Front. Med. 2022, 16(1): 1−9
https://doi.org/10.1007/s11684-021-0898-6

REVIEW

Discovery and repurposing of artemisinin

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Abstract **Malaria is an ancient infectious disease that threatens millions of lives globally even today. The discovery of artemisinin, inspired by traditional Chinese medicine (TCM), has brought in a paradigm shift and been recognized as the "best hope for the treatment of malaria" by World Health Organization. With its high potency and low toxicity, the wide use of artemisinin effectively treats the otherwise drug-resistant parasites and helps many countries, including China, to eventually eradicate malaria. Here, we will first review the initial discovery of artemisinin, an extraordinary journey that was in stark contrast with many drugs in western medicine. We will then discuss how artemisinin and its derivatives could be repurposed to treat cancer, inflammation, immunoregulation-related diseases, and COVID-19. Finally, we will discuss the implications of the "artemisinin story" and how that can better guide the development of TCM today. We believe that artemisinin is just a starting point and TCM will play an even bigger role in healthcare in the 21st century.**

Keywords artemisinin; drug repurposing; cancer; inflammation; COVID-19; traditional Chinese medicine

Introduction

Malaria is a life-threatening and devastating infectious disease, affecting millions of people worldwide each year [1]. It is caused by parasites of the genus *Plasmodium* and transmitted from person to person by the *Anopheles* mosquito. According to available statistics, approximately 229 million malaria cases and 409 000 deaths were reported in 87 malaria-endemic countries worldwide in 2019, particularly in the African region that accounted for approximately 94% of the total cases, with 67% of deceased cases being children younger than 5 years of age [2].

Current antimalarial control is highly reliant on artemisinin combination therapies; however, its molecular pharmacology is not fully understood. Accumulating evidence suggests that "conventional" agents prescribed for certain diseases may be repurposed to treat other diseases [3]. For example, artemisinin and its derivatives have been tested in different types of cancers, including liver cancer, colorectal cancer, gastric cancer, ovarian cancer, lung cancer, breast cancer, cervical cancer, and esophageal cancer [4]. Furthermore, artemisinin and its derivatives could treat and prevent inflammation and immunoregulation-related diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis, and allergic diseases [5]. The potential application of artemisinin and its derivatives in coronavirus disease 2019 (COVID-19) treatment has also been recently proposed [6–8].

Herein, the discovery process of artemisinin was reported, and its use and application in different medical areas, including antitumor, anti-inflammation, and antiviral (anti-COVID-19) therapy, were discussed. The readers interested in the antimalarial effects and mechanisms of action of artemisinin should be redirected to some other recent reviews [9–11].

Discovery of artemisinin

Global Malaria Eradication Program (GMEP; 1955−1969) was launched by the World Health Organization (WHO) in 1955 to eradicate the disease. Although GMEP eliminated malaria in many countries, global eradication has not been achieved [12]. Over the years, parasites with decreased sensitivity to these approaches have gradually

Received: April 6, 2021; accepted: September 23, 2021
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increased, making the global malaria epidemic control difficult. In 1967, the Chinese government launched a national project called "523" to explore new treatments for malaria. In 1969, Youyou Tu, a young scientist at the Institute of Chinese Materia Medica of the China Academy of Chinese Medical Sciences, was appointed as the principal investigator leading the efforts to search for new antimalarial medicines. Youyou Tu used modern science to study traditional Chinese medicine (TCM); systematically collected ancient Chinese medicine books; and examined more than 2000 herbs for internal administration and external treatment; including plants, animals, and minerals. By using mouse malaria and monkey malaria animal models, more than 200 kinds of prescriptions and 380 kinds of extracts were screened, including artemisinin. Further investigation showed that high temperature should be avoided during the process of extracting artemisinin [13]. After repeated studies were conducted, in 1971, the inhibition rate of *Artemisia annua* extract against rodent malaria and monkey malaria reached 100% through a comprehensive study on the variety, harvesting season, medicinal parts, and especially, extraction methods of *Artemisia annua* L. (Fig. 1) [14]. In 1972, the first 30 cases with malaria were successfully treated with artemisinin. In 1973, Youyou Tu's team developed dihydroartemisinin, one of the most pharmacologically active artemisinin derivatives. In the following decades, Youyou Tu's team and other research teams in China jointly carried out a series of work related to artemisinin, such as the three-dimensional structure and molecular formula of artemisinin and the development of other artemisinin derivatives.

In 2006, the WHO officially recommended 3 days of artemisinin-based combination therapies (ACTs) as first-line treatment in the fight against malaria [15]. Artemisinin has also shown remarkable efficacy in treating previously emerging drug-resistant insect strains [16]. In 2015, Youyou Tu was awarded the Nobel Prize in Physiology or Medicine for the discovery [17]. At present, 14 medicines for curative treatment and six medicines for chemoprevention are listed in the WHO Model List of Essential Medicines. These medicines are formulated as single compounds or in combination [18]. One of the most effective ones was based on ACTs, while the use of ACTs has become an integral part of the fight against malaria, thus forming the basis for most modern treatments [19].

Fig. 1 *Artemisia annua* L. in the field.

Repurpose of artemisinin and its derivatives

With growing failure rates and the expensive cost of novel drug discovery, repurposing traditional therapeutic Chinese medicinal agents in the treatment of cancer or other diseases provides a very attractive alternative. Artemisinin and its derivatives have been recommended as attractive candidates for drug repositioning due to their safety and efficacy, in addition to antimalarial properties. Below, the anticancer, anti-inflammation, and anti-infectious properties of artemisinin and its derivatives were discussed (Fig. 2).

Anticancer property of artemisinin and its derivatives

The anticancer property of artemisinin was originally discovered in 1993, and then it has been widely investigated and explored [20]. Since then, growing evidence has indicated that artemisinin and its derivatives exert selective cytotoxicity towards a wide range of cancers [21,22]. A broad range of putative pathways and targets is believed to be closely implicated in regulating anticancer by artemisinin and its derivatives. Given that pathway validation is important in mechanistic study, several representative pathways and targets were described in this study to analyze the antitumor property and actions of artemisinin and its derivatives (Fig. 3).

PI3K-AKT-mTOR pathway

The PI3K-AKT-mTOR pathway is essential for developing cancer by regulating cell cycle, cellular quiescence, and cell proliferation [23]. In previous studies, artemisinin was found to activate lysosomal function and induce autophagy in HCT116 [24] and HeLa [25] cell lines by inhibiting mTOR activity. This finding is in accordance with the discovery of other research team, that is, artemisinin inhibited cell proliferation by suppression of the PI3K-AKT-mTOR pathway [26].

AMP-activated protein kinase (AMPK) pathway

AMPK has a major role in regulating growth and reprogramming metabolism. It can also regulate cellular processes, such as autophagy and cell polarity [27]. Under

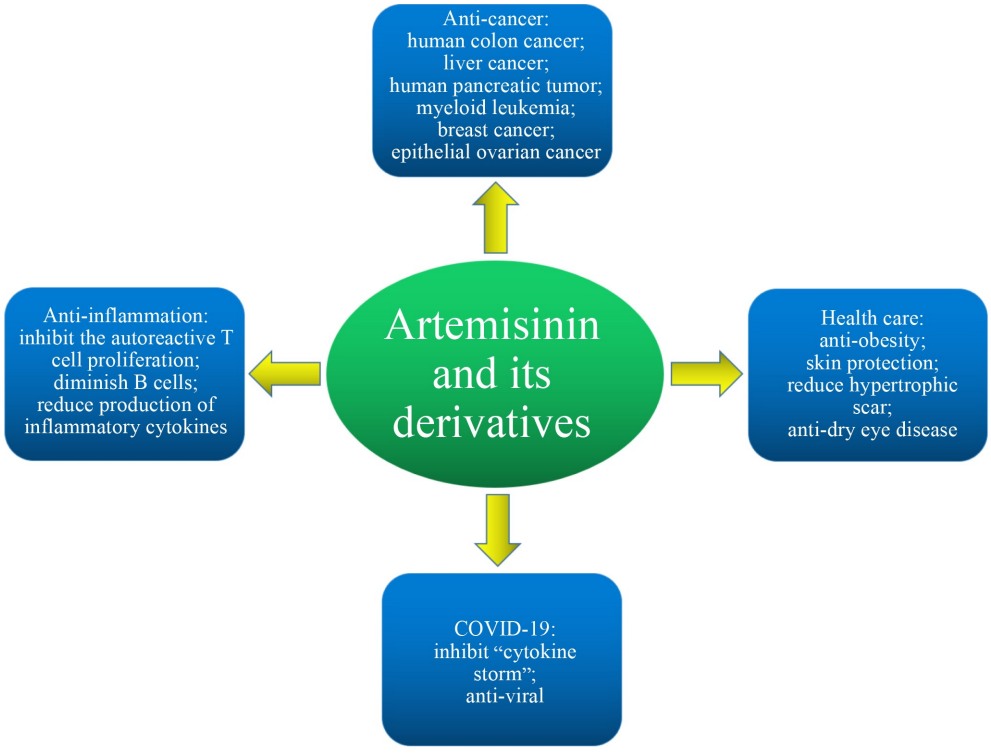

Fig. 2 Repurpose of artemisinin and its derivatives.

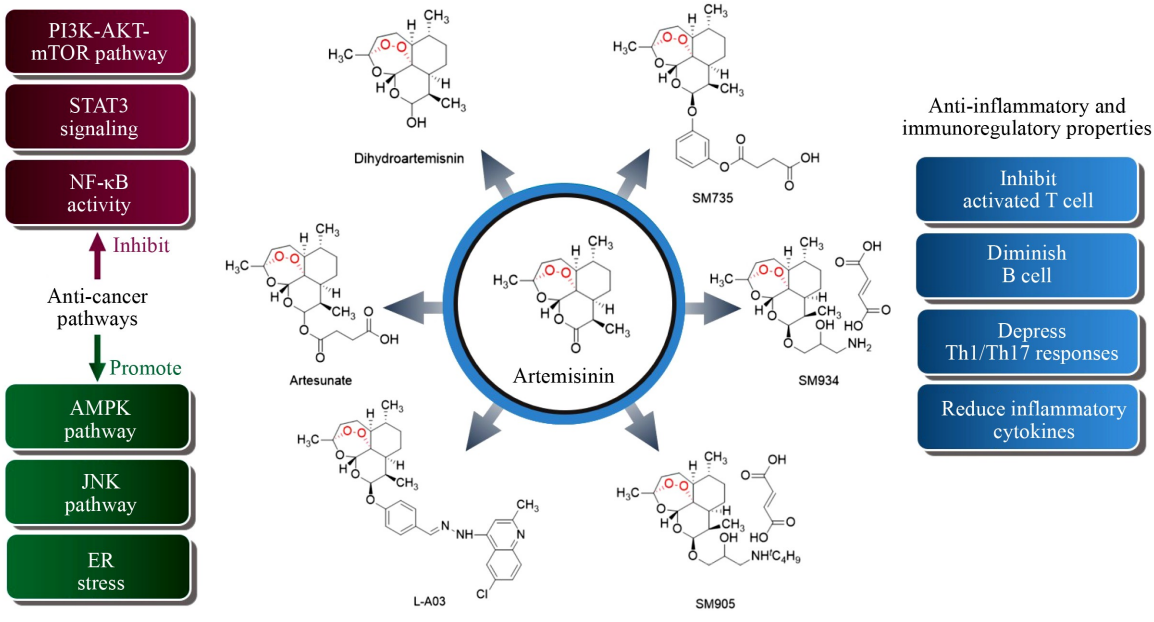

Fig. 3 Structures and anticancer, anti-inflammatory, and immunoregulatory properties of artemisinin and its derivatives.

lowered intracellular ATP levels, AMP or ADP binds to the γ regulatory subunit of AMPK, further leading to its activation. The 172 phosphorylation of AMPKα is necessary for AMPK activation by LKB1, TAK1, and CaM KKβ. Activated AMPK regulates ATP-consuming cellular events (fatty acid, cholesterol, and protein synthesis) and ATP-generating processes (uptake and catabolism of glucose and fatty acids), and maintains cellular energy balance [27]. In addition, the AMPK pathway has been reported to be involved in tumor-specific metabolic regulation [28]. The activated AMPK in tumor cells decreases protein and lipid synthesis via downregulation

of the mTORC1 signaling pathway, thus limiting cell growth and proliferation [29].

Dihydroartemisinin has been demonstrated to induce acute myeloid leukemia (AML) cell death by regulating the proliferation and ferroptosis of AML cells through inducing AMPK/mTOR/p70S6k-mediated autophagy [30]. Moreover, artesunate was reported to induce autophagy-dependent apoptosis by activating the AMPK-mTOR-ULK1 pathway in human bladder cancer cells [31]. Artemisinin derivative SM1044 was found to be a potential treatment for diffuse large B cell lymphoma by the initiation of autophagy through activation of the CaMKK2-AMPK-ULK1 axis [32].

Signal transducer and activator of transcription 3 (STAT3) signaling

STAT3 is an important transcription factor that can promote cancer progression by hyperactivation or mutations in various solid malignancies, including melanoma or lung cancer [33]. *In vitro* experiments have suggested that dihydroartemisinin could suppress STAT3 phosphorylation and STAT3 inactivation, further leading to the downregulation of Mcl-1 and survivin and the enhancement of ABT-263-induced cytotoxicity [34]. Cancer stem cells (CSCs) possess strong invasive and metastatic capabilities. Dihydroartemisinin inhibits CSC-induced invasion and prevents metastasis in laryngeal carcinoma by suppressing STAT3 activation [35]. In addition, researchers discovered that artesunate promoted antitumor, antiproliferation, and apoptosis by suppression of IL-6-JAK-STAT signaling in a hepatocellular carcinoma rat model [36]. Moreover, artesunate potentially participated in the treatment of melanoma by inhibiting the STAT3 pathway and its target proteins [37].

JNK pathway

The JNK pathway is activated by stimuli, such as oxidative stress, when the upstream kinases are activated or the inhibitory phosphatases are inactivated [38]. This pathway inhibits cell growth and induces cell death by regulating Bcl-2 protein-mediated apoptosis [39] and ER stress-related autophagy [40]. Based on previous studies, artemisinin derivative dihydroartemisinin could induce autophagic and apoptotic cell death by producing ROS in human pancreatic tumor and myeloid leukemia through the regulation of JNK and Bcl-2 [41]. Moreover, the JNK inactivation by dihydroartemisinin derivative L-A03 (the structure could be found in Fig. 3) was reported to be responsible for the autophagy-mediated anticancer property in breast cancer [42].

NF-κB activity

NF-κB is regarded as an important therapeutic target due to its ability to decrease tumor cells' sensitivity to apoptosis and enhance tumor cell growth [43]. Without stimuli, NF-κB is kept in the cytoplasm transcriptionally inactive. However, under certain conditions, e.g., stimulation by inflammatory mediators, it is released and translocated into the nucleus, where it serves as the central mediator of the inflammatory process, an important regulator of cell proliferation and oncogenesis [44]. Previous studies found that artemisinin inhibits the NF-κB pathway in the HCT116 colorectal cancer cell line [45]. NF-κB and autophagy are closely involved during tumor generation and progression. For clarification of the association between them, researchers detected major targets of the above two pathways and demonstrated that dihydroartemisinin stimulates the induction of autophagy through inhibition of NF-κB activity [46]. Moreover, artemisinin and dihydroartemisinin have been proven to be potent anticancer drugs towards epithelial ovarian cancer by inhibiting the cell cycle-related NF-κB-signaling pathway [47]. The above findings may help improve the understanding of the underlying actions of artemisinin and its derivatives for its therapeutic anticancer property.

Endoplasmic reticulum (ER) stress

ER stress is generated by the imbalance between the ER protein folding and the ER lumen capacity. Under pathological conditions, the unfolded protein response (UPR) is further activated, resulting in apoptosis and inflammatory response to enhance tumor development [48]. Researchers recently discovered that artemisinin may inhibit non-small cell lung cancer *in vivo* and *in vitro* by triggering ER stress [49]. Artesunate has been recommended as one of the treatments for lymphoma. It could induce the specific upregulation of ER stress markers ATF-4 and DDIT3 in malignant rather than normal B cells [50]. In addition, dihydroartemisinin, as the first-generation derivative of artemisinin, has been reported to inhibit tumors by the regulation of ER stress [51].

Anti-inflammatory and immunoregulatory properties of artemisinin and its derivatives

Potential anti-inflammation and immunoregulation properties of artemisinin and its derivatives have been recently reported. Autoreactive T cell proliferation is closely involved in the pathogenesis of autoimmune diseases, such as RA and SLE [52].

As shown in Fig. 3, researchers screened new compounds for *in vitro* immunosuppressive activity for artemisinin and discovered that derivatives SM735 [53], SM934 [54], and SM905 [55] possess potent immunoregulatory properties through the regulation of T cells. In addition, artemisinin derivative SM934 remarkably inhibited IL-2-regulated proliferation and survival of activated T cells

and enhanced activated T cells into early apoptosis without trigger resting T cells [56]. Furthermore, artemisinin analog artesunate has shown the ability to significantly ameliorate RA in K/BxN mice by diminishing B cells [57]. Moreover, artemisinin derivatives also showed potential effects on RA patients. *In vitro* study demonstrated that artesunate could inhibit the generation and production of inflammatory cytokines such as IL-6, IL-8, and IL-1β when the synovial cells (obtained from RA patients) were stimulated with TNF-α [58].

As a chronic autoimmune disease, SLE is generated when abnormal autoreactive T lymphocytes are accumulated and autoantibody against self-antigen is secreted. Artemisinin derivative SM934 remarkably lengthened the span of life and reduced the glomerulonephritis by inhibition of Th1 and Th17 responses based on the SLE model *in vivo* [59]. Furthermore, SM934 could decrease pathogenic cytokines interferon-γ and IL-10 in serum and reduce the pathogenic autoantibodies secretion and deposition in serum and kidneys to ameliorate renal injury. Dihydroartemisinin effectively improved lupus nephritis, decreased serum TNF-α level, and suppressed its production in peritoneal macrophages in a lupus BXSB mouse model [60].

To sum up, artemisinin and its derivatives exert anti-inflammatory and immunoregulatory properties by inhibiting activated T cells, diminishing B cells, depressing Th1/Th17 responses, and reducing the secretion of inflammatory cytokines.

Potentiality of artemisinin and its derivatives against COVID-19

The current evidence demonstrated that "cytokine storm" contributes to COVID-19-related mortality. Some studies suggested that antimalarial agents, such as artemisinin-family drugs, may be used as an effective approach against the "cytokine storm" in patients with COVID-19 by ameliorating infection-induced acute injuries and decreasing mortality and by regulating immune cells through inhibiting the expression of cytokines IL-1β, TNF-α, and IL-6 [61]. In Africa, five ACTs were useful in treating COVID-19 *in vitro*; among them, mefloquine-artesunate showed the best inhibition rate, as shown in Fig. 4(1–5) [62]. In China, a clinical study indicated that artemisinin-piperaquine could effectively reduce the average time to reach undetectable viral RNA from 19.3 ± 2.1 days to 10.6 ± 1.1 days with mild adverse events compared with that in the control group, as shown in Fig. 4(6) [63]. Thus, artemisinin and its derivative may be used as an alternative approach for treating COVID-19 [64].

Application of artemisinin and its derivatives in health care

Strong evidence recently demonstrated the effect of artemisinin and dihydroartemisinin on obesity. Artemisinin and dihydroartemisinin mechanistically were proven to attenuate pancreatic β-cell damage by provoking endoplasmic reticulum stress [65]. In addition, an *in vitro* study suggested that dihydroartemisinin could markedly improve skin inflammation symptoms, reduce skin injury, and inhibit mast cell infiltration [66]. Interestingly, artesunate, an important artemisinin derivative, was reported to be effective in repairing rabbit hypertrophic scar by suppressing scar formation and reducing fibroblasts and collagen synthesis [67]. Furthermore, a recent study suggested that SM934, as a water-soluble artemisinin derivative, may be used as an alternative treatment for dry eye disease with major features of dryness and irritation by reserving the structural integrity of ocular surface and inhibiting corneal and conjunctival inflammation [68]. The above evidence shed light on the broad applications of artemisinin and its derivatives in different kinds of health problems.

Enlightenment of artemisinin

With a long history, rich resources, and unique theory, TCM has high practical value in healthcare. The success of the "artemisinin story" highlights the importance of applying evidence-based medicine to explore the benefits of TCM, as recently reaffirmed by the world facing unknown infectious diseases without effective cures. In 2003, during severe acute respiratory syndrome, significant therapeutic effects were achieved following the use of TCM [69,70]. In 2009, during the H1N1 pandemic, the State Administration of TCM issued the TCM treatment plan [71]. Now, during the COVID-19 pandemic, TCM, with its proven efficacy, has been used throughout the whole process of prevention and treatment, having a critical role in the successful management of the pandemic in China [72]. Following the guidance of evidence-based medicine, TCM, artemisinin, and alike may have wide application in the 21st century.

Future perspectives

As the first-line antimalaria therapeutic strategy, artemisinin and its derivatives have saved millions of lives. However, its molecular pharmacology is still not fully understood. The outstanding pharmacological features are due to their unique mechanisms. Exact action principles and direct targets of artemisinin and its derivatives against malaria and the mechanism of action and solutions to artemisinin-resistant malaria need to be further investigated. Extended applications of artemisinin and derivatives in non-malarial areas have been investigated. Artemisinin and derivatives have shown promising application in antitumor, anti-inflammation, and antiviral (anti-COVID-19) therapy. However, the specification principles of artemisinin and derivatives in their

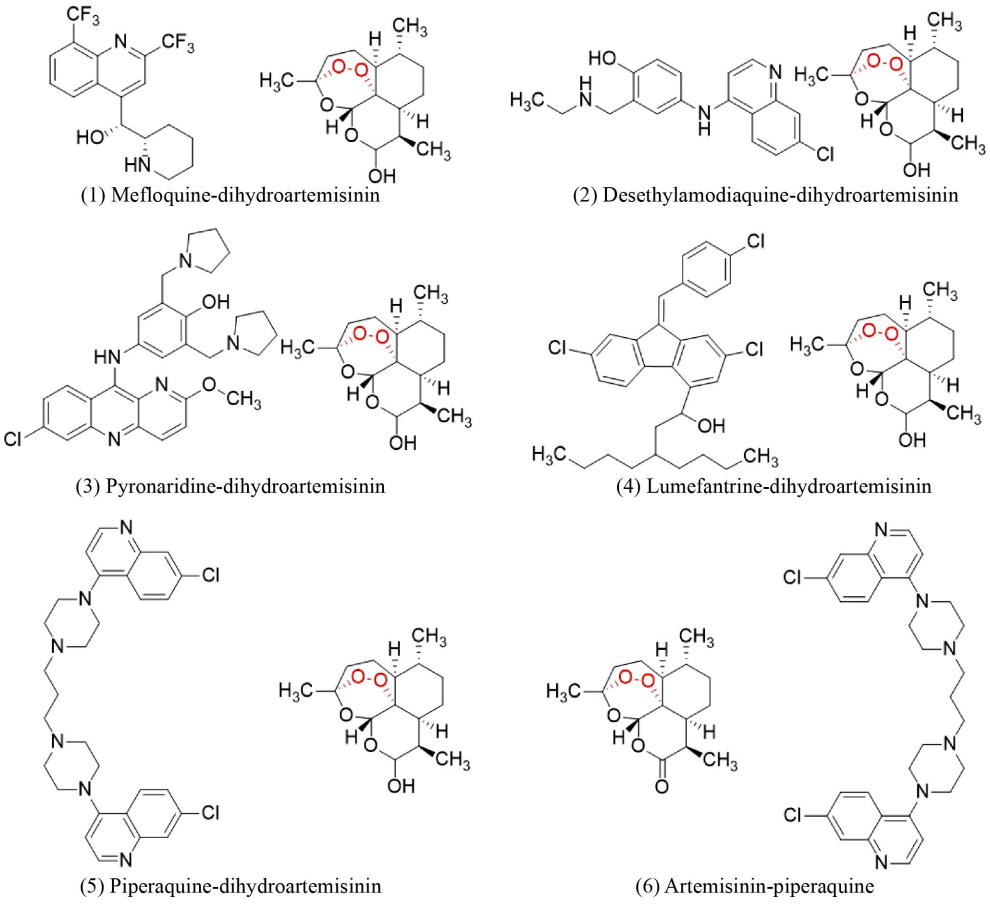

Fig. 4 Artemisinin and its derivatives-based combination therapies against COVID-19.

application in tumor, inflammation, and COVID-19 need to be clarified on the basis of different research models.

From the WHO's establishment of GMEP in 1955 to the release of a new global antimalaria target in 2015, the road to antimalaria has been up and down, and some regional successes have shown that eradication of malaria is completely feasible. Starting from 2017, China has not reported local primary malaria cases for 4 consecutive years and was certified malaria-free by WHO on June 30, 2021. The authors believe that the global goal of "malaria elimination" is within reach.

Artemisinin is a new starting point for the internationalization of TCM. The research ideas, processes, and achievements of artemisinin provide a guiding model for the modernization and development of TCM. At present, TCM culture should be further developed and combined with modern technology, thus making it more easily available to people worldwide.

Acknowledgements

The authors gratefully acknowledge the financial support from the National Key R&D Program of China (No. 2020YFA0908000), the National Natural Science Foundation of China (Nos. 82074098 and 82104480), the Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No. ZYYCXTD-C-202002), the CACMS Innovation Fund (No. CI2021A05101), and the Fundamental Research Funds for the Central Public Welfare Research Institutes (Nos. ZZ14-YQ-050, ZZ14-YQ-051, ZZ14-YQ-059, ZZ14-YQ-060, ZZ14-ND-010, ZZ14-LFL-002, ZZ15-ND-10, ZXKT19018, and ZXKT19021).

Compliance with ethics guidelines

Qiaoli Shi, Fei Xia, Qixin Wang, Fulong Liao, Qiuyan Guo, Chengchao Xu, and Jigang Wang declare that they have no conflict of interest. This manuscript is a review article, and it does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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