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Review

Global research on artemisinin and its derivatives: Perspectives from patents

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ABSTRACT

Background: The isolation of artemisinin in 1971 heralded the beginning of a new era in antimalarial drug therapy, and artemisinin-based combination therapies are currently the mainstay of malaria treatment worldwide. Artemisinin-related studies have been extensively and intensively executed in the last few decades. However, although many purely technological reviews have been completed in this field, studies on artemisinin from the perspective of patents are still very limited. In terms of the importance of patents for academic research and commercial development, this study aims to reveal the overall patent landscape of artemisinin in the temporal, spatial, and technological dimensions. This work may provide a useful reference for relevant decision-making by researchers, investors, and policymakers.

Methods: All available patent data relevant to artemisinin derivatives and artemisinin-based drug combinations developed for use in various therapeutic areas were collected from the Derwent Innovation database. Descriptive statistics and citation analyses were used to analyze the patent landscape.

Results: A total of 4594 patent documents and 1450 simple patent families from 1986 to 2019 were analyzed. A comprehensive patent landscape of artemisinin is presented from the aspects of time trends, filing countries, patent ownership, co-patents, technological categories, therapeutic areas, and citation networks and pathways. **Conclusions:** China and the United States are mainly responsible for the dramatic increase of artemisinin patents over the last three decades. From the point of view of patents, notable technological issues on artemisinin are chemical and biological synthesis, novel combinations, new formulations and administration routes, drug re-positioning, and minimizing the resistance. Furthermore, a critical challenge lies in how to stimulate the industry to develop artemisinin-related drugs by government regulation and public-private partnership.

1. Introduction

In 1971, the Chinese project 523 led by Tu Youyou (the first Nobel laureate in physiology or medicine in China) isolated a non-toxic extract of sweet wormwood plant. The extract is able to induce 100 % parasite clearance in animal models of malaria (*Plasmodium berghei* and *Plasmodium cynomolgi*) [1,2]. In 2006, the World Health Organization (WHO) recommended the adoption of artemisinin-based combination therapies (ACT) as first-line treatment options for the treatment of *Plasmodium falciparum* malaria [3]. During the last 50 years, chloroquine and sulfadoxine-pyrimethamine are the most widely recommended treatments for the potentially lethal malaria infection.

However, an alternative is needed as they were no longer working effectively in most tropical countries. Resistance to these drugs also appeared in Asia and South America and spread to Africa.

Meanwhile, artemisinin and its derivatives show strong antiparasitic action, anti-infectious effects, as well as antitumor, anti-inflammatory, anti-oxidant, anti-angiogenesis, and apparent immunomodulatory effects [4–7]. The anticancer activity of artemisinin derivatives has been extensively studied since being first reported in 1993 [8]. In addition, artemisinin and its derivatives are not only active against cancer cells, but also in human cytomegalovirus (HCMV) infections and other viral infections, as well as *Schistosoma* sp., *Fasciola hepatica*, *Babesia* sp., etc., as discovered in the last few years [2,9–11].

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It is not surprising that a research on existing artemisinin-based molecules and the search for novel artemisinin compounds as potential therapeutic agents have been intensified in recent years, since artemisinin appears to possess a wide spectrum of activity and a relatively low toxicity profile. Such interest has led to abundant patents for artemisinin derivatives. As mentioned above, many technological analyses and reviews exist for artemisinin [1,11–13], but their patents have received little attention. Patents in the life sciences are not only a crucial metric of innovation, but also a cornerstone for the commercialization of a new field in life science and healthcare-related technologies. Moreover, patent analyses can be used to underpin important decision making and analyses by academics, industry, and governments.

To address this gap in knowledge, we reviewed global research on artemisinin and its derivatives from the perspective of patents by highlighting drug resistance and potential clinical benefits in non-malarial indications. This research is expected to show an overall patent landscape of artemisinin in the temporal, spatial, and technological dimensions, which may provide a reference for relevant decision-making by researchers, investors, and policymakers.

2. Methods

The Derwent Innovation platform (a worldwide provider for enhanced patent documents) was used in this study to achieve a dataset of patents dealing with inventions related to artemisinin. We retrieved sample patents with publication date before August 31, 2019, accordingly to the rules of preferred reporting items for systematic reviews and meta-analyses (PRISMA), an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses [14]. In the data search for patents filed on artemisinin and its derivatives, the full names of artemisinin and its main derivatives, abbreviations, or synonyms were inputted into the patent topic (TS) field of the database. As for the dataset cleaning, a fundamental data normalization step was performed to clean duplicate records that had occurred due to abbreviations or misspelling. The unrelated patents were deleted in the document records after being checked manually. This study did not exclude patent applications that are still pending, in order to capture the latest progress in patenting activities due to rapid developments in recent years. Supplementary Fig. 1 shows the detailed process of data inclusion, screening, and exclusion.

Each patent record consists of detailed information about a patent family, which includes the basic patent filed in the original country or office and subsequent equivalent patents on the same invention filed in different countries or offices. The patent analysis described below focuses on family-based patent information, including the basic patent number, patent publication year, assignees, title, abstract, international patent classification (IPC), application details of all the family members, and citation information. The items reported in this patent landscaping are according to the Reporting Items for Patent Landscapes (RIPL) checklist, which is the latest comprehensive standard for patent landscape reporting [15].

Moreover, the study adopted a method of network analysis to review the artemisinin patents, which places emphasis not only on individual patents but also on the citation relationship between them. We constructed a series of patent citation networks, where nodes represent patents, and directed edges and arrows denote citation relationships and directions. Moreover, patents can be clustered together to form an independent network component, in which nodes have relatively frequent internal connections. The structures and features within patent citation networks comprehensively indicate the patterns of technology flows and evolution. This study also used various descriptive approaches including heat maps, rose charts, word clouds, and chord diagrams to illustrate the patent indicators and associations between them.

3. Results

3.1. Data overview

In this study, the patent family was considered as the multiple patent applications of the same invention, filed in multiple patent offices within 12 months of the first filing (priority filing). In total, a dataset of 4594 patent documents and 1450 simple patent families were generated for the analyses. Legal status of all sample patents were checked, in which percentages of rejected and invalid cases are 7.29 % and 4.07 %, respectively. Artemisinin patents publications have been increasing for the last 30 years, starting from the first published patents in 1986 to 343 in 2018 (Fig. 1). Artemisinin patents had a preliminary scale after 2000 and have continued to develop rapidly since 2010 (Fig. 1a). In particular, the years 2011 and 2015 were turning points in the fast growth of artemisinin patents, when Tu Youyou was awarded the prestigious Lasker-DeBakey Clinical Medical Research Award for her role in the discovery and development of artemisinin in 2011 and the Nobel Prize for Physiology or Medicine for her discovery of the artemisinin family in 2015, respectively.

3.2. Geographical distribution

Fig. 1b shows the geographical distribution of artemisinin patents by the nationalities of their inventors, by highlighting the most productive countries, which include China (1328 patents), the United States (1294 patents), Germany (334 patents), France (306 patents), and India (271 patents). Usually, the inventor's nationality roughly reflects where the patent inventions come from. However, inventorship destinations can be observed by their priority countries or regions, that is, where the patent applicants claim their patent rights. Due to regional restrictions, patent applicants usually claim patent protection only in countries with a potential market for the patented products. In Fig. 1c, artemisinin patents are geographically distributed by their priority countries or regions, including China (884 patents), the United States (634 patents), India (100 patents), Canada (93 patents), and European Patent Office (76 patents). This kind of patent location based on priority countries is further depicted with its changes by year in Fig. 1d. From the angle of patent priorities of artemisinin, China and India have become increasingly more important markets, while Australia has fallen into a relative weakened status. Especially in China, there are fewer patents before 2000.

3.3. Patent assignee

Table 1 shows the top 15 assignees by the number of artemisinin patent families. Most of the top assignees are universities and research institutes, from which we identified the Shanghai Jiao Tong University as the outstanding player, with 49 inventions filed in 78 patent documents, followed by the Council of Scientific and Industrial Research, Johns Hopkins University, University of Washington, the Institute of Chinese Materia Medica, and the China Academy of Chinese Medical Sciences. The active companies are the Yuzhou City Tianyuan Biological Technology, with 55 inventions filed in 56 patent documents, followed by the Kunming pharmaceutical corporation, Guilin Nanyao Pharmaceutical, Dafra Pharma International, and Sanofi S.A. Actually in industry, Yuzhou City Tianyuan Biological Technology has the largest artemisinin production line in China at present while Sanofi has become the only producer of semisynthetic artemisinin in the world. Kunming Pharmaceutical Corporation is the Active Pharmaceutical Ingredients (APIs) supplier of Compound Artemether produced by Novartis. It is worth noting that Sanofi S.A. possessed a small number of patent families but a large number of patent documents. On the contrary, players in China have an obviously small patent family size, which implies that China pays less attention to market protection worldwide.

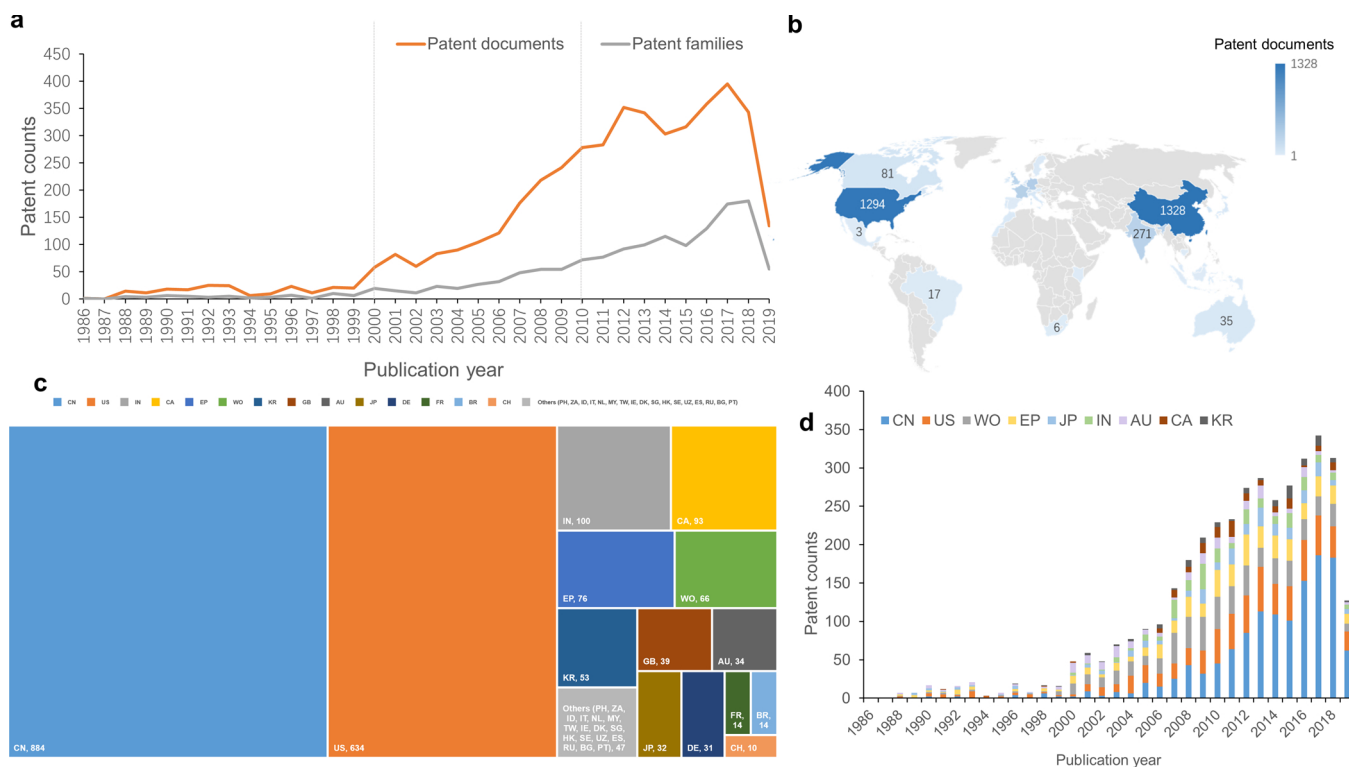


Fig. 1. Temporal and geographic distribution of artemisinin patents.

- a. Publication trend.
- b. Geographic distribution by nationalities of patent inventors. The color intensity denotes the frequency of patent documents.
- c. Geographic distribution by priority countries.
- d. Annual changes of main priority countries.

Fig. 2a shows the change in the organizational types of patent assignees from 2000 to 2019. In the early years, patents owned by individuals accounted for a large proportion. Afterwards, the dominant status of individual patents was gradually replaced by companies, universities, and research centers. In recent years, universities and research centers have played an increasingly important role compared with the companies. These changes indicate a gradual trend of commercialization of artemisinin-related inventions.

In addition, a collaboration chord diagram was constructed to further investigate the collaboration patterns of patent assignees in artemisinin-related inventions (Fig. 2b). In terms of patterns of partnerships

between different organizational forms of assignees, they can be ranked by cooperation frequency as follows: C-U&R, C- C, U&R-U&R, U&R-I, C-I, and I-I. Of these, nearly one-third of the partnership collaborations are between C and U&R.

3.4. Technological characteristics

First, the assigned IPC categories of the patents indicate the technological areas that the inventions involve. Fig. 3a depicts the change in the main IPC categories in 7-digit codes by years. The most prevalent IPC category is A61K-031 (medicinal preparations containing active

Table 1
Top assignees of artemisinin patents.

Rank	No. patent documents	Patent families	Average no. of patents per family	Assignees	Assignee Type
1	56	55	1.02	Yuzhou City Tianyuan Biological Technology (China)	C
2	78	49	1.59	Shanghai Jiao Tong University (China)	U&R
3	164	42	3.9	Council of Scientific and Industrial Research (India)	U&R
4	47	17	2.76	Kunming pharmaceutical corporation (China)	C
5	81	16	5.06	Johns Hopkins University (U.S.)	U&R
6	81	15	5.4	University of Washington (U.S.)	U&R
7	14	11	1.27	Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences (China)	U&R
8	14	11	1.27	Guilin Nanyao Pharmaceutical (China)	C
9	140	10	14	Centre national de la recherche scientifique (France)	U&R
10	48	10	4.8	Dafra Pharma International (Belgium)	C
11	228	9	25.33	Sanofi S.A. (France)	C
12	92	9	10.22	Medicines for Malaria Venture (Switzerland)	U&R
13	63	9	7	University of California (U.S.)	U&R
14	19	9	2.11	Shenyang Pharmaceutical University (China)	U&R
15	8	8	1	Ocean University of China (China)	U&R

Abbreviations: C: company; U&R: university and research institute.

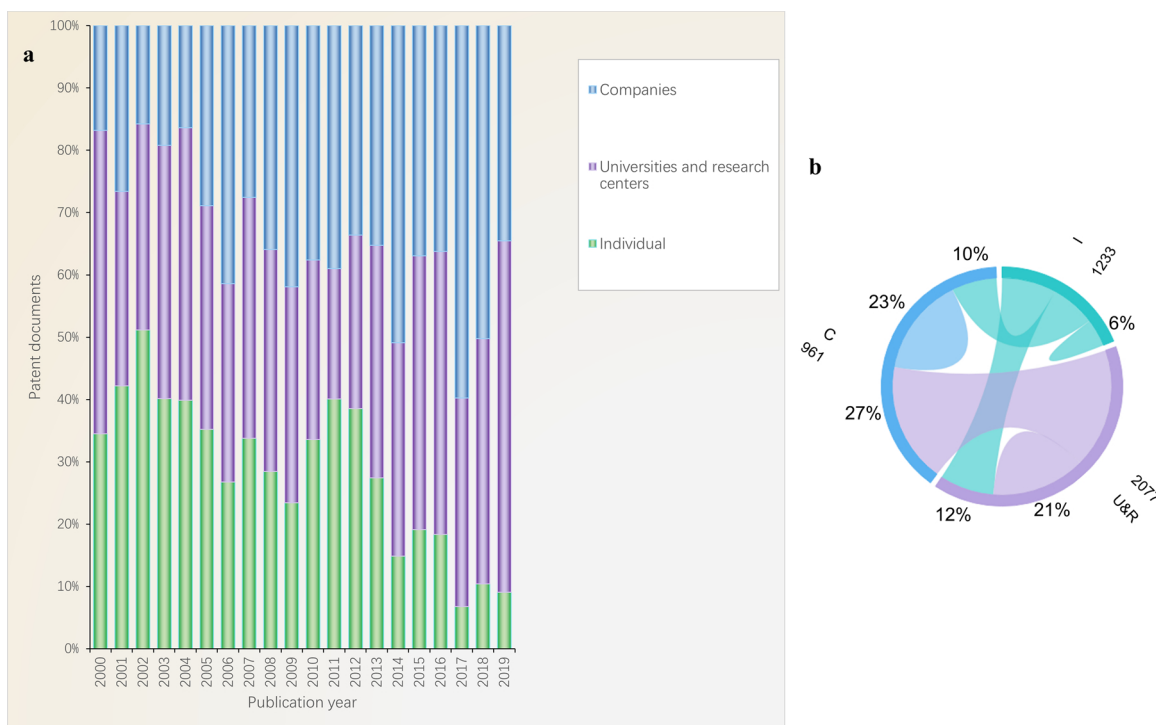


Fig. 2. Types and cooperation of artemisinin patent assignees.
a. Organizational types.
b. Chord diagram of collaboration patterns (C: company; U&R: university and research institute; I: individual).

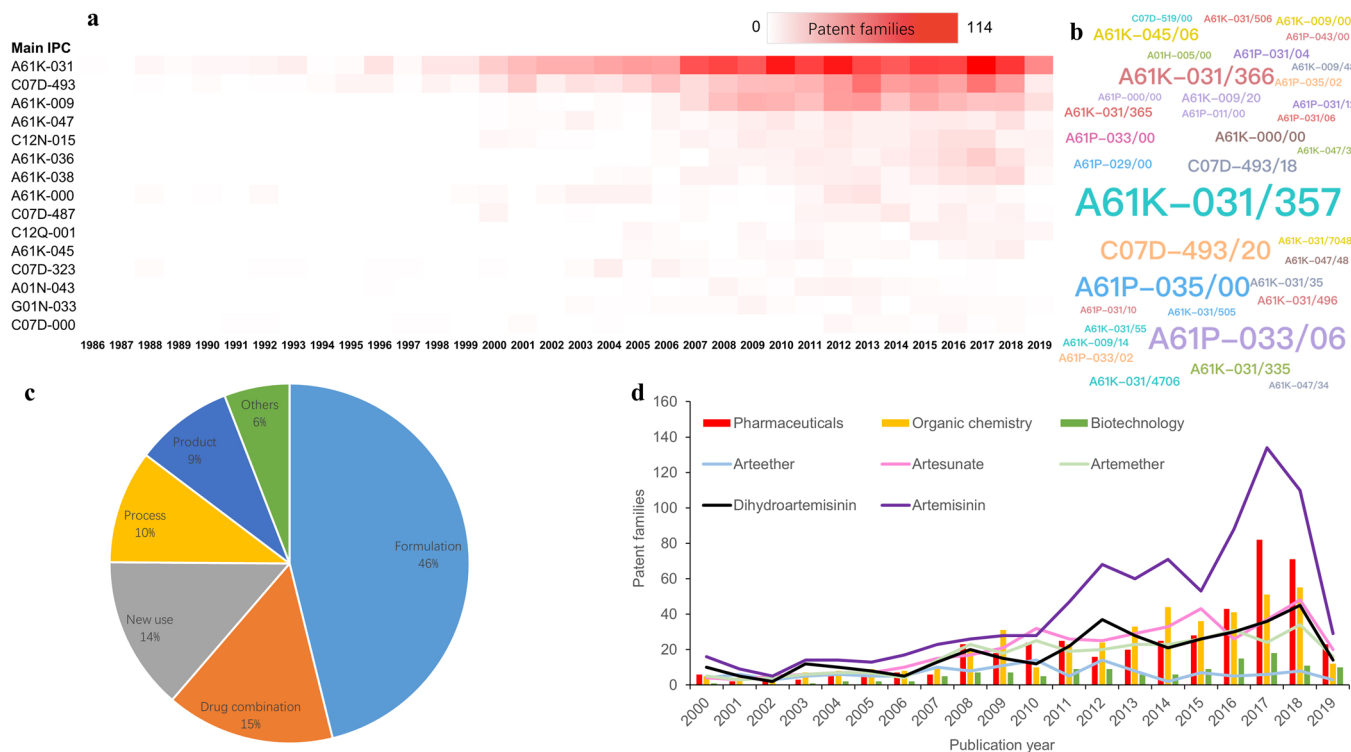


Fig. 3. IPC and technological categories of artemisinin patents.
a. Annual changes of main IPC codes.
b. Word cloud of IPC codes.
c. Static distribution of technological categories.
d. Dynamic changes of technological categories.

organic ingredients), which comprised 1438 patents.

Fig. 3b, illustrates more detailed technological areas of patents by word cloud of the IPC categories in 10-digit codes. A61K-031/357 represents the technical area with two or more oxygen atoms in the same ring, which is dominant among all IPC 10-digit codes categories of the patents. A61P-035/00 (antineoplastic agents) and A61P-033/06 (antimalarials) indicate that antineoplastic agents and antimalarials are the two main disease directions of artemisinin R&D (research and development). A61K-009/20 (pills, lozenges or tablets), A61K-009/08 (solutions), A61K-009/14 (particulate form), A61K-009/48 (preparations in capsules) were ascendant among all medicinal preparations characterized by special physical form (A61K-009). Besides, A61K-009/14, A61K-009/20, A61K-009/127(liposomes), and A61K-009/107(emulsions) are the top 10 % ranking IPCs under A61K-009 based on the growth rate of patent families (Supplementary Fig. 2).

Second, the static distribution and dynamic changes in the drug-relevant technological categories of artemisinin patents are shown in Fig. 3c and d, respectively. Formulation patents account for 46 %, followed by drug combination 15 %, and new use 14 %. That is to say, nearly half of artemisinin patents focus on formulation research that aims to develop preparations of artemisinin drugs with a stable and acceptable bioavailability.

The relatively high proportion of patents on drug repositioning indicates a popular area of R&D. Drug repositioning, namely the new indications of existing clinical drugs, has the advantages of low cost and being less time-consuming compared with the new drugs discovery, and has been emerging as a new access to artemisinin drug R&D. Moreover, after 2000, the type of pharmaceuticals gradually became dominant, while the type of organic chemistry declined. Based on its production mechanism, artemisinin production was segmented as biosynthesis, chemical synthesis, and synthesis in engineered organisms. Patents that focus on the chemical synthesis of artemisinin account for a large number of the patents. Among artemisinin's main derivatives, it is expected that arteether-related patents will remain relatively stable each year with small amount of fluctuation over the years. A number of dihydroartemisinin, artesunate, and artemether-related patents

experienced a series of fluctuations for two decades; however their overall tendency was upward.

Third, Fig. 4 shows the ICD-11 (International Classification of Diseases 11th Revision) of artemisinin patents. As regards the disease profile, the disease indication covered in the title, abstract, and claim of artemisinin patents were extracted and classified by ICD-11, which is the global standard for diagnostic health information. The rose chart shown in Fig. 4a indicates the therapy area mentioned in the artemisinin patents. ICD-11 type of certain infectious or parasitic diseases were the most common therapy areas of all the disease indications either in the patent documents or patent families ($n = 2780$ patent documents, $n = 774$ patent families). Plasmodium infection was the most commonly investigated subtype of the certain infectious or parasitic diseases (patent documents $n = 2342$). More indications sorted in order included neoplasms ($n = 277$ patent families), diseases of the immune system ($n = 64$ patent families), diseases of the nervous system ($n = 47$ patent families), and diseases of the skin ($n = 34$ patent families). Endocrine, nutritional, or metabolic diseases and diseases of the circulatory system had lower-ranking patent families but relatively greater number of patent documents. This highlights that these two kinds of disease patents have fewer technology types, but more active applications.

Furthermore, all ICD-11 types in Fig. 4 (examples of specific diseases and corresponding patents) are shown as below: developmental anomalies (usher syndrome by WO2018068051); diseases of the ear or mastoid process (sudden idiopathic hearing loss by WO2015028901, meniere disease by WO2015028901); sleep-wake disorders (sleep disorders by EP2929881); injury, poisoning and certain other consequences of external causes (injury by CN106492207, scald and burns by CN105343332); diseases of the genitourinary system (prostatic hyperplasia by CN102552451, menopause by CN104922106, dysmenorrhea by CN106890217); diseases of the visual system (macular degeneration by WO2015135306, glaucoma by CN109288986); mental, behavioural or neurodevelopmental disorders (autism by WO2017040564, depression by CN106563041); diseases of the blood or blood-forming organs (anemia and hemophilia by WO2019079607);

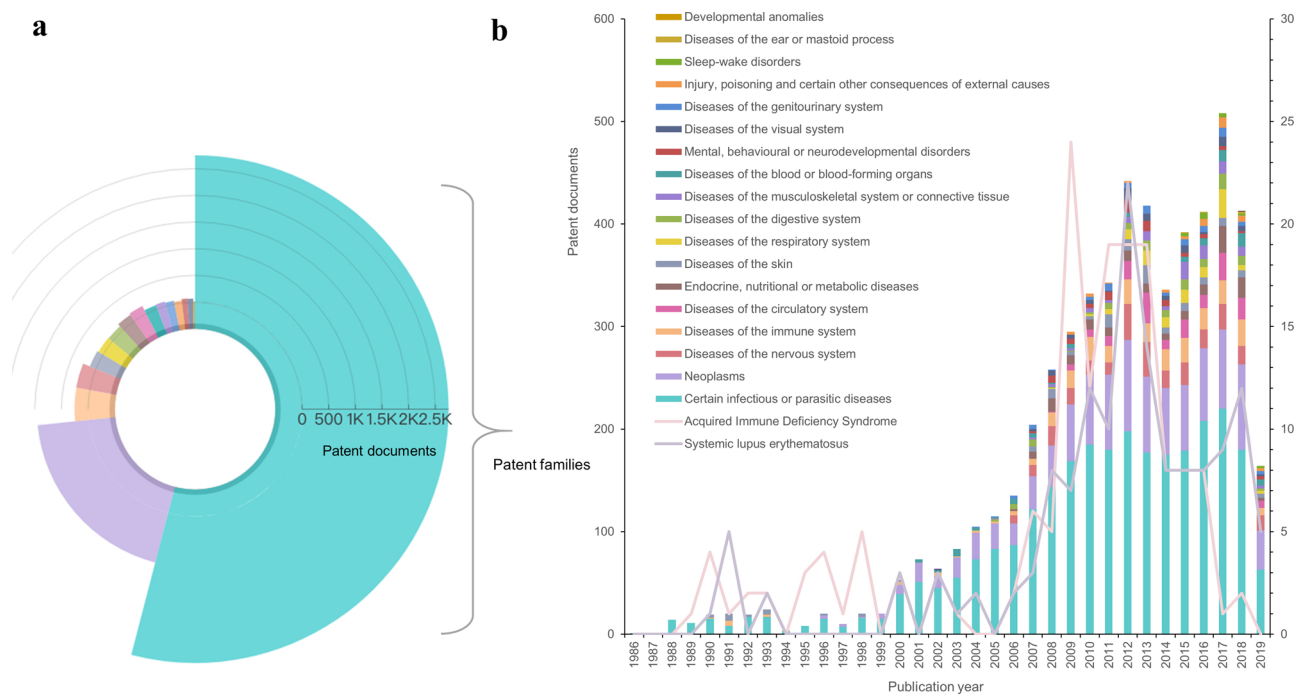


Fig. 4. ICD of artemisinin patents.

a. Rose chart.

b. Annual changes.

diseases of the musculoskeletal system or connective tissue (osteoporosis by KR1487761); diseases of the digestive system (gastroesophageal reflux and peptic ulcer by WO2007125397); diseases of the respiratory system (respiratory disease and chronic obstructive pulmonary disease by CN105998328); diseases of the skin (acne by WO2012088382); endocrine, nutritional or metabolic diseases (diabetes by EP2929881); diseases of the circulatory system (atherosclerosis and hyperlipidemia by CN103239439, hypertension by WO2011017533); diseases of the immune system (autoimmune disease by WO2015084721, systemic lupus erythematosus by CN101632657, photosensitive diseases by CN1266683); diseases of the nervous system (Alzheimer's disease by US2019201376, Parkinson's disease by CN107802621); and neoplasms (lung cancer, breast cancer and leukemia by WO2007112451, WO2004034976, WO2007116135 and CN103393672). The last but notable class occupying the biggest share is certain infectious or parasitic diseases (where several examples come with SARS-CoV by CN101099804, CN1672717, CN1480194 and CN1470282, respiratory syncytial virus by CN108623589, cytomegalovirus by US8883765, influenza virus, adenovirus and human papillomavirus by US20070142459, herpesvirus by US20110166106, ebola virus by WO200044359, zika virus by US2016250181, hepatic viruses by WO2008033466, dengue virus by WO2012108892, human immunodeficiency virus by EP713877, hand, foot and mouth disease by CN105125453, fungal infection by US6127405, bacterial infection of tuberculosis by CN104418864, and various parasitic diseases by WO2009067797).

Early patents on artemisinin were mostly focused on certain infectious or parasitic diseases. However, since 2007, research has entered a new paradigm for exploring novel indications. The proportion of disease types of neoplasms, diseases of the immune system, and diseases of the nervous system increased. The patent share of treatments for Acquired Immune Deficiency Syndrome declined to the lowest with each passing year after 2011. Tu Youyou firstly claimed the application of dihydroartemisinin for the treatment of Systemic Lupus Erythematosus in China in 2000. From Fig. 4b, we can see that this type of patent developed rapidly after 2000 and entered a stable period after 2014.

In addition, artemisinin resistance is currently receiving much research attention. All patents related to drug resistance have been extracted (Supplementary Table 1). The continued use of oral artemisinin-based monotherapies is considered to be a major contributing factor to the development of resistance to artemisinin derivatives and ACTs are now recommended by the WHO. It can be seen that combining drugs ($n = 22$ patent families) is the most commonly used technology. Combinations in which artemisinins are proposed for formulation with drugs used to treat co-morbidities that accompany malaria or independently occurring disease conditions aimed at minimizing the development of resistance but also at potentiation of activity. The patents of drug resistance reversal agents ($n = 6$ patent families) indicate that artemisinin has the potential to reverse drug resistance, which is of great importance considering that multidrug resistance is currently a major impediment to cancer treatment.

3.5. Patent citation network

Fig. 5 shows the citation networks of artemisinin patents. In total, 1724 nodes and 2091 edges are plotted in Fig. 5a. It is obvious that some patents are linked together more closely to form network clusters. To highlight the main technology clusters, we marked clusters with more than five patent members in different colors. The largest community, colored in blue, represents 9.18 % of the nodes, the second, in orange, comprises 8.56 % of nodes and the third, in green, 8.01 %. The blue community includes patents with many big nodes, highlighting its importance to the network since it gathered the most cited patents.

Patents with a high out-degree, which means patents that are mainly cited by subsequent patents, represent the most basic and

innovative technologies with high creativity, which others in the field are trying to imitate [16]. The most cited patents were labeled with patent numbers and are shown in Supplementary Table 2. These influential patents played critical roles in technological flows, such as patent US5578637, WO2009088404, US5225562, US6127405, and US6649647.

In order to reflect the evolution of network clusters, the 28 clusters with more than five patents were extracted and divided into three time periods, 1986–1999, 2000–2009, and 2010–2019, as illustrated in Fig. 1a, based on the average year that the patents were granted within a specific cluster. Here, it can be seen that the most cited patents are mostly for the type of certain infectious or parasitic diseases. (Fig. 5b) The broad coverage of the largest component in the network may imply some kind of technical coherence and the strong diffusion capability of artemisinin-related inventions.

In order to show the historical pathway of artemisinin R&D clearly, Fig. 5c highlights the annual milestone patents using the Search Path Count (SPC) algorithm in patent citation networks. All of the influential patents, cited as the key prior technologies in the patent portfolios, led to the following extensive technology spillover. This process constructed the main trunk of technology development in the field of artemisinin-related inventions. The route starts with US4791135, which was published in 1988 from the United States Secretary of the Army. It describes the use of artemisinin for the treatment of malarial infections. The US4791135 patent cited by EP362730 is from Hoechst AG. It is related to artemisinin-derivate for the treatment of protozoal infections. The next is US5225562. It refers to the preparation method of deoartemisinin. Patents US6160004 and WO2003048167 introduce the new artemisinin derivatives such as substituted artemisinin-like trioxane derivatives for the treatment of cancer. Patent WO2007043057 proposes the compositions for nasal delivery. Patent WO2009053758 indicates pharmaceutical compositions that are administered by sublingual spray in comparison to oral administration by tablet, leading to increased bioavailability. Patent data mining using the SPC method has further resulted in a technological trend path that includes patents with the greatest future exploratory potential.

4. Discussion

Considering wide implications of patents in scientific, industrial and social dimensions, we further discuss global research on artemisinin and its derivatives in the three aspects.

4.1. Scientific implications

Based on research results by the above analysis of patenting activity, it is worth discussing the following technological areas on artemisinin: chemical and biological synthesis of new derivatives, novel combinations among known compounds, new formulations and administration routes, drug repositioning, and minimizing resistance.

First, ongoing research on artemisinin and its derivatives has revealed its potential use in treating infectious and noninfectious diseases. Notably, it was reported that artemisinin derivatives exert their anticancer effects through distinctly different mechanisms than those of most existing anticancer agents [17]. Cancer cells are more prone to cytotoxic effect of artemisinins due to their high intracellular iron levels [18]. Thus, introducing these derivatives into the anticancer armamentarium may address current critical challenges facing cancer chemotherapy, namely drug resistance and severe toxicity. In addition, with the emergence of infectious diseases such as SARS and MERS in recent years, chloroquine, the anti-malaria drug, has been used in experiments against these viruses and has good inhibitory effect with safety in vitro [19–21]. Artemisinin, which has antimalarial effect with an excellent safety index, may also have possibility and potential. Mateon announced that its COVID-19 directed antiviral screening program discovered that artemisinin is highly potent at inhibiting the ability of

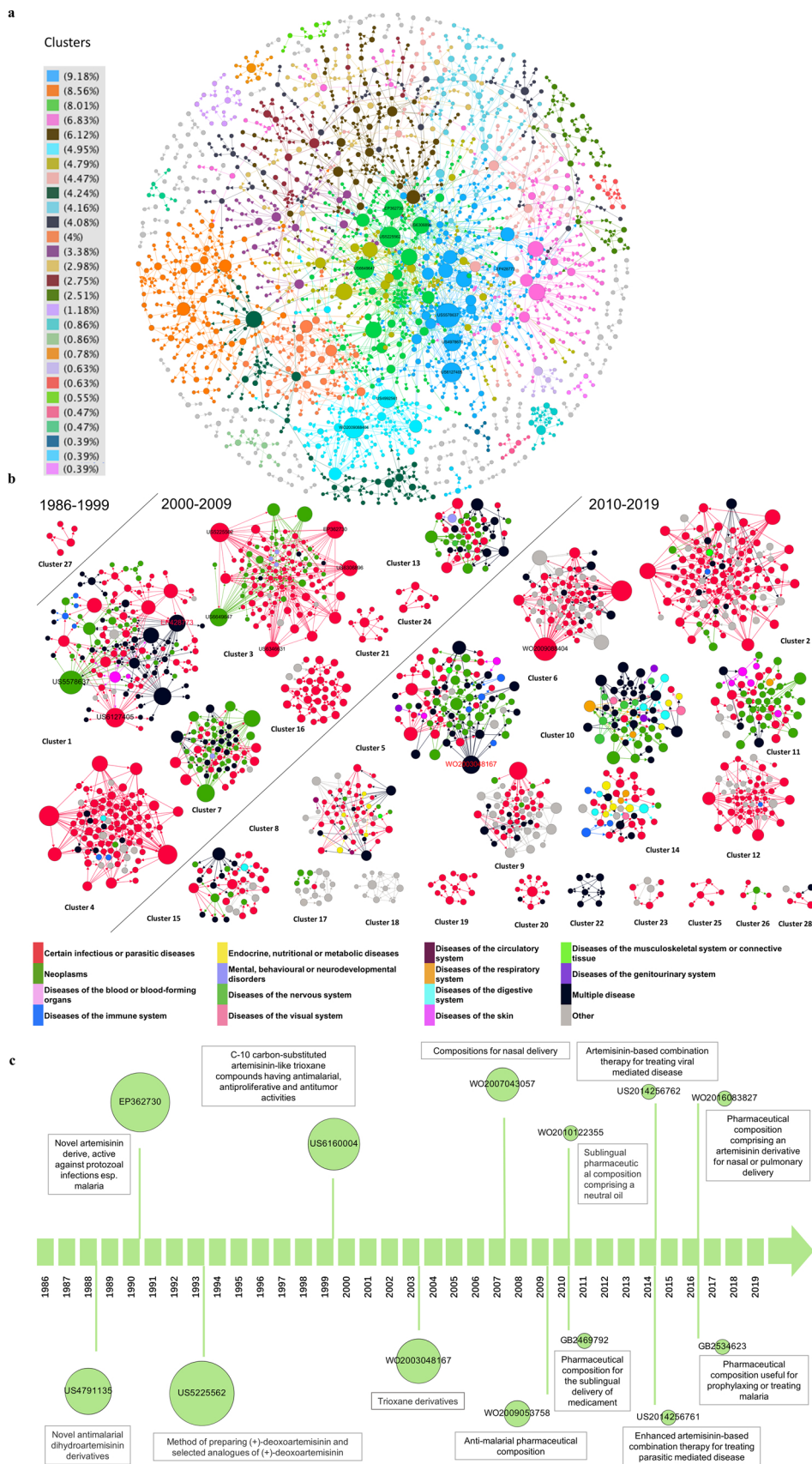


Fig. 5. Citation analysis of artemisinin patents.
a. Global citation network including all patents and their citation links. Bigger nodes represent highly cited patents. The node size was set according to its out-degree value, that is, the greater the out-degree, the larger the node size, and the more citations a given patent received.
b. The isolated cluster of the patent citation network showing different communities identified by the metrics of modularity. According to the ICD-11, patents are classified into 17 types, each with a different color. The cluster numbers are ordered by node and edge ranking from the highest to lowest within the cluster network. The nodes are colored based on the different ICD-11 classification while the edges are colored based on the source of the citation.
c. The technological temporal route derived from the global network based on the main path of patent citation. The node size was set according to its out-degree value.

the COVID-19 causing virus to multiply [22]. In response to serious public health crisis caused by worldwide outbreak of COVID-19, various urgent clinical trials for COVID-19 treatments have been initiated, including two artemisinin-related studies recorded in ClinicalTrials.gov, Artesunate (NCT04387240) and ArtemiC (NCT04382040). Besides, a recent patent application CN111150755, claiming to treat COVID-19 by herbal combinations with *Artemisia Annuua* was published on May 2020. In general, the efficacy of artemisinin in new therapeutic areas remains to be tested in well controlled and sufficiently powered clinical trials. In particular, it received high attention due to the lack of effective antiviral drugs against new emerging viruses.

As is well-known, like "looking for needle in a haystack", drug discovery is a time-consuming, costly, and risking work. New uses for old medications can significantly save time and cost with shortening R&D cycle, which can reduce the risk and improve the success rate of drug R&D. It is reported that this strategy can save about 40 % of the R&D cost [23] and shorten the R&D pipeline by 3–12 years [24,25]. In this sense, the development of new therapeutic areas related to artemisinin seems to be a promising work. However, some fields, such as, anti-cancer or antiviral infections have been very competitive. Whether artemisinin can show comparative advantages with positive control drugs is a great challenge. Furthermore, even if new indications are approved, off-label use may discourage original sponsors, who usually hold patents of new indications, but only blocking competitors to claim new indications in their official labels.

In addition, drug combinations targeting multiple conditions can help to achieve medical compliance and work against drug resistance. Novel artemisinin combinations also have the advantage of improving therapeutic efficacy against resistant Plasmodium strains and greatly minimize disease transmission and resistance propagation [26,27]. However, the beneficial effects of different combinations are neither obvious nor predictable. Consequently, the search for new artemisinin-based combinations is an ongoing process. As far as artemisinin-related new formulations and administration routes are concerned, sublingual, nasal or pulmonary delivery are potential orientation of administration route, while pills, lozenges or tablets, particulate form, liposomes and emulsions may be promising medicinal preparations.

Thus, the search for new artemisinin-based combinations with reduced dose, better amenability to combination with other drugs, novel derivatives with superior pharmacokinetic and toxicity profiles, large-scale synthesis in low cost, administration route demonstrating good bioavailability on rate and extent of absorption, as well as dosage forms that is active, stable and acceptable to the patient should be a continuous process.

4.2. Industrial implications

For discussing industrial implications, it is necessary to make a brief review on the process of scientific discovery and commercial operation related to artemisinin. In the 1970s, Chinese scientists successfully extracted artemisinin. However, since there was no patent law in China at that time, no patent was applied for the invention, which was just summarized in a Chinese paper [28]. The powerful R&D institutions and pharmaceutical companies in France and Switzerland further conducted extensive research about artemisinin in the process of artificial synthesis, purification and preparation according to the technology disclosed in this paper, and applied for a large number of patents for technological improvement and related peripheral technologies (e.g., WO2015140709, WO2014078813, WO2011006143, and WO9202217). In most parts of the world, falciparum malaria has become resistant to conventional treatment [29], and in 1990, WHO recommended that countries use the combination of drugs to fight malaria [30]. Under this background, Coartem® (Artemether-Lumefantrine Tablet) was originally developed based on patent CN1085527, which was applied by the Academy of Military Medical Sciences in China and further licensed to Novartis [30–33]. Based on this patented

drug, relevant generic drugs (corresponding companies) were developed, including Artefan® (Ajanta Pharma Ltd, India), and Lumart® (Cipla Ltd, India), and Laritem® (Ipca Laboratories Ltd, India) [34].

In 2006, the further recommendation of WHO on ACTs made Novartis the biggest beneficiary and Novartis received a large number of orders from the WHO [35–37]. Currently, as one of five ACTs [36,38] recommended by the WHO, Coartem occupies about 85 % of the public sector market of ACTs [39]. According to a report of Grand View Research [40], global market size of ACTs is expected to reach nearly USD 697.9 million by 2025.

However, in the public market of antimalarial drugs, Chinese enterprises benefit less, accounting for at most 10 % [41]. Due to a limited awareness of intellectual property rights, China has faced foreign patent barriers in the process of artemisinin industrialization. Without core patents, China is only the largest producer of APIs of artemisinin in the world, located in the upstream of industrial chain with small profits.

It is worth noting that China has begun to pay close attention to artemisinin-related patent protection these years. For example, Kunming Pharmaceutical Corporation paid CNY 70 million in 2016 and formally obtained relevant patents (CN1116036) of Tu Youyou's project called "New Indication of Dihydroartemisinin Tablets: Systemic Lupus Erythematosus". After Tu Youyou's team announced the research results and news [42], share price of Kunming Pharmaceutical Corporation rose sharply. With great profits generated by core patents, this corporation's revenue from antimalarial drugs reached CNY 69.36 million in 2018 with a gross profit margin of 52.71 % [43]. Another example come with Guilin Nanyao Pharmaceutical, whose 19 oral and injectable antimalarial drugs have passed the Prequalification of Medicines Programme (PQP) of WHO with several patents: CN85100781 (Artesunate), CN101647799 (Amodiaquine Hydrochloride/Artesunate), CN103705475 & CN100418524 (Artesunate + Sodium Bicarbonate + Sodium Chloride for Injection), and CN101954090 (Dihydroartemisinin/Piperaquine) [44]. One more example comes with Dihydroartemisinin and Piperaquine Phosphate Tablets of Holley Pharmaceutical Group Co., Ltd., which was originally developed based on patents CN1135974 & CN1092048 & CN1305810 & CN1237416 and can be orally used for malaria of the *P. falciparum* and *P. vivid* types. The related generic products (companies) are Malacur® (Elder pharmaceuticals Ltd) and P-Alaxin® (Bliss Gvs Pharma Ltd) [34].

4.3. Social implications

From the social angle, due to nonprofit nature of artemisinin products on malaria control, a critical challenge is how to keep a balance of pharmaceutical development between commercial motivation and social benefits.

In this study, only 36 % artemisinin-related patents are owned by companies and the majority, 64 % held by individuals, universities or research institutes. It is difficult only by academic institutions or persons to develop new drugs, while academic patents are not easy to be licensed out to the industry. In fact, the process of commercialization of scientific and research achievements is immature in many countries. Although there are many scientific research institutions, they do not have production conditions and skills to turn them into real commodities. In this regard, policy support is needed to promote technology transfer from academia to industry. Co-patenting activities between firms and universities could exhibit a positive association with market value [45], whereas co-patenting among firms has generally been considered disadvantageous to commercial performance and a second-best strategy that firms have preferred to avoid [46,47]. Governments in the United States and the European Union are also trying to encourage partnerships between universities, research centers, and companies to promote the movement of medical research from 'bench to bedside' [48].

At present, 90 % of the antimalarial market is supplied by public sector [41], which is in the framework of international procurement

agencies of Global Fund and WHO. The WHO PQP helps to ensure that medicines provided by procurement agencies can meet acceptable standards of quality, safety and efficacy. Antimalarial drugs in the public sector must be recommended by "Guidelines for the Treatment of Malaria" and be prequalified by WHO. The products also should meet standard Good Manufacturing Practices (GMP) and Good Clinical Practice (GCP) by WHO. More importantly, WHO not only strictly controls the quality of the drugs, but also has a requirement of profit limited of less than 15 % [41]. Obviously, enterprises may not produce such products if there is no enough profit.

As we mentioned before, before a drug is to be approved to market, it must be proved to be safe and effective through clinical trials at a quite high cost. The industry has to consider whether they can recoup the huge R&D expenditure by possible cheap price of artemisinin products in the market. In terms of the nature of public goods of medicines, worldwide governments try to keep a balance of pharmaceutical development between commercial motivation and social benefits by various means of drug registration and regulation, such as, accelerated approval, orphan drug designation, data exclusivity, patent term extension, price negotiations, reimbursement drug list and volume-based tendering. A notable example comes when China recently implemented a so-called "4 + 7" procurement initiative to impel market access of cheaper drugs [49]. The public is willing to choose drugs with better therapeutic effect and lower price. From the industrial angle, different social classes have different affordability for medical expenses. Pharmaceutical companies may create diversified product portfolios by differential product positioning.

The intervention of public sector and favorable policy environment of motivating pharmaceutical companies are necessary, in terms of promising scientific and social value but relatively low commercial expectation of artemisinin. In a word, public needs, government regulation and industry diversification underpin cheap drugs like artemisinin, as long as they exactly may treat diseases.

However, this work has still some research limitations. Although a patent is a key innovation indicator, this patent-based analysis cannot reflect all R&D work on artemisinin and its derivatives. But, considering the existing numerous technological reviews on artemisinin, we believe that this kind of patent landscape analysis is still a necessary supplement to prior work. In addition, some recent inventions with potential creativity may be neglected in the citation-based analysis, because newer patents were often cited less obviously. We think it would be valuable to make a continuous observation that would allow updating of the patent landscape of artemisinin and its derivatives.

5. Conclusion

The number of artemisinin patents have been rising for the last 30 years. China and the United States are the most productive countries in terms of artemisinin patents and are important markets for artemisinin. Furthermore, in terms of patenting activity, the most attractive technological options on artemisinin include chemical and biological synthesis of new derivatives, novel combinations among known compounds, new formulations and administration routes, drug repositioning especially from infectious diseases to non-infectious ones, and minimizing the development of artemisinin-related resistance. Given scientific and social significance of above technological options, a critical challenge lies in how to motivate the industry to develop artemisinin-related drugs. Government regulation as well as public-private partnership have played and will continuously play an indispensable role in tomorrow's artemisinin products originated from today's patents.

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Data availability

All data included in this study are available upon request by contact with the corresponding author.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

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Appendix A. Supplementary data

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