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Emerging trends and new developments in global research on artemisinin and its derivatives

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ABSTRACT

Background: The World Health Organization recommends the use of artemisinin (ART) and its derivatives for malaria treatment. Furthermore, these compounds exhibit encouraging pharmacological effects for the treatment of several diseases. Nevertheless, ongoing antimalarial treatment efforts have been significantly hindered by the emergence of drug resistance. A systematic evaluation and analysis of relevant studies may yield insights to help resolve this dilemma and reveal options for future research.

Purpose: The objective of this study was to provide researchers with a comprehensive synopsis of the advancements made in the study of ART and its significant derivatives, as well as to visually present the data and provide insightful observations that can inform subsequent investigations in this domain.

Methods: We searched the Web of Science Core Collection for relevant studies published by December 31, 2023. The research hotspots and frontiers pertinent to this field in terms of countries, institutions, authors, journals, references, and keywords were ascertained through scientometric analysis via CiteSpace software.

Results: This study included an extensive assemblage of 12,985 data points, and the findings suggest that ART and its derivatives have garnered considerable interest among scientists. Prolonged international collaboration has fostered progress in this research field. "Antimalarials," "synthesis," "drug resistance," and "*Plasmodium vivax*" are areas of intense research. Potential areas for future investigations may include "proliferation," "oxidative stress," "pathways," and "mechanisms."

Conclusion: This study offers a comprehensive compendium of the developments and trends in the relevant research field over the past fifty years. Since pharmaceutical drug synthesis can influence both drug efficacy and cost-effectiveness, ongoing efforts to improve drug synthesis are warranted. Although the advent of novel therapeutic approaches has partially mitigated drug resistance, further investigations into the underlying mechanisms are needed. While better treatments for malaria have been developed, the therapeutic potential of ART and its derivatives for numerous additional important diseases is also possible, and future research in this area can lead to dramatic improvements in health.

Abbreviations: ACTs, Artemisinin-based combination therapies; ART, Artemisinin; SCI-E, Science Citation Index Extended Edition; WOS, Web of Science.

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1. Introduction

Malaria is a mosquito-borne, life-threatening disease caused by five *Plasmodium* parasite species. In 2022, there were approximately 249 million cases of malaria and 608,000 deaths caused by malaria across 85 countries worldwide [1]. *Artemisia annua* L., also known as qinghao or huang hua hao, has a long history of use in traditional Chinese medicine for treating fever, particularly symptoms associated with malaria. This usage can be traced back to the book "Zhou Hou Bei Ji Fang" (Handbook of Prescriptions for Emergency Treatments) written by Ge Hong in 340 CE. On the basis of Ge Hong's manual, which states, "immerse a handful of qinghao in 2 L of water, wring out the juice, and consume it in its entirety," a low-temperature extraction method for the plant was proposed, promoting the discovery of artemisinin (ART), which has potent antimalarial activity, by Tu Youyou, a Chinese pharmacologist. She was subsequently honored with the Nobel Prize in Medicine and Physiology in 2015.

ART, a sesquiterpene lactone ($C_{15}H_{22}O_5$), possesses a unique structural feature called a peroxide bridge, which plays a substantial role in its antimalarial activity via several mechanisms [2,3]. However, owing to the low solubility of ART in water or oil, as well as its low bioavailability, derivates such as dihydroartemisinin, artesunate, and artemether are more commonly used than the original compound [4]. ART and its derivatives are recommended for malaria treatment by the World Health Organization, and artemisinin-based combination therapies (ACTs) have emerged as the primary components of first-line antimalarial medications for severe and uncomplicated *Plasmodium falciparum*-induced malaria owing to their ability to eradicate the parasite [1]. However, the partial resistance of *P. falciparum* to ART, the central component of ACTs, is a growing concern. Fortunately, at present, almost all individuals afflicted with ART-resistant parasites who receive treatment with an ACT achieve complete recovery as long as the partner drug is effective [1]. Moreover, there has been substantial investment in the development of novel artemisinin derivatives that display strong antimalarial effects, specifically those that target malaria strains that are resistant to multiple drugs [5–8]. Importantly, for human diseases such as malaria, cancer, viral, bacterial, and parasitic infections, and cardiovascular diseases, ART and its derivatives have been demonstrated to have a wide range of pharmacological properties via a variety of molecular and cellular mechanisms [9]. A systematic analysis of these findings could provide valuable guidance for future investigations.

CiteSpace, a Java application for visualizing and analyzing trends and patterns in scientific literature, was designed by Chaomei Chen, a Professor of Information Science at the College of Computing and Informatics at Drexel University in the USA [10]. Previous research has employed bibliometric tools such as VOSviewer and CiteSpace to visually analyze academic research on natural plants and their active constituents [11,12] and to illustrate the hotspots and trends in ART studies from 2000 to 2021 [13]. Despite these contributions, a comprehensive bibliometric analysis focusing specifically on ART and its derivatives, including artemether, artesunate, and dihydroartemisinin, has yet to be conducted. Our study aims to bridge this gap by conducting a systematic, objective, and comprehensive analysis of scholarly articles related to ART and its derivatives. Using CiteSpace, our objective is to map the intellectual structure of this field, offering a thorough and detailed understanding of the current research status and identifying the frontier areas that are driving innovation in this domain. This analysis will not only contribute to the existing body of knowledge but also guide

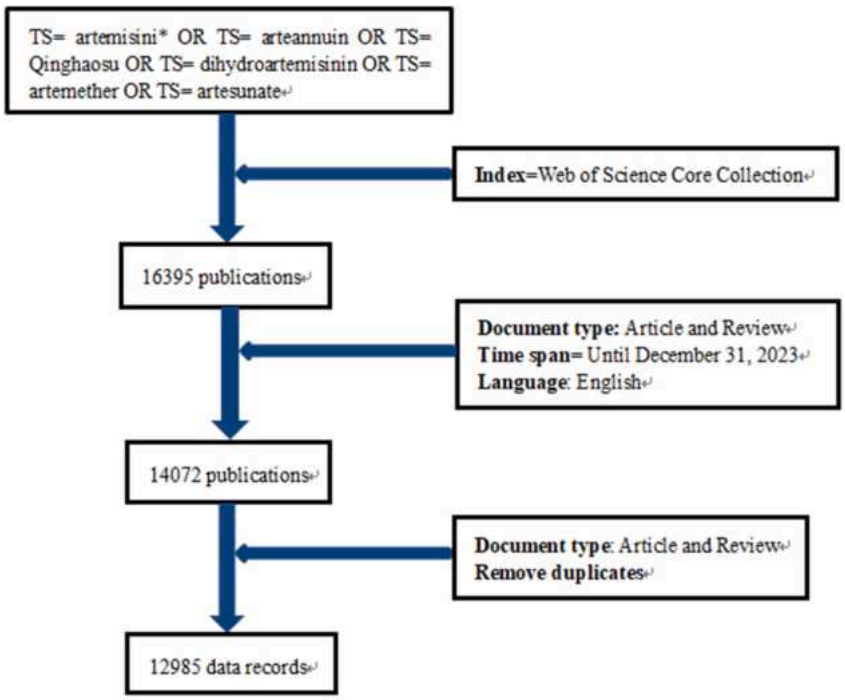

Fig. 1. Flow chart of the search strategy.

future research endeavors by highlighting areas of opportunity and potential for further exploration.

2. Materials and methods

2.1. Data sources

The raw data for this study were downloaded from the Science Citation Index Extended Edition (SCI-E) database of the Web of Science (WOS) Core Collection. As a premier database of digitally accessible literature resources, the WOS has gained widespread attention among researchers. SCI-E includes more scientific and authoritative publications than other databases do and is considered the most suitable database for bibliometric analysis. CiteSpace is based on the WOS data format, making the WOS database the primary and most preferred input source for its analyses. Searches for articles related to ART and its key derivatives were conducted using the following formula: TS = artemisini* OR TS = arteannuin OR TS = Qinghaosu OR TS = dihydroartemisinin OR TS = artemether OR TS = artesunate. Data accuracy was ensured through the selection of indexing conditions. The time span ranged from 1973 (when the first publication appeared) to 2023, with the language limited to English and the document type defined as articles and reviews. After the articles were screened using the database according to the above inclusion and exclusion criteria, the two reviewers performed an independent reassessment and discussed disagreements to ensure the validity of the articles. The screened documents were exported in plain text format. After duplicate studies were removed, 12,985 studies met the selection criteria. The search process and selection criteria are summarized in Fig. 1.

2.2. Bibliometrics and visualization analysis

An essential aspect of bibliometrics is scientific mapping, which depicts the discipline's current situation and development. This study included visual mapping through CiteSpace (6.3. R1), developed by Professor Chao-Mei Chen [10]. By importing all the data into CiteSpace, the data are converted into a format for visual analysis. In the graph for visual analysis from January 1, 1973, to December 31, 2023, "Years Per Slice" is set to 1 year. Nodes and links constitute the knowledge graph, which is used to analyze indicators such as countries, journals, institutions, authors, references, and keywords. Node sizes and colors indicate the frequency and year of occurrence, respectively. Connections among nodes signify co-occurrence, cocitation, or collaboration relationships. The outermost nodes with purple rings are typically considered turning points or important points in the field. The following formula can be used to determine how important a given node is in the network by calculating the percentage of shortest paths to which it belongs [14].

$$g(v) = \sum_{s \neq v \neq t} \frac{\sigma_{st}(v)}{\sigma_{st}}$$

The centrality value of vertex v is denoted by $g(v)$, while $\sigma_{st}(v)$ represents the count of the shortest paths connecting vertex s to vertex t via v. σ_{st} represents the sum of all shortest routes from vertex s to vertex t. Furthermore, J. Kleinberg created algorithms for predicting future developments in the field by detecting significant changes in the number of keywords over a given period [15,16].

3. Results

3.1. Analysis based on publication year

From 1973 to December 31, 2023, 12,985 papers were published and included in the SCI-E, including 11,378 articles (87.62 %) and 1607 reviews (12.38 %). Their content focuses primarily on pharmacology, pharmacy, tropical medicine, infectious diseases, parasitology, chemistry, biochemistry, and molecular biology. The cumulative number of papers published each year showed a continuous upward trend with some fluctuations. As illustrated in Fig. 2, the study period can be divided into three phases. For the first phase (1973–1996), the number of published papers was consistently less than 100 per year. ART did not attract scholars' interest for a long

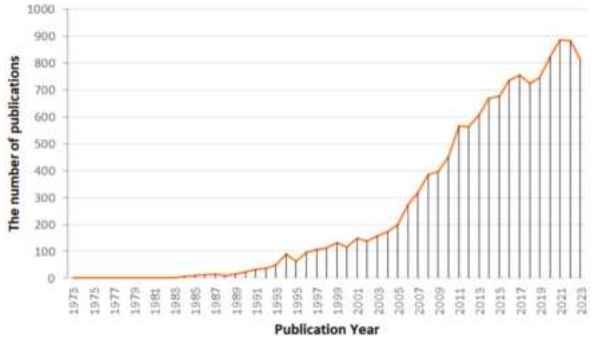

Fig. 2. Annual trends.

period after the first article was published. During the second phase (1997–2010), the research entered a developmental stage, and the number of papers increased steadily and rapidly. In the third phase (2011–2023), more than 500 papers were published annually, and scholarly inquiry in associated domains surged and reached its pinnacle in 2021 (887). Thus, ART and its derivatives have become a global research hotspot, attracting the attention of scientists worldwide.

3.2. Countries and institutions

The relevant literature has been published in 1193 countries or regions and 34,210 institutions. Collaboration and communication between academic and national research organizations have contributed to the development of the field. On the basis of CiteSpace analysis, we mapped out the level of collaboration among countries and organizations (Figs. 3 and 4). As shown in Table 1, the United States, China, the United Kingdom, India, and Thailand were the top 5 countries, accounting for 77.82 % of the articles published. Although China is the leader in related research, its centrality is only 0.03, suggesting that transnational academic exchanges should be enhanced. Collaboration between different countries can further increase the attention and resources devoted to a research area, broaden the scope of research, improve the overall quality of articles, and ultimately contribute to innovation and development in the field. The University of Oxford had the most publications in the field among all the institutions, with 860 articles. Mahidol University was ranked second with 859 publications, followed by the University of London, the London School of Hygiene & Tropical Medicine, and the University of California System (Table 1). Notably, all 5 institutions, except for the University of California System, had a centrality greater than 0.1, especially the University of Oxford and London School of Hygiene & Tropical Medicine, which tied for first place with a centrality of 0.2. A robust level of communication has been established between these high-producing institutions, furthering research on ART and its derivatives.

3.3. Analysis of authors

The author network comprised 314 nodes and 577 connections (Fig. 5). The top five authors, who are active and specialize in their respective fields, published 646 articles, accounting for 4.97 % of the total publications. As shown in Table 2, Nicholas J. White published 248 high-quality and high-impact articles related to ART. His articles focused on strategies for the rapid diagnosis and effective treatment of malaria and the complications of anemia due to malaria [17–19]. Nicholas J. White sought antimalarial medicines until Youyou Tu was granted the 2015 Nobel Prize in Medicine for her contribution to the discovery of ART [20,21]. Since then, he has concentrated on various ART-based therapies. In the treatment of uncomplicated *P. falciparum*-induced malaria, combination therapy with ART is the first-line treatment. The use of highly effective and well-tolerated antimalarials has significantly contributed to the reduction in the number of malaria-related deaths and complications worldwide. Nicholas J. White recommended the use of triple antimalarial drug regimens to combat the emergence of ART resistance in *P. falciparum* parasites, which poses a challenge for malaria treatment [22,23]. He also concluded that, considering the current methods for evaluating the effectiveness of prophylactic and therapeutic antimalarial medications, pharmacometric antimalarial resistance monitoring is the most promising and recommended method for assessing their effectiveness [24]. This method is simpler and more sensitive, distinguishes between low drug exposure and emerging resistance, and can be used for therapeutic and prophylactic purposes. While there are several key groups of authors, some of the core authors do not collaborate consistently, and more author collaboration is needed, as the centrality of all authors is less than 0.1.

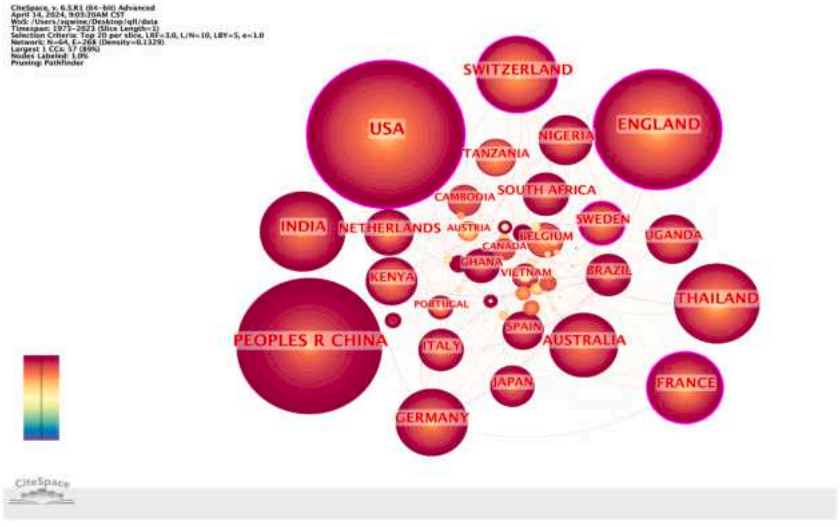

Fig. 3. Publication distribution and cooperation of countries.

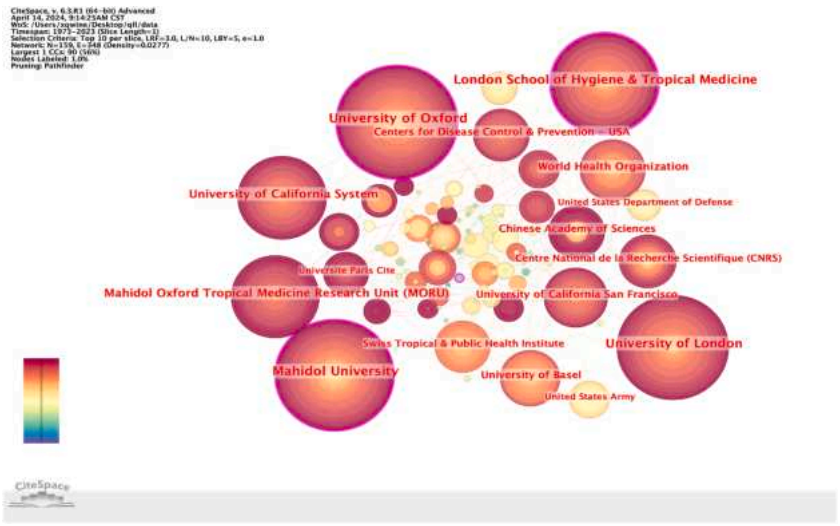

Fig. 4. Publication distribution and cooperation of institutions.

Table 1
Top 5 countries and institutions with published articles.

Rank	Country	Count	Centrality	Institution	Count	Centrality
1	USA	3057	0.26	University of Oxford	860	0.20
2	PEOPLES R CHINA	2697	0.03	Mahidol University	859	0.12
3	ENGLAND	2132	0.28	University of London	766	0.10
4	INDIA	1112	0.06	London School of Hygiene & Tropical Medicine	674	0.20
5	THALAND	1107	0.09	University of California System	451	0.01

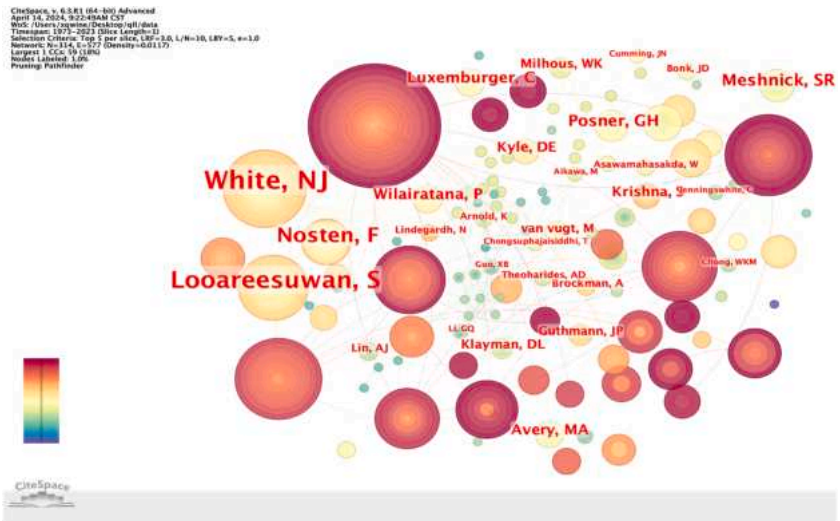

Fig. 5. Network of authors.

3.4. Analysis of journals

Understanding the subject distribution, monitoring the expansion of research, and contributing to future article submissions on a particular subject are all possible with the aid of disciplinary analysis of works in a field. The subject distribution of the periodicals is illustrated in Fig. 6 via the dual-map overlay. The cited journals on the right and the citing journals on the left serve to illustrate the correlations between them. The orange citation path reveals that studies published in Molecular/Biology/Immunology journals frequently referenced research articles published in Molecular/Biology/Genetics journals. As the green path indicates, works

Table 2
The top 5 authors with the most publications.

Rank	Authors	Count	Centrality
1	Nosten, Francois White, NJ	248	0.01
2	Rosenthal, Philip J Dorsey, Grant	111	0.01
3	Looareesuwan, S	107	0.01
4	Nosten, Francois White, NJ	103	0.01
5	Rosenthal, Philip J Dorsey, Grant	77	0.00

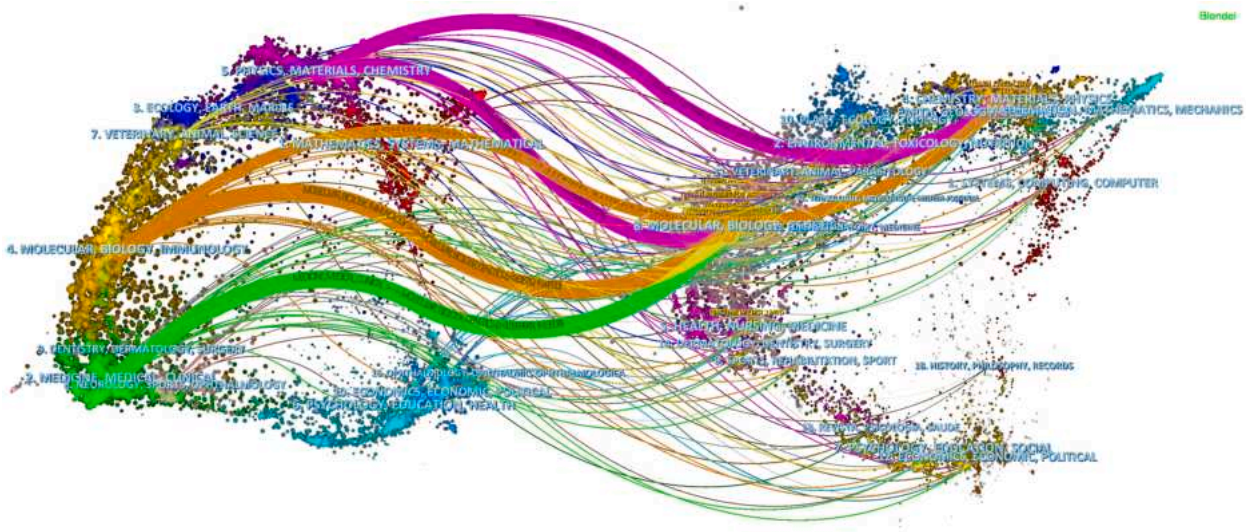

Fig. 6. Overlay map of journals.

published in molecular, biological, or genetic journals were frequently cited in research articles from Medicine/Medical/Clinical publications. Furthermore, papers published in Chemistry/Materials/Physics were frequently referenced in research from Physics/Materials/Chemistry, as indicated by the pink path.

3.5. Cocitation analysis of cited references and clusters

The knowledge network structure of the references can be seen in Fig. 7. According to the five most cocited articles (Table 3), articles on ART resistance in *P. falciparum*-caused malaria published in the New England Journal of Medicine were the most frequently cited [25]. ART and its derivatives are highly effective for treating patients infected with chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*, resulting in a significant reduction in associated morbidity and mortality [2]. As an emerging site of antimalarial resistance, the Thai–Cambodian border has received extensive scientific attention, in addition to some previous reports of reduced efficacy due to counterfeit ART-related combination therapy drugs [26–28]. The emergence of ART resistance would have disastrous consequences for global malaria control, and four of the five papers are related to such resistance. Effective measures must be taken to contain and eradicate this problem. The correlation between artesunate resistance and considerably extended parasite clearance has been established by evaluating *P. falciparum* susceptibility, pharmacokinetics, and the molecular markers of resistance [29,30]. A pilot clinical study examined clinical isolates from patients with falciparum malaria in Senegal, Cambodia, and French Guiana and reported that the S769N *PfATPase6* mutation, noted exclusively in French Guiana, was associated with increased artemether IC_{50} values [31]. To prevent a worldwide threat to malaria control, limiting parasite transmission, mapping resistance ranges, and monitoring the spread of ART resistance are necessary measures.

In cluster evaluation, both modularity (Q) and the mean silhouette (S) are used. When Q exceeds 0.3, it is recommended to conduct a network analysis, and when S exceeds 0.5, it is logical to conduct a clustering analysis. Using indexed terms extracted from the document citations, the top ten clusters of cocitations in research on ART and its derivatives were determined. The details are summarized in Fig. 8. A robust overall clustering effect and reliable and significant findings were indicated by the average Q and S values for clustering, which were 0.7982 and 0.9439, respectively. Scholars' interest in the synthesis and chemical structure of ART and its derivatives, as well as their research into malaria treatment, is indicated by cocitation clustering. Some clusters depend on numerous other clusters, while the latter serve as a knowledge base for the former, as indicated by the arrows on the icon. For example, the chart illustrates that the literature in cluster 0 cites the literature in cluster 1, meaning that the themes of cluster 1 gradually develop into those of cluster 0.

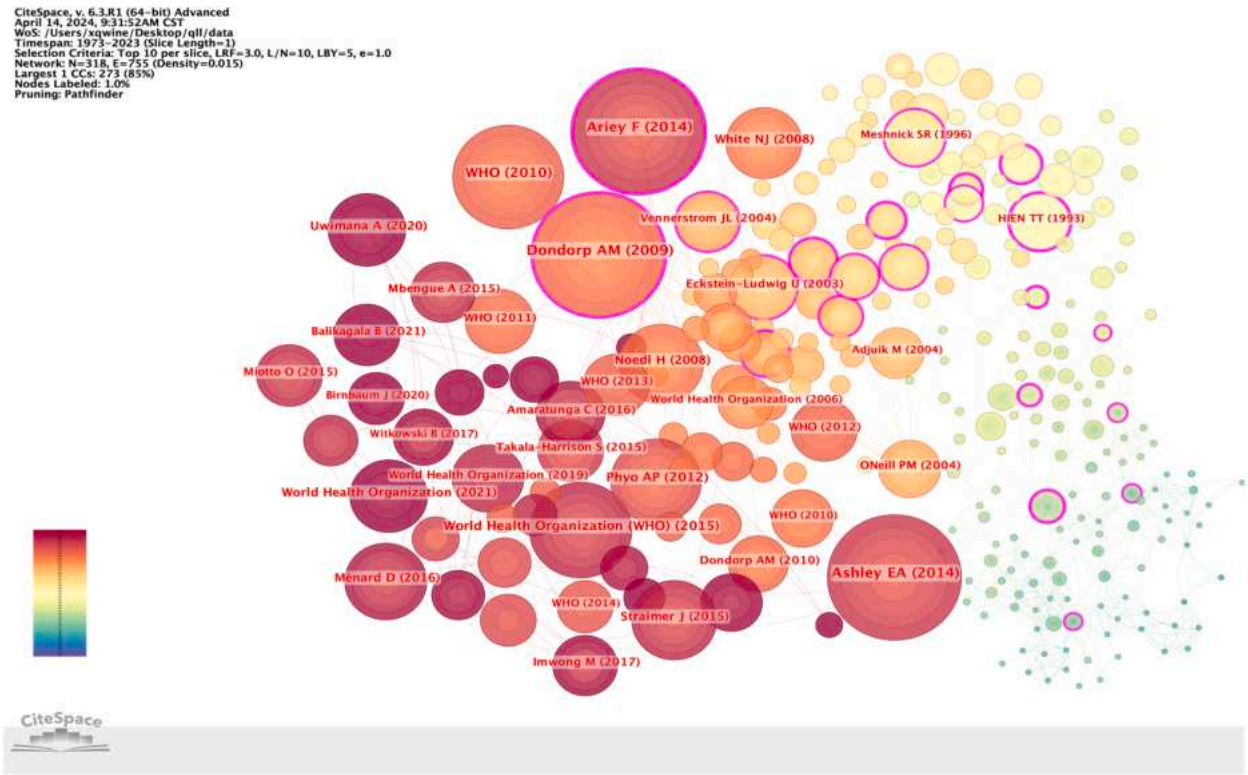

Fig. 7. Network of references.

Table 3
The top 5 references with the most cocitations.

Rank	Cited references	Count	Centrality
1	Ashley EA, 2014, NEW ENGL J MED, V371, P411, DOI 10.1056/NEJMoa1314981	1472	0.15
2	Ariey F, 2014, NATURE, V505, P50, DOI 10.1038/nature12876	1003	0.60
3	Dondorp AM, 2009, NEW ENGL J MED, V361, P455, DOI 10.1056/NEJMoa0808859	895	0.01
4	WHO, 2010, GUID TREATM MAL, VO, P0, DOI 10.1080/03630269.2023.2168201	876	0.11
5	World Health Organization (WHO), 2015, GUID TREATM MAL, VO, PO	711	0.03

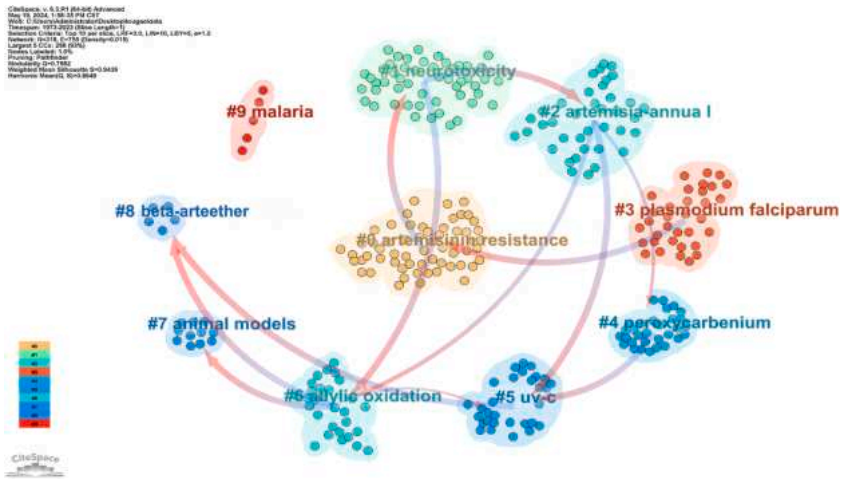

Fig. 8. Cluster visualization based on the reference cocitation network.

3.6. Analysis of keywords and clusters

An analysis of high-frequency keywords was conducted to identify relevant research hotspots. The top 10 keywords with the greatest frequency and centrality are shown in Table 4. In addition to the search phrases, these keywords were associated with the core topics of the study, which included diseases, drug research, and study populations (Fig. 9). The terms "*Plasmodium falciparum*" (2466), "artemisinin" (1975), and "malaria" (1660) were most common. "*Plasmodium falciparum*" (0.27), "artemisinin" (0.18), and "antimalarial activity" (0.18) were the three keywords with the highest centrality. A log-likelihood ratio (LLR) algorithm was used to extract keywords from the cited articles and apply them to the labeled clusters to represent the research frontiers associated with certain knowledge bases. On the basis of the results of this study, 24 clusters were identified, and the first 10 clusters are shown in Fig. 10. The Q value of the network was 0.8586, and the average S value of the clusters was 0.9565, indicating that the clusters were categorized into a satisfactory structure. Table 5 contains detailed information about these clusters, together with keywords that imply the subject areas of study pursued by the scholars.

The timeline view (Fig. 11) provides insight into the field's evolution by revealing the dynamics of the research hotspots over time. Cluster 0 was characterized by extensive research by experts from the beginning, who realized the drawbacks of the drug as the relevant knowledge areas became more fully understood. Chloroquine was once widely used to treat malaria and has greatly improved public health. However, owing to the emergence of drug resistance in various regions, scientists have become more committed to researching new drugs to solve this dilemma. The fact that new keywords have not continued to appear in recent years is partly due to the difficulty in generating breakthroughs and partly due to the success of the use of ART-related medicines in malaria, which has elicited significant scholarly interest. Children, especially those in Africa, were the main subjects of the study. From the keyword trends observed for clusters 5, 6, and 8 on the timeline, it can be deduced that scientific research is progressively shifting away from the exclusive use of ART. Instead, attention is being directed toward the exploration of ART derivatives, with an emphasis on their pharmacological effects and therapeutic mechanisms. By examining clusters 2 and 3, it is evident that research on the plant *A. annua* continues, and following Tu Youyou's procedure for extracting ART, other natural components may also be extracted from the plant itself. Clusters 1, 3, and 9 have continued to attract scientific interest until the present.

3.7. Keywords with the strongest citation bursts

An increase in the use of keywords reflects, in part, a sudden change in the direction of research related to these topics. Detecting and analyzing burst keywords provides insights into the evolution and historical progression of research frontiers. Early burst keywords denote frontiers of research in their infancy, whereas current burst keywords signify trends and future directions in research. Fig. 12 illustrates the top 25 keywords with the most potent citation bursts, with a red line indicating the cycle of keyword bursts and a blue line revealing the time interval between them. As the number of keywords increases in intensity, their influence also increases. Qinghaosu is the keyword with the highest intensity, and it maintains its dominance through 2023. "Analogs" have the greatest prevalence, suggesting that similar molecular structures or chemical compositions are the current focus of studies on ART and its derivatives and that analogs hold great promise for curing infectious diseases, especially "malaria." A burst of citations for keywords such as "pathway," "proliferation," "oxidative stress," and "mechanisms" continues through 2023, representing current frontier research topics.

4. Discussion

The antimalarial medicine ART, derived from the herb *A. annua*, has drawn enormous scientific attention and has been extensively utilized, yielding exciting results. As a result of the emergence of ART resistance, the effectiveness of ART-only medications has decreased, putting pressure on first-line therapies and raising concerns regarding ART derivatives and compounded ARTs. Despite considerable advancements in relevant research, there is still a substantial knowledge gap regarding the pharmacological mechanisms and etiology of resistance, among other aspects. Thus, it is imperative to evaluate past, present, and future developments and research directions to develop innovative applications for ART and important derivatives and to control malaria. The data were obtained through a search of the Web of Science Core Collection (WOSCC) database and subsequent manual screening, as the WOSCC is the sole

Table 4
The top 10 keywords.

Rank	Keywords	Count	Keywords	Centrality
1	plasmodium falciparum	2466	plasmodium falciparum	0.27
2	artemisinin	1975	artemisinin	0.18
3	malaria	1660	antimalarial activity	0.18
4	in vitro	1323	artemether	0.15
5	artesunate	1184	growth	0.12
6	resistance	1015	malaria	0.11
7	artemisinin resistance	1008	derivatives	0.10
8	plasmodium falciparum malaria	884	chloroquine	0.10
9	artemether lumefantrine	842	soluble dihydroartemisinin derivatives arteether	0.10
10	derivatives	828	plasmodium falciparum	0.09

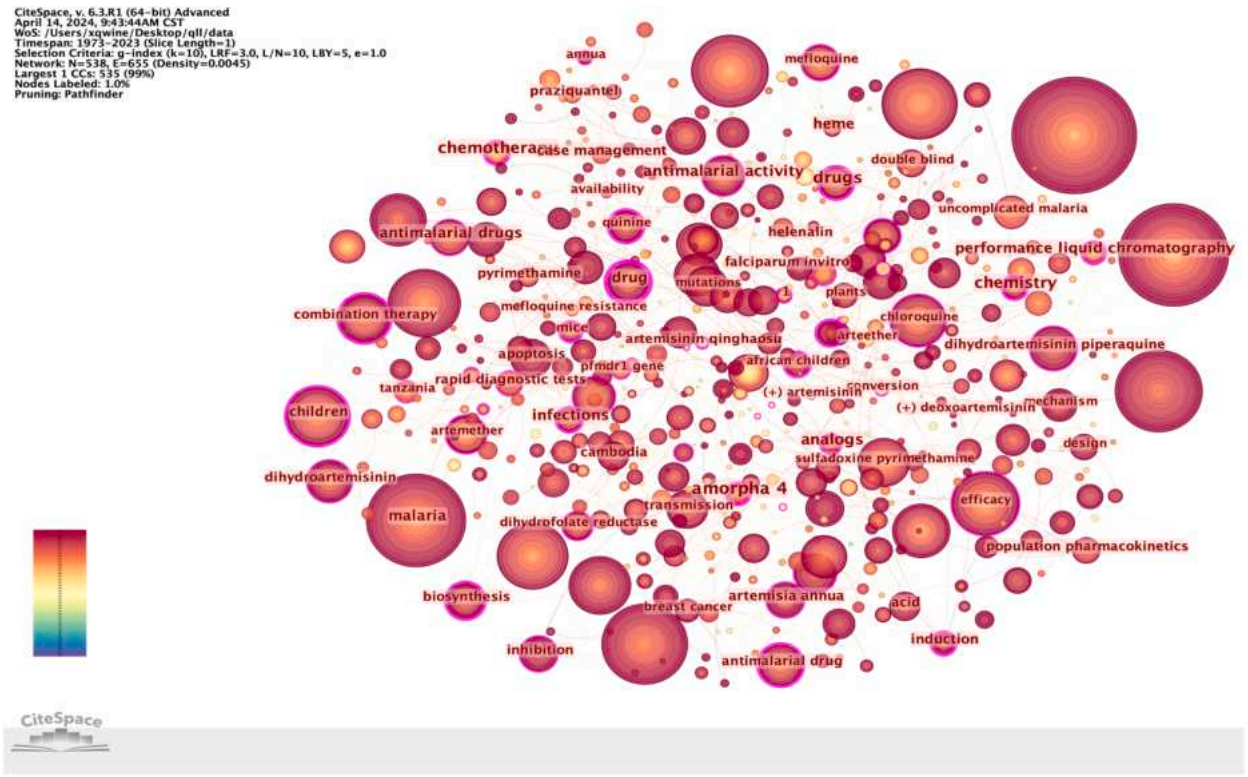

Fig. 9. Network of keywords.

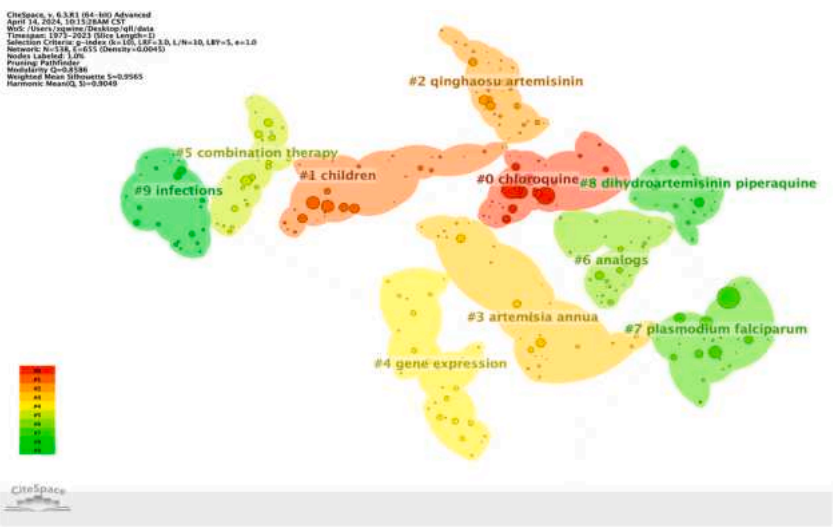

Fig. 10. Cluster visualization based on keywords.

database that fully utilizes the capabilities of CiteSpace. A total of 12,985 publications related to ART and its important derivatives published between 1973 and 2023 were reviewed in this study. With the aid of scientometric and visual analysis, the overall landscapes, hotspots, and trends in the field were systematically summarized by analyzing countries, institutions, authors, journals, references, and keywords.

4.1. General information

There has been increasing interest in the study of herbal medicine in recent years, and it is evident that certain chemical

Table 5
Detailed information on active keyword clusters.

Cluster ID	Size	silhouette	Mean Year	Major keywords
0	38	0.939	1998	chloroquine; resistance; mefloquine; qinghaosu; antimalarial drugs
1	32	0.984	2001	children; artemether; cerebral malaria; plasmodium falciparum malaria; falciparum malaria
2	31	0.968	1999	qinghaosu artemisinin; chemistry; antimalarial activity; identification; biological activity
3	29	0.931	2006	artemisia annua; apoptosis; hepatocellular carcinoma; plasmodium falciparum; autophagy
4	27	0.996	2012	gene expression; artemisinin biosynthesis; secondary metabolites; transcription factor
5	27	0.943	2009	combination therapy; spread; Cambodia; parasite clearance; plus sulfadoxine pyrimethamine
6	25	0.929	2005	analogs; inhibition; antimalarial agent artemisinin; 1,2,4 trioxanes; reveals
7	25	0.914	1996	plasmodium falciparum; drug resistance; malaria; drug; efficacy
8	24	0.979	2010	dihydroartemisinin piperaquine; population pharmacokinetics; uncomplicated malaria; vivax malaria; artemisinin combination
9	24	0.992	2008	infections; epidemiology; inflammation; elimination; nf-kappa b

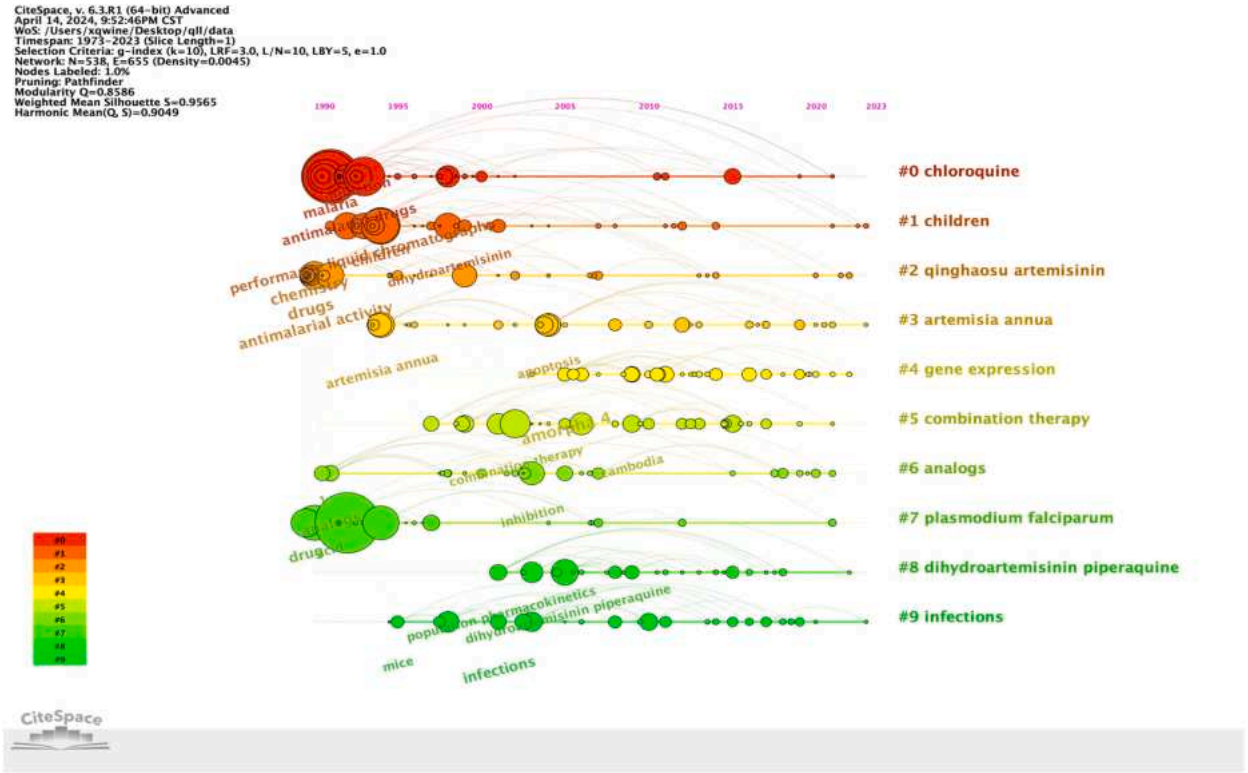

Fig. 11. Timeline of keywords.

constituents present in plants have potential applications in the therapeutic management of diseases. According to Fig. 2, there has been an increasing trend in the number of publications related to ART and its derivatives during the past 51 years. An exciting feature is the rapid increase in the number of articles from 2011 onward, highlighting the growing interest in this research area, with presumably a further increase in publications in subsequent years. According to a review of the types of publications, a relatively high proportion of research papers play an important role in advancing the field. Among national and regional distributions, the United States has led in terms of scholarly contributions over the past decade, as indicated by the number and centrality of publications. China ranks second in terms of productivity despite its limited engagement in international collaboration. To advance its domestic and international scholarship, China should pursue more frequent partnerships with other nations. The five most productive institutions play a vital role in promoting the field. Additionally, five influential authors whose publications were highly recognized and cited were identified. The countries, institutions, and authors that are most productive have established representative research teams that collaborate closely internally, providing solid academic support for future investigations.

In addition to the five most frequently cited articles, several other articles are noteworthy for their combined importance. Trager W et al. successfully cultured *P. falciparum* in human erythrocytes continuously, and the resulting parasites remained infectious [32]. This finding has greatly facilitated future studies on the inhibition and killing of *P. falciparum* by ARTs. According to Meshnick SR et al., the

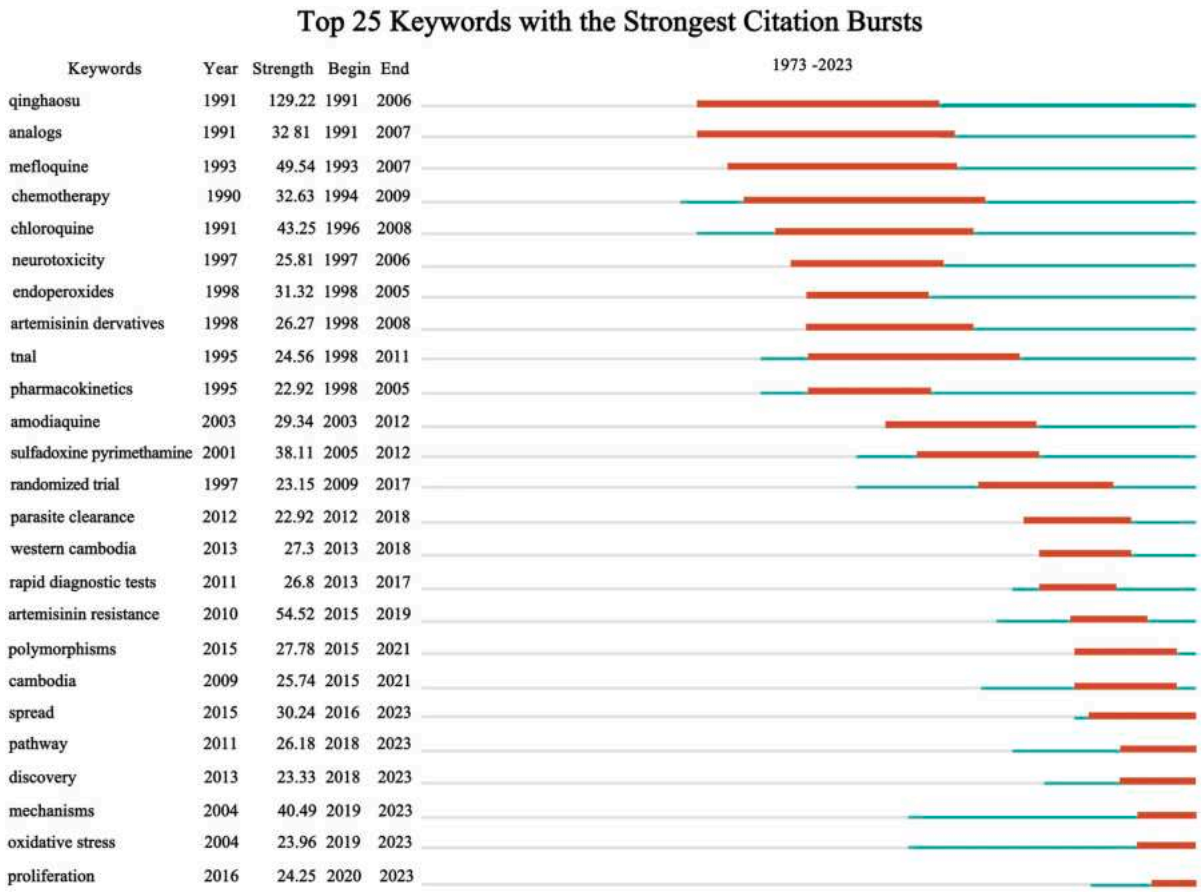

Fig. 12. The top 25 keywords with the strongest citation bursts.

use of ART-containing herbs and ART alone is limited in clinical applications, while existing derivatives of ART are capable of alkylating specific malaria proteins, and combinations with other antimalarial agents offer the potential for the first-line treatment of serious diseases [33]. After tracing the use of *A. annua* in ancient Chinese literature, Hien TT et al. discussed ART extraction, pharmacological mechanisms, and clinical applications [34]. ART compounds are superior to all other antimalarials in terms of safety, rate of onset of action, and usability, as demonstrated by numerous clinical trials; consequently, ART research has proliferated.

4.2. Hotspots

The following three sections cover the research hotspots related to ART and its derivatives on the basis of keyword and cluster analysis.

4.2.1. Treatment and control of the disease by drugs

Malaria, a significant human parasitic disease, has garnered considerable interest from the scientific community and global health organizations. Quinine continues to be a significant antimalarial agent due to its therapeutic effectiveness, notwithstanding the numerous adverse effects it can induce. However, its dominance has been challenged by the introduction of ART and its derivatives, which have been demonstrated to be more cost-effective and associated with fewer adverse events. Furthermore, they have been extensively used as antimalarials in African populations, particularly among children, with remarkable success due to the widespread development of resistance to quinine [35,36]. Typically, different antimalarial agents target distinct stages of *Plasmodium* infection. Quinine, for example, acts only against the mature parasite form. In contrast, ART derivatives demonstrate distinct stage-specific profiles, enabling more precise treatment than conventional antimalarials do. Moreover, severe malaria is responsible for a substantial increase in mortality rates because of its associations with brain dysfunction, renal failure, acidosis, and chronic diseases. Its role as the primary cause of avoidable infant fatalities in tropical regions underscores the need for substantial international investment in malaria eradication and control [37]. It is possible to effectively reduce global malaria-related mortality by administering broad-spectrum antibiotics and rectal artesunate to children who are suspected of having severe malaria at an early stage [38]. Cerebral malaria, a hazardous neurological complication of *P. falciparum*-induced malaria, can result in coma and mortality. Survivors may exhibit enduring neurological sequelae. Intravenous artesunate is regarded as the preferred therapeutic approach for treating

cerebral malaria [39]. Bertinaria and colleagues synthesized a collection of hybrid compounds by affixing furoxan and NONOate NO-donor moieties to the dihydroartemisinin scaffold [40]. All the hybrid compounds exhibited comparable antiplasmodial activity to artesunate and artemether, both in vitro and in vivo, against *P. berghei* ANKA [40]. Surprisingly, in comparison with artemether, hybrid 10 increased the survival rate of mice with late-stage cerebral malaria from 27.5 % to 51.6 %. ART-NO-donor hybrid compounds are highlighted in this discovery as potential new therapeutics for cerebral malaria, which offers novel concepts for future investigations. ART and its important derivatives are clearly superior to traditional antimalarials for the treatment and control of malaria and its complications.

In addition to their antimalarial functions, ART and its derivatives display a wide range of pharmacological activities, such as anticancer, antiparasitic, antifungal, antimicrobial, antiviral, cardioprotective, and immunomodulatory effects, which highlights the promising therapeutic role of these compounds in human diseases [9]. In the case of coronavirus disease 2019 (COVID-19), which has caused a global pandemic in recent years, these antimalarials can inhibit the in vitro proliferation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), making them leading candidates for the research and development of anti-SARS-CoV-2 drugs [41–43]. More fundamental and clinical studies are needed to explore and validate the extensive pharmacological effects of ART and its derivatives.

4.2.2. Drug synthesis

The limited availability of plant-derived ART and the related prohibitive cost for most malaria patients have generated a demand for novel synthesis techniques that can considerably reduce the cost of ACTs. Although the total synthesis of ART was reported in 1983, the reaction process is complicated, and the final yield is low [44]. One inexpensive, environmentally benign, high-quality, and consistent source of ART could be the semisynthesis of ART or any derivative from microbially sourced artemisinic acid, its immediate precursor. With an engineered mevalonate pathway, amorphadiene synthase, and a novel cytochrome P450 monooxygenase (*CYP71AV1*) from *A. annua* that oxidizes amorpha-4,11-diene to artemisinic acid, a previous study reported the engineering of *Saccharomyces cerevisiae* to produce high titers of artemisinic acid [45]. A subsequent investigation detailed the development of novel strains of *S. cerevisiae* and procedures aimed at generating amorpha-4,11-diene. This endeavor resulted in a 250-fold increase in amorpha-4,11-diene production to a concentration of 40 g/L and a method for its efficient chemical conversion to the ART precursor dihydroartemisinic acid [46]. More importantly, Paddon et al. illustrated the comprehensive biosynthetic pathway, which included the identification of a second cytochrome and a plant dehydrogenase that facilitate the biosynthesis of artemisinic acid at a rate of 25 g/L [47]. By employing a chemical source of singlet oxygen, this group successfully devised a practical, scalable, and efficient chemical process to convert artemisinic acid to ART, thereby circumventing the requirement for specialized photochemical equipment. Significant advancements in yeast strain engineering, fermentation, and ART synthetic chemistry establish a foundation for an industrial process that can augment the global ART supply from an alternative source, free from the uncertainties inherent in botanical production.

4.2.3. Impact of drug resistance on ACTs

Despite the continued high clinical efficacy of combination therapies based on antimalarial ACTs, the recent development of resistance to ACTs by *P. falciparum* has become a cause for concern. In Eritrea, the emergence and dissemination of *P. falciparum* lineages harboring deletions in *hrp2* and *hrp3*, as well as partial resistance to ART mediated by the *Pfkelch13* R622I variant, present considerable barriers to regional malaria elimination and control [48]. A descriptive epidemiological study recently revealed the concerning finding that dihydroartemisinin–piperaquine was no longer an option for treating *P. falciparum* malaria in South America because of the high prevalence and spread of piperaquine resistance in that region [49]. Resistance to ART and partner drugs in *P. falciparum* has posed significant obstacles to the eradication and control of malaria, and this unfavorable situation has accelerated the development of new strategies. Triple artemisinin-based combination therapies (TACTs) might offer efficient treatment and postpone the development of antimalarial drug resistance by combining currently coformulated ACTs with a second partner drug [50]. In a multicenter, open-label, randomized trial, patients with uncomplicated *P. falciparum* malaria were recruited via the Tracking Resistance to Artemisinin Collaboration at 18 hospitals and health clinics across eight countries [51]. The results from the TRACII trial indicated that TACT had similar efficacy and safety to ACT. Moreover, compared with ACT, TACT reduced *P. falciparum* reinfection risk and time. Nevertheless, it is critical to recognize that TACT, while effective, may not be a long-term solution, as resistance may evolve even against these innovative medications.

There is additional evidence that numerous bioactive compounds produced by marine organisms, such as cyanobacteria, algae, sponges, and soft corals, are potential candidates for managing malaria [52]. These compounds, comprising mainly alkaloids, terpenoids, and polyketides, possess potential antimalarial activities with unique structure-activity relationships and target different growth stages of the malaria parasite, including the ring and trophozoite stages [52]. However, no relevant clinical studies have been conducted. In a recent study, a stressful environment was mimicked in vitro by exposing parasites to dihydroartemisinin or chloroquine [53]. Irrespective of the *Pfkelch13* genotype, an unidentified extracellular signal of less than 3 kDa that was secreted by dying trophozoites induced threshold-dependent temporary growth arrest in the early ring stage of *P. falciparum*, consequently reducing its susceptibility to dihydroartemisinin. These findings provide invaluable insights into the molecular underpinnings of *P. falciparum* antimalarial drug resistance. In addition to the prevailing drug resistance landscape, enhanced vector control, improved surveillance, enhanced detection of drug-resistant *P. falciparum*, ongoing drug development, and targeted drug utilization are imperative factors [54]. The scientific community has been making continuous efforts to address the problem of ART resistance.

Collectively, the research hotspots identified in the field of ART and its derivatives are intricately linked to the pressing challenges in malaria treatment and prevention, with profound implications for public health. The hotspots highlight the shift from quinine to

ART-based treatments due to increased resistance and the need for more targeted therapies. The ability of ART derivatives to address distinct stages of *Plasmodium* infection offers a more precise approach to treatment, which is crucial for reducing the high mortality rates associated with severe malaria, particularly in vulnerable populations such as children. The development of hybrid compounds with improved survival rates in cerebral malaria models suggests potential new avenues for therapeutic intervention. Moreover, the broad-spectrum activities of ART and its derivatives, including potential applications in COVID-19 treatment, underscore their importance in global health. The pursuit of novel synthesis techniques to reduce the cost of ACTs is essential for improving accessibility and, consequently, outcomes in malaria-endemic regions. Finally, research hotspots have focused on the growing issue of drug resistance, which necessitates the development of new strategies, such as TACTs, to combat the spread of resistant strains. These connections between research trends and public health challenges underscore the urgency and relevance of our findings in shaping future efforts to control and eradicate malaria.

4.3. Emerging topics

The frontiers of the field can be easily identified on the basis of the analysis of keyword citation burst results. ART derivatives are well-tolerated antimalarial drugs that also exhibit anticancer properties by regulating different signaling pathways. The mitochondrial pathway and Bim/Bcl-2 balance are involved in dihydroartemisinin-induced apoptosis in human breast cancer in vitro [55]. A preliminary study revealed that neuroblastoma malignancies are artesunate sensitive and that chemoresistant neuroblastoma cells are susceptible to treatment with artesunate [56]. Artesunate also prevents thyroid cancer cells from proliferating and migrating by blocking the PI3K/AKT/FKHR signaling pathway [57]. Moreover, artesunate inhibits corneal neovascularization by inducing reactive oxygen species-dependent apoptosis in vascular endothelial cells [58], suppresses proliferation, and induces ferroptosis in Burkitt's lymphoma model in vivo by triggering the ATF4-CHOP-CHAC1 pathway [59]. These studies highlight the importance of signaling pathways in the antitumor mechanisms of ART derivatives.

Accumulating evidence has shown that the mechanism of ART resistance is a complex process with multifactorial involvement consisting of mutations in *PfKelch13*, the metabolic profiles and genetic background of the parasites, and the dynamic interplay between cellular heterogeneity, environmental stress, and ART [60]. As an emerging topic, oxidative stress is implicated in ART resistance in malaria parasites. An earlier study indicated a notable overlap between the parasite's reaction to oxidative stress, its ability to survive malaria fever, and the development of resistance to ART [61]. A follow-up study revealed that the antimalarial effectiveness of ART against parasites cultivated under intraerythrocytic oxidative stress was considerably diminished in comparison with ideal culture conditions [62]. Thus, prolonged intraerythrocytic microenvironmental oxidative stress may predispose malaria parasites to develop tolerance to ART-induced oxidative damage. Moreover, in *Theileria annulata*-transformed cells, ART derivatives induce oxidative stress, which results in DNA damage and caspase-mediated apoptosis [63]. These emerging areas of research herald advancements in ART-related fields, providing new insights into the treatment of disease, particularly highlighting the critical therapeutic role of ART derivatives in cancer, which is currently the greatest threat to human health.

5. Limitations

Despite our efforts to cover all the articles published from the first publication through the end of 2023 in the bibliometric study, certain limitations were unavoidable. The first issue was that all the data were gathered solely from the WOSCC SCI-E database, which excluded articles from alternative sources. Moreover, only articles written in English were included in this investigation, and some documents published in other languages were omitted. Finally, manual deletion of papers irrelevant to the study by researchers may have led to selection bias. These factors may result in an incomplete and inaccurate analysis, possibly leading to discrepancies with real-world conditions.

6. Conclusions

By employing CiteSpace, this study offers an all-encompassing and comprehensible examination of scholarly articles about ART and its derivatives, an area of study attracting increasing interest worldwide. This study demonstrates that institutions and authors work closely together. The United States and China are significant players in this field, and an increasing number of nations and regions are participating. Collaborations should become more extensive and robust. The findings from our study indicate that "synthesis," "drug resistance," "antimalarials," and "*Plasmodium*" are the primary research areas of interest, with African children identified as the primary target group. The terms "proliferation," "oxidative stress," "pathway," and "mechanism" are at the forefront of current research. Subsequent investigations should prioritize the surveillance and resolution of drug resistance. We recommend that future studies focus on two main frameworks: first, the establishment of a robust global surveillance system to monitor and combat the rise of drug resistance in malaria treatment, especially for ART derivatives; second, the pursuit of in-depth mechanistic studies to uncover how ART and its derivatives interact with biological targets, which will inform the development of more precise therapeutic strategies. These targeted research directions will provide a clear path forward, enhancing our ability to address the challenges of drug resistance and to broaden the applicability of these crucial antimalarial drugs.

CRediT authorship contribution statement

Yu Lai: Writing – original draft, Funding acquisition, Data curation. **Huize Zhang:** Visualization, Data curation. **Xi Chen:** Writing –

review & editing, Software, Methodology, Conceptualization.

Availability of data and materials

All the data used in this study are available upon request from the corresponding author.

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Declaration of competing interest

The authors declare no conflicts of interest.

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