue) focused on chloroquine, apoptosis, and autophagy studies. Group 4 (yellow) focused on chloroquine and hydroxychloroquine used for the treatment of autoimmune diseases, as well as the toxic side effects on the retina. The paper reported by Dondorp, AM in 2009 had the maximum burst strength (Figure 4D). Due to the large number of authors, the minimum number of co-citations for a paper was set at 130. For the analysis, 181 authors out of the 137,042 authors cited in the retrieved publications were selected (Figure 4E). Supplementary Table S2 presents the top 10 fabricators. The World Health Organization was cited the most number of times (2,148), followed by Mizushima, N (1,225) and White, NJ (1,014). The World Health Organization had the highest total link strength (21,232), followed by White, NJ (12,494) and Price, RN (10,570).

Global citation score trends

Figure 5 presents the annual global citation score numbers for the top 10 publications. Gautret, P’s study in 2020 ranked first with a global citation score of 2,505. Gautret, P reported in this paper that chloroquine had a superior therapeutic effect on SARS-CoV-2 patients compared to chloramphenicol, resulting in a significant reduction and disappearance of SARS-CoV-2 load. Yao et al. [10], conducted a study that demonstrated hydroxychloroquine’s more effective inhibition of SARS-CoV-2 compared to chloroquine in vitro. Sanders et al. [11], found no evidence from randomized clinical trials supporting any potential treatment method to improve outcomes in confirmed or suspected COVID-19 patients. There was also no clinical trial data supporting preventive treatment. Arrey, F utilized whole genome sequencing to associate mutations in the PF3D7_1343700 Kelch-Propeller domain (“K13-Propeller”) with artemisinin resistance in vivo and in vitro [12]. The mutant K13 propeller allele was concentrated in provinces with widespread drug resistance in Cambodia, suggesting its role in the recent spread of drug resistance in western Cambodia. The presence of mutant alleles, ectoparasite
Figure 3 The visualization of energetic authors and affiliations analysis. (A) Analysis of cooperation among affiliations. (B) Top 20 representative burst affiliations. (C) Timeline distribution of cluster analysis of affiliations. (D) Analysis of cooperation among authors. (E) Top 20 representative burst authors. (F) Timeline distribution of cluster analysis of authors.

Table 3 The top 10 authors with the most publications

<table>
<thead>
<tr>
<th>Rank</th>
<th>Author</th>
<th>Country</th>
<th>Np</th>
<th>Nc</th>
<th>H-index</th>
<th>Average per item</th>
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<td>3</td>
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<td>2131</td>
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<td>UK</td>
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<tr>
<td>7</td>
<td>De Kock, Carmen</td>
<td>South Africa</td>
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<tr>
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<td>10</td>
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<td>36</td>
<td>980</td>
<td>21</td>
<td>28.11</td>
</tr>
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</table>

Table 4 The top 10 most active journals

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
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<th>H-index</th>
<th>NC</th>
<th>IF(2020)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Malaria Journal</td>
<td>498</td>
<td>36</td>
<td>4629</td>
<td>2.979</td>
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<tr>
<td>2</td>
<td>Plos One</td>
<td>230</td>
<td>39</td>
<td>5178</td>
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<tr>
<td>3</td>
<td>Antimicrobial Agents And Chemotherapy</td>
<td>178</td>
<td>31</td>
<td>2905</td>
<td>5.191</td>
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<td>4</td>
<td>Scientific Reports</td>
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<td>31</td>
<td>2522</td>
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<tr>
<td>5</td>
<td>European Journal Of Medicinal Chemistry</td>
<td>122</td>
<td>35</td>
<td>2549</td>
<td>6.514</td>
</tr>
<tr>
<td>6</td>
<td>American Journal Of Tropical Medicine And Hygiene</td>
<td>98</td>
<td>25</td>
<td>1694</td>
<td>2.345</td>
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<tr>
<td>7</td>
<td>Cell Death Disease</td>
<td>94</td>
<td>35</td>
<td>2654</td>
<td>8.469</td>
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<tr>
<td>8</td>
<td>Autophagy</td>
<td>74</td>
<td>42</td>
<td>4326</td>
<td>16.016</td>
</tr>
<tr>
<td>9</td>
<td>Biochemical And Biophysical Research Communications</td>
<td>71</td>
<td>21</td>
<td>1302</td>
<td>3.575</td>
</tr>
<tr>
<td>10</td>
<td>Frontiers In Pharmacology</td>
<td>67</td>
<td>12</td>
<td>439</td>
<td>5.811</td>
</tr>
</tbody>
</table>
survival rate, and in vivo parasite clearance strongly correlated with the K13 propeller mutation, indicating its significance in determining artemisinin resistance. The K13 polymorphism served as a useful molecular marker for large-scale surveillance efforts and could aid in controlling artemisinin resistance in the Greater Mekong Subregion, as well as preventing its global spread. Inciardi, RM et al. reported a case of COVID-19 in which the patient was treated with antiviral drugs (lopinavir/ritonavir), dobutamine, chloroquine, steroids, and heart failure drugs [13]. This case highlighted the association between cardiac complications and COVID-19, even in the absence of signs and symptoms of interstitial pneumonia. Mauthe, M et al. discovered that chloroquine and hydroxychloroquine were not true substitutes for other late lysosomal inhibitors used in vivo [14]. Furthermore, chloroquine and hydroxychloroquine (HCQ) caused multiple cellular changes, suggesting that results obtained by blocking autophagy with these drugs should be interpreted with caution. Borba, Mayla Gabriela Silva, et al. reported the risks associated with COVID-19, particularly when using a combination of chloroquine and azithromycin or

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oseltamivir [15]. It was emphasized that the chloroquine dose should not be increased with the increase in the CQD dose. Guzik, TJ et al. discussed the effects of various drugs, including remdesivir, hydroxychloroquine, chloroquine, ribavirin, interferon, tocilizumab, and lopinavir/ritonavir, as well as experimental therapies like human recombinant angiotensin converting enzyme 2, on the cardiovascular health of patients [16]. Devaux, CA et al. found encouraging results in the initial trials of chloroquine for treating COVID-19 patients in China, leading to subsequent trials [17]. They also discussed the possible mechanism by which chloroquine interferes with the SARS-CoV-2 replication cycle. These papers highlight different aspects of chloroquine and present groundbreaking results that can guide future research endeavors.

**Keyword analysis**
The analysis focused on keywords of publications (Figure 6). A retrospective analysis was conducted, categorizing the publications into four groups. Group 1 primarily investigated the pathways and mechanisms of chloroquine in inhibiting the autophagy process (Figure 6A). Additionally, the potential of chloroquine as an autophagy inhibitor in cancer treatment was explored. Group 2 focused on chloroquine-based treatment for malaria, particularly in African children, with an emphasis on efficacy and drug resistance. Group 3 examined the efficacy of chloroquine against COVID-19, with a specific focus on safety and treatment mechanisms. According to prior research, it has been indicated that chloroquine and hydroxychloroquine possess the potential to impede coronaviruses by means of a sequential progression. Initially, these pharmaceutical agents have the capability to modify the pH of the cellular membrane surface, thereby hindering the attachment of the virus to the cell membrane. Additionally, they can impede various processes including nucleic acid replication, glycosylation of viral proteins, viral assembly, transportation of nascent viral particles, and viral release, thereby attaining their antiviral properties [18]. In 2020, Wang et al. conducted an evaluation of the impacts of five FDA-approved drugs and two broad-spectrum antiviral drugs on SARS-CoV-2 clinical isolates in vitro [19]. Among their findings, it was concluded that chloroquine exhibited significant efficacy in the management of SARS-CoV-2 infection in vitro. Group 4 concentrated on in vitro studies of chloroquine therapy for plasmodium. Supplementary Table S5 presents the top 20 most frequently used keywords, revealing that “in vitro”, “chloroquine”, “plasmodium falciparum”, “artesunate”, “malaria”, “drug resistance”, “artemisinin”, and “artemisinin resistance” were the most common keywords. This suggests that chloroquine-related research primarily involves clinical and basic research. The keywords were color-coded using VOS viewer based on the average year of publication (Figure 6B). Notably, the keywords autophagy, COVID-19, cancer, and signaling pathway were more frequently used than malaria and chloroquine resistance, indicating a shift in research direction. By comparing the data presented in Figure 7A and Figure 7B, it was observed that the treatment of COVID-19 using chloroquine has been a prominent research topic in the past two years. Figure 7C displays the top 20 keywords most frequently utilized concerning burst time, burst duration, and burst strength, which reveals that there was significant exploration of the drug resistance mechanism linked to Plasmodium falciparum in the initial phases of chloroquine research.

**Bibliographic coupling analysis**
Bibliographic coupling occurs when two documents cite the same reference. According to the latest issue of the Journal Citation Report, the impact factor is widely used as the primary indicator of a journal’s influence and quality. Figure 7 displays the network analysis of bibliographic coupling. The Supplementary Table S4 presents the top 10 countries contributing to this field. The American occupies the leading position with the highest number of citations, documents, and total link strength. China ranks second in terms of literature volume, while India surpasses China in terms of total link strength. The remaining countries have reported fewer than 1,000 documents. When considering affiliations, the Oxford University claims the top spot in terms of citations, literature, and total link strength. Although Shanghai Jiao Tong University has a large number of papers, its overall link strength is lower compared to other institutions (Supplementary Table S5). Smith, Peter J. has the maximum number of references, citations, and total link strength (Supplementary Table S6). De Kock, Carmen, Price, Ric N., Egan, and Timothy J. have a relatively high total link strength despite ranking lower in terms of the number of literature reports. Supplementary Table S7 presents the top 10 journals, with the Malaria Journal publishing the highest number of papers, citations, and overall link strength. It is closely followed by PLOS ONE and Antimicrobial Agents and Chemotherapy. The paper published in 2018 by Plantone has the maximum total link strength and number of citations (Supplementary Table S8).

**Figure 6 Network on keywords of chloroquine.** (A) The keywords that occurred more than 60 times were divided into 3 clusters by different colors: cluster 1: red, cluster 2: green, cluster 3: blue. The size of the nodes represents the frequency of occurrences. (B) Visualization of keywords according to the average year of publication. Keywords in blue appeared later than that in red. (C) Top 20 representative burst keywords.
**Discussion**

Chloroquine and its analogs belong to the 4-amino-quinolone family. Quinine was the first member of the family to be reported as having medicinal value. It was isolated from the Cinchona tree and is also the first natural antimalarial drug. In 1934, Paul Ehrlich and his research group synthesized chloroquine by structurally modifying previously reported quinine analogs like pamaquine, quinacrine, and tetaquine. Chloroquine has been widely used to treat malaria since its discovery. Chloroquine has replaced quinine as the first-line treatment for malaria due to its low toxicity relative to chloroquine [20]. Despite being discovered and widely researched in the past, chloroquine has gained significant attention in recent years due to its reported role as an autophagy inhibitor. Chloroquine gained significant attention after Professor Yoshinori Ohsumi won the 2016 Nobel Prize in Physiology for his groundbreaking research on autophagy. Regulating autophagy is crucial because it significantly impacts various physiological processes, including stress response, differentiation, growth regulation, and repair [22]. Numerous experimental studies have been conducted in the past two years to confirm the effectiveness of chloroquine in treating COVID-19 and elucidate its specific antiviral mechanism.

In this paper, the literature metrology method, VOS viewer, and Citessspace were utilized to examine the research focuses and research directions in the field of chloroquine based on the data presented in WoSCC. The global NP experienced a rapid increase in 2020-2021, which can potentially be attributed to the outbreak of COVID-19 in late 2019. This led to the rapid development of the research field focused on studying the resistance of SARS-CoV-2 to chloroquine. The United States had the highest NP, indicating a high output in this field. Although China ranked second in terms of NP, its NP began to rise rapidly from 2018 to 2021, suggesting that it could surpass the United States in this field. This can be attributed to the increasing research on chloroquine-based treatment of COVID-19 in China during this period.

Keyword analysis revealed that among the keywords related to chloroquine research, the primary focus was on its anti-malarial applications and mechanisms of action. The mechanism by which HCQ and chloroquine exert anti-malarial effects is still not fully understood. The mechanism is presumed to involve the detoxification of plasmodium [23]. Various mechanisms for the inhibition of ferritroporphyrin IX using chloroquine have been reported in the literature. Accumulated chloroquine in food voids can inhibit the aggregation of FPIX. The formation of a complex with the highly toxic FPIX moiety can induce the inhibition of aggregation. This process can induce the lysis of parasite cells [24]. Sullivan et al. reported that the chloroquine/hemoglobin complex could hinder the process of polymerization by covering the increasing amount of hemoglobin polymer. This, in turn, leads to the accumulation of toxic hemoglobin, which damages the parasite [25]. Another hypothesis suggests that chloroquine targets the nucleus instead of the lysosome. Chloroquine can directly bind to RNA and DNA, negatively affecting the processes of replication and transcription. As a result, the processes of growth and proliferation are inhibited, or apoptosis of host cells is induced [26].

Secondly, Plasmodium falciparum is frequently mentioned in the keyword analysis. Most articles aim to explore the development of chloroquine in treating Plasmodium falciparum infection and the recent emergence of resistance. The first reported case of Plasmodium falciparum malaria resistant to chloroquine was in 1957 on the Thai-Cambodia border. Since then, chloroquine-resistant strains of Plasmodium falciparum have spread from Southeast Asia to Africa and are now found in almost all endemic areas [27–29]. The spread and emergence of chloroquine-resistant strains have led to a rapid increase in malaria incidences worldwide. In chloroquine-resistant Plasmodium falciparum, resistance may be traced back to two proteins [30, 31]. Increased activity of certain enzymes that promote the detoxification of FPIX and mutations in the two transporters contribute to chloroquine/HQX resistance [32].

Connective tissue diseases are commonly identified in keyword analyses, and HCQ is widely utilized for long-term treatment of these conditions. HCQ has been shown to improve skin and arthritis symptoms in individuals with systemic lupus erythematosus (SLE). Additionally, it can be used to prevent kidney involvement and thrombosis. Limiting the consumption of corticosteroids can help prevent the onset of osteoporosis. The European Alliance against Rheumatism and the American College of Rheumatology have recommended the use of HCQ as the standard treatment for SLE to prevent recurrence [33, 34].

Potential modes of action of chloroquine and HCQ in SLE include correlated anti-inflammatory effects, immunosuppression, photoprotection, lysosomal stabilization, and inhibition of prostaglandin and cytokine synthesis [35–39]. Furthermore, there is growing evidence that chloroquine and HCQ inhibit the process of receptor-mediated immune activation, leading to the formation of pro-inflammatory cytokines. The results suggest that TNF-α may have a protective effect in SLE patients. Antimalarials interfere with the release of TNF-α in both mouse and human cells. However, the exact mode of action has yet to be fully understood [40]. Reports suggest...
that the use of chloroquine has the potential to hinder TNF-α release by inhibiting immune activation mediated by the Toll-like receptor.

An analysis of recently emerged keywords reveals that research on chloroquine in the field of oncology treatment is progressing. There is mounting evidence that the use of chloroquine enhances the sensitivity of cancer cells to anti-cancer drugs and radiation. Based on data from ongoing clinical trials, it can be inferred that this drug has the potential to alter cancer treatment strategies [41]. Although the exact mechanism by which chloroquine exerts its anticancer effects remains unclear, it is believed to involve autophagy. It has been reported that chloroquine/HCQ regulates lysosome function by inhibiting the fusion of lysosomes and autophagosomes [14, 42]. Autophagosomes and lysosomes influence autoimmune activation, presentation, and antigen processing. The presence of the basic side chain in chloroquine/HCQ leads to a significant increase in lysosome pH, allowing drugs to accumulate in lysosomes [43, 44]. This, in turn, reduces the maturity of lysosomes and autophagosomes, thereby inhibiting autoimmune activation [45]. As autophagy appears to promote cancer, chloroquine may sensitize cancer cells by inhibiting autophagy.

Research has primarily focused on studying the antiviral mechanism of chloroquine and its related drugs. The alkalinity of chloroquine is primarily responsible for its antiviral activity. Chloroquine use can lead to the alkalization of acidic organelles, including endosomes and lysosomes [45]. The antiviral activity of chloroquine can be explained by two mechanisms. Most viruses undergo fusion, infiltration, or undressing during infection at a low pH. The endoboby pathway plays a crucial role in viral replication and host infection [46]. The use of chloroquine can prevent endosomal acidification, leading to the inhibition of lysosomal functions under elevated pH conditions. This inhibition affects the activity of several viruses, including hepatitis A virus and influenza B [47, 48]. Chloroquine use has the potential to inhibit the post-translational modification of viral envelope glycoproteins. This inhibition occurs by negatively impacting the activity of specific enzymes that function at a low pH [49, 50]. The immunomodulatory effects of chloroquine may also be linked to its mechanism of action.

Since 2019, the COVID-19 pandemic has spread extensively to 210 countries and regions worldwide, significantly disrupting human daily life and economic development. Consequently, the development of drugs to treat COVID-19 has become crucial. The efficacy of chloroquine as a potential treatment for COVID-19 has gained increasing attention, overshadowing its previous focus on antimalarial and antiviral properties. An analysis of keywords revealed a substantial number of articles published between 2020 and 2021 that explored the use of chloroquine as a therapeutic drug for COVID-19. These studies primarily aimed to verify the clinical effectiveness of chloroquine and investigate its potential mechanism of action. Liu et al. conducted studies using Vero E6 cells and found that HCQ could inhibit SARS-CoV-2 infection. They reported that HCQ, being less toxic than chloroquine and possessing anti-inflammatory properties, could be a preferable treatment option [51]. Furthermore, HCQ exhibited stronger antiviral properties than chloroquine, as demonstrated in studies using Vero cells [10]. Weston et al. examined the antiviral activities of 20 drugs approved by the Food and Drug Administration in Vero cells and reported that both HCQ and chloroquine could inhibit the replication and expression of SARS-CoV-2 mRNA [52]. Tourret et al. screened a chemical library consisting of 1,520 drugs approved by relevant authorities and identified 90 compounds, with chloroquine/HCQ being the most effective against COVID-19 [53]. The infection pathway associated with COVID-19 involves the interaction between ACE2 on the host cell and the spike (S) protein on the virus [54]. Chloroquine has been reported to inhibit the glycosylation process of the ACE2 receptor, directly impeding the spread of SARS-CoV infection in host cells [55]. Additionally, recent in silico simulations show that chloroquine/HCQ can prevent the S protein from entering the ACE2 protein on the host cell surface through their interaction [56]. Thus, the inhibition of the ACE2-S protein interaction may partially explain the preventive effect against COVID-19. Furthermore, studies have indicated that chloroquine inhibits the expression of the phosphatidylinositol binding clathrin assembly protein, affecting clathrin-mediated endocytosis of nanoparticles [57]. Chloroquine, being a weak basic molecule, accumulates in acidic organelles like lysosomes, leading to changes in its acidified state [58]. This alteration can inhibit the enzymatic activity of lysosomal proteases under elevated pH conditions, thereby impeding the infection process. The inhibition of autophagy by chloroquine/HCQ may also contribute to the preventive effect observed in COVID-19 cases. Virus replication occurs in the intermediate interval between the Golgi complex and endoplasmic reticulum, which is closely associated with autophagosome biogenesis [59]. Treatment with chloroquine/HCQ increases the pH of lysosomes, inhibiting the autophagy process and potentially affecting virus replication.

Chloroquine and its analogs have been found to have various detrimental effects on antiviral immunity. The use of chloroquine may lead to serious complications, including cardiomyopathy, retinopathy, neuromyopathy, and myopathy [20]. Chloroquine is often associated with retinopathy, and the American Academy of Ophthalmology has outlined the risk factors associated with retinopathy when using chloroquine and HCQ, along with recommendations for screening [60]. Prolonged use of HCQ and chloroquine can result in lysosomal enzyme dysfunction, hindering intracellular degradation and promoting of metabolic process (phospholipids and glycogen) [61, 62]. Furthermore, chloroquine use can block sodium and calcium channels, leading to membrane stabilization, negative inotropic effects, and peripheral vascular dilation. This membrane stabilization can cause conduction disorders, atrioventricular block, and widening of the QRS interval in the heart [63]. Excessive use of high doses of chloroquine can cause various toxic manifestations, including arrhythmias, coma, hypotension, fatal cardiac arrest, and acute respiratory distress syndrome [64-66]. In high concentrations, HCQ and chloroquine directly affect sodium and potassium channels in the heart, potentially causing life-threatening cardiovascular toxicity. This blocking of cardiac channels results in QRS and prolonged QT intervals on electrocardiograms, as well as hypotension [67]. Severe poisoning cases often exhibit negative muscle strength and timing, along with common ventricular arrhythmias such as ventricular fibrillation and polymorphic and monomorphic ventricular tachycardia. Thorough risk assessments should be conducted prior to administering chloroquine to COVID-19 patients with pre-existing conditions or diseases. Special attention should be given to patients with cardiovascular diseases. A pilot study was conducted in Brazil to investigate the use of chloroquine diphosphate for treating COVID-19 patients. The study had to be prematurely terminated due to several patients experiencing fatal arrhythmias. Additional studies are required to determine the efficacy of chloroquine in treating COVID-19 patients and its suitability for clinical use. Further research should be conducted to elucidate the specific mechanism by which chloroquine affects COVID-19 patients.

Through an analysis of keywords and annual trends, this study explores the prominent focus areas and recent developments in chloroquine research spanning the last decade. Research in the past decade has primarily focused on investigating the antiviral mechanism of chloroquine. However, there has been a noticeable increase in the number of articles concerning clinical trials of chloroquine for treating new-coronavirus since 2019. Moving forward, we anticipate that chloroquine will play a significant role in the treatment of various diseases, and exploring its pharmacological mechanisms of action will be a key area of future research. The potential of chloroquine in tumor treatment is expected to be a prominent area of research in this field.

This study presents a bibliometric analysis of 8350 articles published on chloroquine between 2012 and 2021. It visualizes the authors, institutions, and journal links associated with these articles. The study examines the research directions and areas of focus in chloroquine over the past decade. Additionally, it discusses the applications and feedback received during the chloroquine neocoronavirus pandemic. Furthermore, the study provides a
predictive analysis of the future directions in chloroquine research. However, there are certain limitations to this study. Only articles and reviews published in English were considered. VOS may disregard information if it cannot analyze the full text of a publication. The applicability of the results may be potentially limited due to the exclusion of some recently published literature reports.

Conclusion

This study conducted quantitative and qualitative analyses on the most relevant authors, major journals, authors’ research results, most cited papers, and relevant countries. The study included information on chloroquine reported between 2012 and 2021 to provide an intuitive evaluation of the research results. The number of publications on chloroquine has consistently increased over the past decade. The research area of chloroquine has been significantly influenced by the American and China. The progress of chloroquine research is further propelled by fruitful collaborations among various countries. Researchers have extensively studied the anti-malarial effect, drug resistance mechanism, and autophagy of chloroquine for the development of a treatment method for COVID-19 based on chloroquine. Bibliometric analysis can be employed to identify hotspots, new directions, and frontiers in the field of chloroquine research.

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