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Artemisinins, Chinese Army Weapon with a Multitude of Scenarios

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ABSTRACT

Artemisinins are extracted from extracts of sweet wormwood (*Artemisia annua L.),* natural herbal treatment for recurrent fever, and are widely used to treat parasitic infection (malaria) in China. Prof. You-you Tu developed Artemisinin in the 1960s, earning her the Nobel Prize in Philosophy of Medicine in 2015. Artemisinins contain a sesquiterpene lactone backbone. Their activity is due to a unique endoperoxide group. Artemisinin and its analogs are anti-*Plasmodium falciparum* drugs with the quickest anti-Plasmodium falciparum activity of any available treatment. Even though Artemisinin remains the cornerstone of antimalarial therapy, significant hurdles to its sustained use and development have emerged. Such limitations include prolonged clinical response to artemisinins in malaria and initiatives to use artemisinins for non-malarial purposes. This review provides an outline of the discovery history of Artemisinin. Also, the present knowledge of artemisinins' mechanism of action and the need for basic research to treat results in malarial and non-malarial situations has been high pointed out.

INTRODUCTION

Malaria is a fatal disease that has a broad impact. Since ancient times, it has been one of the most public and dangerous transmittable illnesses. [1] Malaria's pathogenic and parasitic nature remained unknown until the late 1800s, when Charles Louis Alphonse Laveran and Ronald Ross demonstrated its transmissible and parasitic nature. Their studies proved that the *Plasmodium protozoa* caused malaria by the *Plasmodium protozoa* and that Mosquitos were the primary carriers. Laveran and Ross were the first recipients of the Nobel Prize in Philosophy or Medicine for their discoveries. [2]

Pioneering progress has been made in the fight against the disease decades after their findings. ART was discovered due to a battle started by the Taiwanese government in the 1960s to find malaria remedies. ART and its various analogs are sesquiterpene lactone substances (figure 1) obtained from a sweet wormwood plant *Artemisia annua. L.* (figure 2) with a distinctive chemical structure. Their activity is due to a unique endoperoxide group. Since its discovery, it has risen to prominence as an essential and powerful antimalarial therapy. [3]

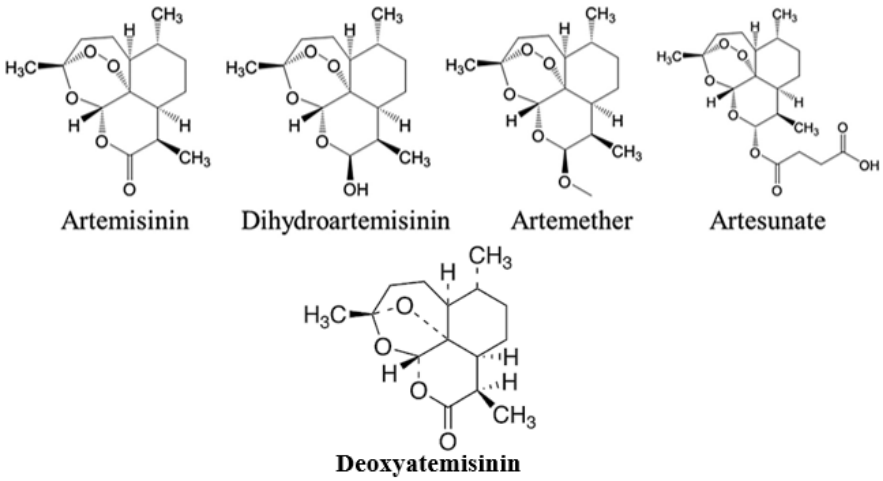


Figure 1: ART and its semi-synthetic analogs

Figure 2: *Artemisia annua L*. plant

ART is a brilliantly exciting drug in many respects. Artemisinin has commanded much interest since its dramatic discovery, rooted in Chinese traditional medicine, to its significant effectiveness in malaria treatment. Since ART's introduction to the globe, it has piqued the public's attention [(1).] For almost 40 years, ART has been a barrier against malaria, and it lies at the heart of all effective antimalarial medicines. [(4)]

The discovery and comprehension of ART's antimalarial activity have taken years of research from various fields [(5)]. Besides, many attempts to change ART filarial uses have been made, which has piqued interest in the drug's future development. [(6)]

Considering all that, we believe this is a perfect moment to take a comprehensive look at the history of this vital medicine, including its past, present, and future.

I begin by looking at the history of ART discovery and development, followed by a review and discussion of current knowledge of ART's mechanism of action in malarial infection. Finally, we pay attention to recent efforts to reuse ART for purposes other than malaria treatment. We believe this study will fully explain ART and provide helpful insights into this great drug's fundamental challenges.

History of Discovery

Artemisia (Qinghao) plants as therapeutic herbs have been documented for thousands of years. Artemisia plants were first recorded as a cure for hemorrhoids in (168 BC). Later, during the Jin Dynasty, Hong Ge wrote the Handbook of Prescriptions for Emergency Treatments, in which Artemisia was first described as a specialized cure for malarial

symptoms. Artemisia was notably specified as a fever treatment in Shi-Zhen Li's Compendium of Materia Medica (1518–1593 AD).

Artemisinin was discovered and developed using this ancient knowledge. Using a potent pesticide (DDT) and novel antimalarial treatments such as chloroquine (CQ) improved the fight against the illness. In the 1950s, the WHO started a program to manage and eliminate the condition, but resistance difficulties were ultimately limited. The evolution of the resistance has resulted in a recurrence of such infection, particularly in primarily epidemic regions like Southeast Asia and sub-Saharan Africa. [7]

As a result of this failure, it seems to be a great need for novel therapeutic medications. Because of the Vietnam War and the high frequency of CQ-resistant cases in this country, the American state had undertaken significant efforts. In the same era, the Chinese government began investing in malin aria studies. Specifically, Project 523 is a nationwide initiative. Over 500 experts from around 60 organizations and institutions participated in this project[8]. The goals of Project 523 were to screen synthetic chemicals and look for formulas and techniques that could lead to the development of new antimalarial medications. [9]

Tu Youyou's Work

Professor Youyou Tu was introduced to the Project 523 project in the Chinese province, where she examined individuals whose malaria was just diagnosed. Youyou was the leader of the research group in 1969. So, Tu came up with the notion of sifting through Chinese herbs. She began by looking into the history of Chinese medical classics. Around 2000 medicinal herbs were collected and examined by Tu and her team, with 640 be labled as potential "hits." Tu's team prepared over 380 extracts from 200 plants (containing Artemisia isolates). These extracts were then studied *in vivo*, with the most unacceptable findings.[1,10]

According to Ge Hong's book (Handbook of Emergency Prescriptions), Youyou observed that the *A. annua* remedy required drinking the squeezed "juice" of the herb after soaking in two litlitres water. Starting from Ge's recipe, which includes the preparation of this juice or the herb extract at low temperature, Tu understood that the heat had already degraded the plant's active substance; hence she advised extracting the active ingredient with low-temperature ether. In mice and monkeys, animal studies revealed it was indeed totally successful. Tu figured out how to remove it, and her improvements increased the extract's efficiency while lowering its toxicity. In October 1971, the resulting chemical was set at 100

percent efficient against rodent plasmodium during studies carried out. This fantastic outcome was later validated in animal malaria experiments, showing the Qinghao extract's efficacy without hesitation. [1]

The medication development was far from over; however, the success had been achieved. Clinical studies of new applicants for medicines for human safety during that period in China were challenging because of the country's conditions. Due to specific conditions in malaria research and making the clinical trials quickly, Tu and her workers became the first volunteers to test toxicity and dosing. [8]Such an act proved the Artemisia extract's safety and effectiveness and permitted clinical studies to start soon in the second half of 1972, her team,er team discovered the pure ingredient (Artemisinin) in 1972, saving many lives. Tu likewise analyzed Artemisinin's chemical composition and pharmacology. Tu unintentionally developed dihydroartemisinin (DIHA) in 1973 while confirming the carbonyl group in the artemisinin structure. [11,9]DHA is ART's most effective analog.

In 1977 and 1979, Tu's research was published [9-13]. Her findings on ART used in the treatment of malaria were a significant revolution in medical sciences in the 1920s, leading to better care in South Asia, Africa, and South America.

In the next years, more drug development was done in partnership withcentrescenters around China, such as identifying stereo-structure and other derivatization of Artemisinin [14, 15]. Then other presentations about ART and its antimalarial activities drew a large audience. In 1982, the presented results were published [16, 17], and the Chinese medicine's gift to the rest of the world was provided. ART and its derivatives were reported to help large numbers of infected people in China in the 1980s [1]. Even as the issue of drug-resistant malaria grew worse everywhere, clinical trials with ART began in several epidemic areas in Asia. [18-21]. Favorable results drive similar investigations, especially in Africa [22-24]. ART-combination therapy, combined simultaneously, tolerance was excellent, with few toxicity and safety problems. [25]

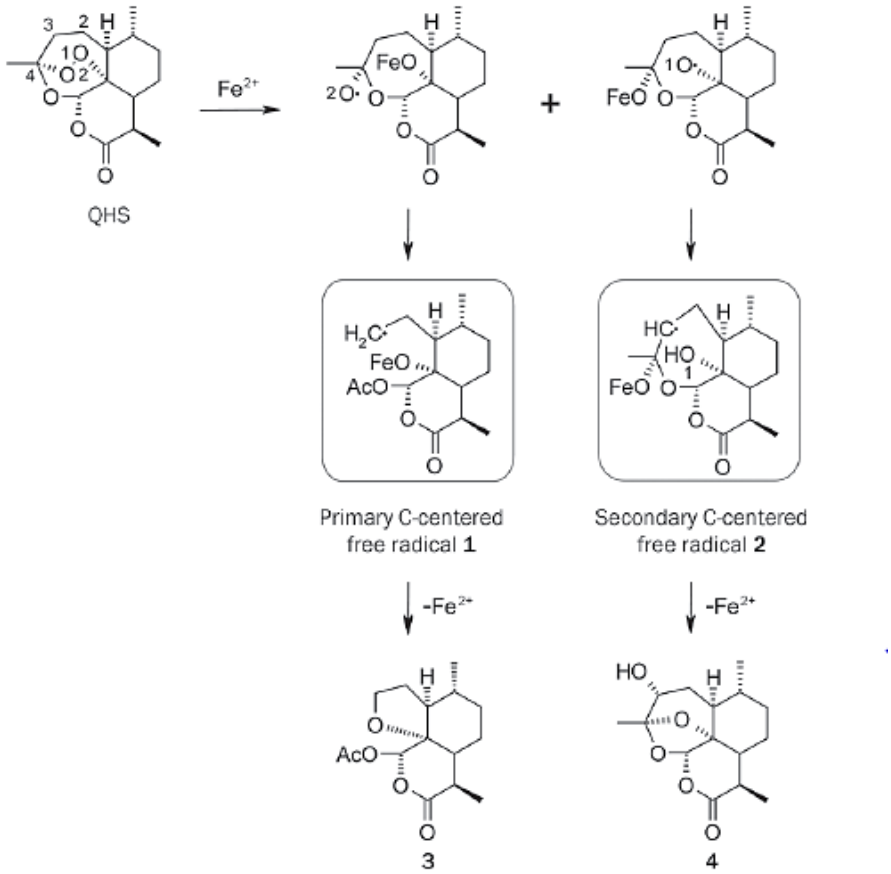
Last but not least, in 2006, the WHO changed its strategy by stating that first-line malaria therapy should be ACTs.[26]These ACTs continue to be the most effective and commonly used antipalmological treatment. [4]

ART's Activity Mechanism

ART derivatives are the newest hit antimalarial medications licensed and released for general use. The principal moiety of ARTs is 1, 2,4- trioxane.[27] This moiety is vital for the antimalarial effect of ARTs. The ineffectiveness of deoxyartemisinin(figure3) against *P. berghei* in mice highlighted the importance of the peroxy group. Other simple peroxides, such as monoterpene ascaridol, were soon discovered to have no antimalarial action. These findings showed that the peroxy group is a necessary element. It was discovered that the molecule had a rare segment -O-C-O-C-O-C=Oandhypothesised that the entire molecular skeleton could be crucial for antimalarial activity. When it was discovered that dihydroartemisinin (DHA) was more potent than ART but had bad solubility and stability than ART, more than 50 DHA derivatives were synthesised and analyzed. [28,29]The first 25 compounds (in oil solution) were evaluated intramuscularly in mice infected with chloroquine-resistant *P. berghei.*[30] The majority of these compounds outperformed ART and DHA in terms of activity. Artemether out performs arteether and others in the ether series. After that, activity, stability, toxicity, and cost were examined between artemether, ester (R=C2H5) and carbonate, R=n-C3H7). Artemether was chosen for its high lipid solubility and good stability than other compounds. Hydrophilic sodium artesunate (ester, R=COCH2CH2COONa) was developed [31]. In 198, the ART suppository was approved, followed by an artemether oil injection and sodium artesunate aqueous injection in 1987. Since then, other antimalarial drugs have been developed in China, including DHA, coartem (artemether and benflumetol), co-naphthoquine (naphthoquine phosphate and ART), and compound-DHA.[8,32]Since the 1980s, ART derivatives, and their combinations have saved millions of malaria victims worldwide (mostly in China, Southeast Asia, and Africa). Because ARTs can kill drug-resistant *P. falciparum*, their antimalarial mechanism must be distinct from historically utilized antimalarials. It's a fascinating project to figure out how it works. There have been a lot of research papers published so far[33-38]. ART medicines exhibited a clear activity against *P. falciparum* in the erythrocytic stage both *in vitro* and *in vivo*, and their morphologic modifications were discovered by Chinese researchers in 1979[13,39]. The major pathophysiological changes generated by ART were swelling and spiral distortion of the food vacuole membrane, limiting membrane, and mitochondrial membrane, followed by swelling ofthe nuclear membrane endoplasmic reticulum. A sequence of ART's and Fe^{2+} reactions that involve the intermediate of oxygen-centred or carbon-centred free radicals is noteworthy among the latter results obtained in China. [41- 42] The chemists

thoroughly researched the interaction of ART with Fe^{2+} to determine the way of action [43,44]. According to Scheme1, the main products tetrahydrofuran 3 and 3-hydroxydeoxyartemisininfourareobtained were from primary C- centred free radical one and secondary C- centred free radical 2. It was found that compounds 3and 4 are the major metabolites of ART in *vivo* or in humans. [45,46]

The close link between antimalarial activity and primary C-centered free radicals suggests that Fe^{2+}-induced peroxide bond cleavage in artemisinins results in C-centered free radicals, a highly potent alkylating species. Heme, heme-containing protein, translationally controlled tumor-associated protein (TCTP), and sarcoendoplasmic reticulum Ca^{2+}ATPase (SERCA)-type protein encoded by PfATP6 have all been identified as potential targets. [38] ARTs are transported to malarial mitochondria and directly affect their functioning, according to Chinese researchers. [47]



Scheme 1: Carbon-centered free radical's formation and ART's metabolites

The procedure of the alkylation of targets was another major topic. Reduced glutathione levels are high in malaria-parasite-infected red blood cells (GSH). Abundant GSH may protect the pathogen from heme toxicity; Chinese scientists have carried out experiments involving artemisinins reacting with cysteine or GSH in the presence of a catalytic quantity of ferrous ion. [48-51]

The efficient isolation and identification of these adducts demonstrated the development of a covalent bond in cysteine-artemisinins or GSH-artemisinins adducts. The fact that C-centered radicals produced from ART and their analogues can target free cysteine and cysteine residue in peptides and proteins.

Other Therapeutic Applications of ARTs

ART is a medication of primary concern for repurposing research because of its demonstrated safety and availability. When ART was initially publicly revealed, there was a strong rise in interest in non-malarial treatments of the drug [52]. As ART represents the only licensed treatment for malaria, its future benefits in anticancer, anti-inflammatory, anti-parasite, and anti-viral remedies have been studied extensively for a long time. [52-55]In terms of cancer applications, ART's potency in cancer cultures was originally described in 1993 and has been thoroughly researched and developed[56,57]. Artesunate was found to have anticancer efficacy against fifty-five tumour cell lines, with leukaemia and colon cancer cell lines being the most active. There was no cross-resistance to Artesunate in any of the CEM leukaemia sublines that were resistant to doxorubicin, vincristine, methotrexate, or hydroxyurea [58]. ART and its derivatives (Artesunate and DHA) have been shown in both *in-vitro* and *in-vivo* studies to have specific cytotoxic effects against various forms of cancer. [59]Clinical trials have yielded positive results, except in small numbers and on a small scale [60-62].

More ART derivatives and analogs have been developed and verified versus human cancer cells. Certain substances showed high nano- to micromolar concentrations [54], e.g., DHA ether having cyanoarylmethyl group 5 (Figure 3) was particularly active, but its deoxy-analogue6 (Figure 3) was inactive. As a result, the peroxy group is necessary for anticancer action, just for antimalarial activity. [63, 64] Furthermore, the sort of derivative has been demonstrated to target the G1 phase of the cell cycle. [65]Artemisinins' anticancer efficacy and mechanisms have been extensively explored [66-71], although few clinical trials have been published.

The immunosuppressive agent was antimalarial chloroquine. As a result, in the 1980s, research into ART and its derivatives' immunological activity became a popular topic in China. In the beginning, China's laboratories focused on new antimalarial drugs (ART, artemether, and Artesunate). Artesunate was tested for rheumatoid arthritis, polymorphous light eruption, and chronic actinic dermatitis in clinical trials. For example, when sodium artesunate was given intravenously (60 mg/dayfor 15 days a course), it was beneficial in 56 patients with lupus erythematosus, with effective rates of 94 percent, 90 percent, and 80 percent, respectively. [(72)] More ART derivatives were developed and analysed in searching for extremely powerful, low-toxic immunosuppressive drugs against T cell activation, including SM735,SM 905,SM 933 and SM 9349 (figure 3). [(73-77)]These ART derivatives have been examined in autoimmune disease conditions[(78,79)].

During the manufacture of SM 934, SM 1044 was known as a by-product and exhibited antileukemia activity in vitro and the animal. [(80-82)]Alkaline ART could be a new type of interesting candidate.

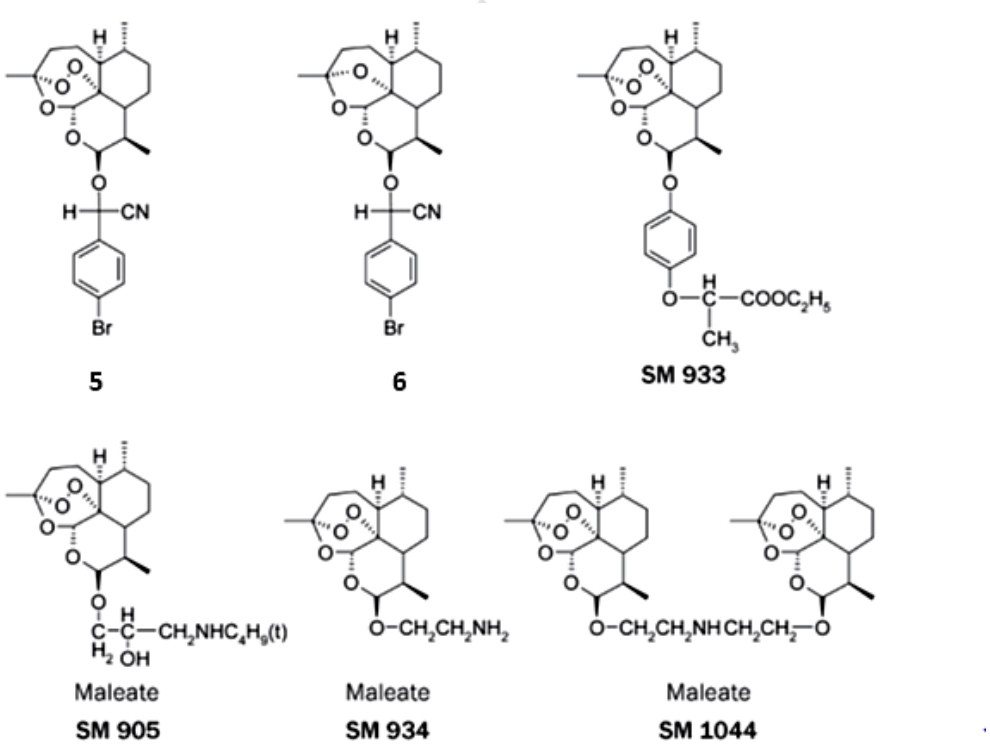


Figure 3: artemisinin derivatives with anticancer or immunosuppressive actions

ART has been proven to have potent antifungal activity against herpes and hepatitis B and C viruses and other parasite infections such as bilharzia.[83-87]Recently, the importance of ARTs as a possible treatment for diabetes was identified due to their effect on stimulating the transformation of pancreatic glucagon (producing cells into insulin) secreting cells in rats. [88]Several studies reported the Arts' role in type 2 diabetics that have received a lot of interest in recent years. ART treatments offer therapeutic potential for diabetes sequelae such as diabetic kidney disorders, mental retardation, and diabetic CV disease [89-92] and reduce insulin resistance in type 2 diabetes. [93]ART derivatives demonstrated their capacity to avoid weight gain, lower the severity of fatty liver, and protect β-cells in the pancreas. [93, 95]

These applications' main mechanisms of action can be explained by the ROS generation and oxidative damage of the Endoperoxide Bridge or by endoperoxide- independent cleavage model especially shown in immunomodulation cases. It would be essential to understand the drug mechanisms and the importance of drug activation conditions under different applications. It is also interesting to note that the recurrent studies can be effectively conducted in patients and non-infected areas to ensure that intervention or comorbidity is precluded.

CONCLUSION

Throughout many areas of the world, malaria is the most common disease. Malarial monitoring parasites have become practically impossible, dangerous, and ineffective as the number of drug-resistant parasites increase. These areas should have access to an effective, low-cost *Artemisia annua* L. medication. The ARTs are a fantastic group of drugs that have altered the nature of antiplasmodial treatment. Artemisinin is at the frontlines of the intense conflict against the disease menace due to its exceptional efficacy, safety, and availability. Since the discovery, the world community has worked together to create an image of therapy with distinct qualities which make it nearly the optimum drug against malaria. Artemisinin has a wide range of potential applications beyond malaria. Because of this, we think it's only reasonable to try to increase the drug's utility in as many ways as possible. In the case of malaria, the mechanism for ART activation and action must be clarified, while its pharmacological qualities must be promoted either alone or combined. Together with a thorough understanding of artemisinin activity principles, it might be the path to resolving the issues with artemisinin resistance. Thus, medicine would resume its purpose to a similar or even larger extent in the future. It is expected that future research on Artemisinin will be

guided by a thorough knowledge of the various MOAs associated with different disorders and systems. For so many years, we genuinely want this contribution of Chinese medicine to help those seeking health around the world persist.

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REFERENCES

1- Tu Y. Artemisinin—a gift from traditional Chinese medicine to the world (Nobel lecture). Angew. Chem Int Ed. 2016; 55(35):10210–26.
2- Cox FE. History of the discovery of the malaria parasites and their vectors. Parasites and Vectors. 2010; 3(1):5.
3- Krishna S, Bustamante L, Haynes RK, Staines HM. Artemisinins: their growing importance in medicine. Trends Pharmacol Sci. 2008; 29(10):520–527.
4- World Health Organization. World malaria report 2017. Geneva: World Health Organization; 2017.
5- Ding XC, Beck HP, Raso G. Plasmodium sensitivity to artemisinins: magic bullets hit elusive targets. Trends Parasitol. 2011;27(2):73–81.
6- Efferth T, Romero MR, Bilia AR, Osman AG, ElSohly ME, Wink M ,Bauer R, Khan Ik, BergonziMC, Jose J G. Marin. Expanding the therapeutic spectrum of Artemisinin: activity against infectious diseases beyond malaria and novel pharmaceutical developments. World J Tradit Chin Med. 2016;2(2):1–23
7- D'Alessandro U, Buttiëns H. History and importance of antimalarial drug Resistance. Trop Med Int Health. 2001;6(11):845–848
8- Zhang JF, Zhou KD, Zhou YQ, Fu LS, Wang HS, Song SY, A detailed chronological record of project 523 and the discovery and development of qinghaosu (Artemisinin). Yangcheng Evening News Publishing Company, Guangzhou. 2006.
9- Tu Y. The discovery of Artemisinin (Qinghaosu) and gifts from Chinese medicine. Nat Med. 2011; 17(10):1217–1220.
10-Liao F. Discovery of Artemisinin (Qinghaosu). Molecules. 2009;14(12):5362–5366
11-Miller LH, Su X. Artemisinin: Discovery from the Chinese herbal garden. Cell. 2011; 146(6): 855-858.
12-Qinghaosu Coordinating Research Group.A new sesquiterpene lactone-qinghaosu. Chin Sci Bull. 1977; (3): 142.
13-Qinghaosu Antimalaria Coordinating Research Group. Antimalaria studies on Qinghaosu. Chin Med J, 1979, 92: 811–816
14-Collaboration Research Group for Qinghaosu. A new sesquiterpene lactone—Qinghaosu. Chin Sci Bull. 1997; 3:142.
15-Wang MY. Publication process involving the discovery of Artemisinin (Qinghaosu) before 1985. Asian Pac J Trop Biomed. 2016; 6(6):461–467.
16-Chemical studies on qinghaosu (artemisinine). China Cooperative Research Group on qinghaosu and its derivatives as antimalarials. J Tradit Chin Med. 1982 Mar;2(1):3-8.
17-Klayman Dl. Qinghaosu (Artemisinin): an antimalarial drug from China. Science. 1985; 228(4703):1049–1055.
18-Nosten F, Luxemburger C, terKuile FO, Woodrow C, Eh JP, Chongsuphajaisiddhi T, White NJ. Treatment of multidrug-resistant Plasmodium falciparum malaria with 3-day artesunate-mefloquine combination. J Infect Dis. 1994; 170 (4):971-977. Erratum in: J Infect Dis 1995; 171(2):519.

19-Tran TH, Day NP, Nguyen HP, Nguyen TH, Tran TH, Pham PL, Dinh XS, Ly VC, Ha V, Waller D, Peto TE, White NJ. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. N Engl J Med. 1996; 335(2):76-83.
20-Looareesuwan S, Wilairatana P, Viravan C, Vanijanonta S, Pitisuttithum P, Kyle DE. Open randomised trial of oral artemether alone and a sequential combination with mefloquine for acute uncomplicated falciparum malaria. Am J Trop Med Hyg. 1997; 56(6):613–617.
21-Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N; International Artemisinin Study Group. Artesunate combinations for treatment of malaria: meta-analysis. Lancet. 2004; 363(9402):9-17.
22-Von Seidlein L, Jaffar S, Pinder M, Haywood M, Snounou G, Gemperli B, Gathmann I, Royce C, Greenwood B. Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. J Infect Dis. 1997;176(4):1113-1116.
23-Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K, Kivaya E, Agbenyega T, Nguah SB, Evans J, Gesase S, Kahabuka C, Mtove G, Nadjm B, Deen J, Mwanga-Amumpaire J, Nansumba M, Karema C, Umulisa N, Uwimana A, Mokuolu OA, Adedoyin OT, Johnson WB, Tshefu AK, Onyamboko MA, Sakulthaew T, Ngum WP, Silamut K, Stepniewska K, Woodrow CJ, Bethell D, Wills B, Oneko M, Peto TE, von Seidlein L, Day NP, White NJ; AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010; 376(9753):1647-57.
24-WWARN Artemisinin based Combination Therapy (ACT) Africa Baseline Study Group, Dahal P, d'Alessandro U, Dorsey G, Guerin PJ, Nsanzabana C, Price RN, Sibley CH, Stepniewska K, Talisuna AO. Clinical determinants of early parasitological response to ACTs in African patients with uncomplicated falciparum malaria: a literature review and meta-analysis of individual patient data. BMC Med. 2015; 7; 13:212.
25-Efferth T, Kaina B. Toxicity of the antimalarial Artemisinin and its derivatives. Crit Rev Toxicol. 2010;40(5):405–421
26-World Health Organization. Guidelines for the treatment of malaria. Geneva: World Health Organization; 2006
27-Van Agtmael MA, Eggelte TA, van Boxtel CJ. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. Trends Pharmacol Sci. 1999;20(5):199–205
28-Li Y. Synthesis of some derivatives of artemisinine. Reprinted from KexueTongbao. 1979; 24:667-9.
29-Li Y, Yu PL, Chen YX, Li LQ, Gai YZ, Wang DS, Zheng YP. [Studies on analogs of artemisinine. I. The synthesis of ethers, carboxylic esters and carbonates of dihydroartemisinine . Yao XueXue Bao. 1981; 16(6):429-439.
30-Gu HM, Lu BF, Qu ZX. [Antimalarial activities of 25 derivatives of artemisinine against chloroquine-resistant plasmodium berghei (author's transl)]. Zhongguo Yao Li Xue Bao. 1980; 1(1):48-50.
31-Liu X. Study on artemisinin derivatives. Yao Xue Tong Bao. 1980;15(183):0.
32-Li Y, Wu YL. A golden phoenix arising from the herbal nest—a review and reflection on the study of antimalarial drug Qinghaosu. Frontiers of Chemistry in China. 2010;5(4):357-422.
33-Meshnick SR, Thomas A, Ranz A, Xu CM, Pan HZ. Artemisinin (qinghaosu): the role of intracellular hemin in its mechanism of antimalarial action. Molecular and biochemical parasitology. 1991; 1;49(2):181-9.
34-Posner GH, Oh CH. Regiospecifically oxygen-18 labeled 1, 2, 4-trioxane: a simple chemical model system to probe the mechanism (s) for the antimalarial activity of artemisinin (qinghaosu). J. Am. Chem. Soc. 1992; 114(21):8328- 8329.
35-Jefford CW. Why artemisinin and certain synthetic peroxides are potent antimalarials. Implications for the mode of action. Curr Med Chem. 2001; 8(15):1803-1826.
36-Olliaro PL, Haynes RK, Meunier B, Yuthavong Y. Possible modes of action of the artemisinin-type compounds. Trends Parasitol. 2001;17(3):122-126.
37-Posner GH, O'Neill PM. Knowledge of the proposed chemical mechanism of action and cytochrome p450 metabolism of antimalarial trioxanes like artemisinin allows rational design of new antimalarial peroxides. Acc Chem Res. 2004; 37(6):397-404.

38-O'Neill PM, Barton VE, Ward SA. The molecular mechanism of action of artemisinin--the debate continues. Molecules. 2010; 15(3):1705-21.
39- Li GQ, Guo XB, Jin R, Wang ZC, Jian HX, Li ZY. Clinical studies on treatment of cerebral malaria with qinghaosu and its derivatives. J Tradit Chin Med. 1982; 2(2):125-30.
40-Wang JY, Yuan LZ, Wang MD. Inhibition of sodium artesunate on rat erythrocyte membrane Na+-K+-exchanging ATPase *in vitro*. Yao Xue Xue Bao 1995; 16 (6): 524–526.
41-Shi XC, Zhang QL, Wu K, Wang S, Sun CP, Wang ZQ. Hemopoieto toxicity in pregnant mice and their embryos induced by free radicals derived from sodium artesunate. Chin J PharmacolToxicol. 1997; 11: 226–228.
42-Cheng F, Shen JH, Luo XM, Zhu WL, Gu JD, JI RY, et al.Molecular docking and 3-D-QSAR studies on the possible antimalarial mechanism of artemisinin analogues. Bioorg Med Chem. 2002; 10 (9): 2883–2891
43-Wu WM, Yao ZJ, Wu YL, Jiang K, Wang YF, Chen HB, Shan F, Li Y.Ferrous ion induced cleavage of the peroxy bond in qinghaosu and its derivatives and the DNA damage associated with this process. Chem Commun. 1996; 18: 2213–2214.
44- Wu WM, Wu YK, Wu YL, Yao ZJ, Zhou CM, Li Y, Chan F. A unified mechanism framework for the Fe (II)-induced cleavage of qinghaosu and derivatives/analogs. The first spin-trapping evidence for the earlier postulated secondary C-4 radical. J Am Chem Soc. 1998; 120(14): 3316–3325.
45-Zhu DY, Huang BS, Chen ZL, Yin ML, Yang YM, Dai ML, Wang BD, Huang ZH. Isolation and identification of the metabolite of artemisinine in human. Zhongguo Yao Li Xue Bao. 1983;4(3):194-197.
46-Lee IS, Hufford CD. Metabolism of antimalarial sesquiterpene lactones. PharmacolTher. 1990; 48 (3): 345–355.
47-Wang J, Huang L, Li J, Fan Q, Long Y, Li Y, Zhou B. Artemisinin directly targets malaria mitochondria through its specific mitochondrial activation. PLoS ONE 5(3): e9582. https://doi.org/10.1371/journal.pone.0009582
48-Wang DY, Wu YL, Wu YK, Liang J, Li Y. Further evidence for the participation of primary carbon-centered free-radicals in the antimalarial action of the qinghaosu (artemisinin) series of compounds. Chem Inform. 2001; 32(6): 605–609.
49- Wang DY, Wu YL. A possible antimalarial action mode of qinghaosu (artemisinin) series compounds. Alkylation of reduced glutathione by C-centered primary radicals produced from antimalarial compound qinghaosu and 12-(2,4-dimethoxyphenyl)-12-deoxoqinghaosu. Chem Commun. 2000; 22: 2193–2194.
50-Wu YK, Yue ZY, Wu YL. Interaction of qinghaosu (artemisinin) with cysteine sulfhydryl mediated by traces of non-heme iron. Angew Chem Int Ed. 1999; 38 (17): 2580–2582.
51-Wu WM, Chen YL, Zhai ZL, Xiao SH, Wu YL. Study on the mechanism of action of artemether against schistosomes — the identification of cysteine adducts of both carbon-centered free-radicals derived from artemether. Bioorg Med Chem Lett. 2003; 13(10): 1645–1647.
52-Ho WE, Peh HY, Chan TK, Wong WS. Artemisinins:pharmacological actions beyondantimalarial. PharmacolTher. 2014; 142(1):126–139.
53-Crespo-Ortiz MP, Wei MQ. Antitumor activity of Artemisinin and its derivatives: from a well-known antimalarial agent to a potential anticancer drug. J Biomed Biotechnol. 2012; 2012: 247597.

54- Lai HC, Singh NP, Sasaki T. Development of artemisinin compounds for cancer treatment. Invest New Drugs. 2013; 31(1):230–246.
55-Efferth T. Artemisinin—second career as anticancer drug? World J Tradit Chin Med. 2015; 1(4):2–25.
56-Woerdenbag HJ, Moskal TA, Pras N, Malingré TM, El-Feraly FS, Kampinga HH, Konings AW. Cytotoxicity of artemisinin-related endoperoxides to Ehrlich ascites tumor cells. J Nat Prod. 1993; 56(6):849-856.
57- Lai H, Singh NP. Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin. Cancer Lett. 1995; 91(1):41–46.
58-Efferth T, Dunstan H, Sauerbrey A, Miyachi H, Chitambar CR. The anti-malarial artesunate is also active against cancer. Int J Oncol. 2001; 18(4):767–773.
59-Efferth T, Sauerbrey A, Olbrich A, Gebhart E, Rauch P, Weber HO, Hengstler JG, Halatsch ME, Volm M, Tew KD, Ross DD, Funk JO. Molecular modes of action of artesunate in tumor cell lines. Mol Pharmacol. 2003; 64(2):382-94.
60-Zhang ZY, Yu SQ, Miao LY, Huang XY, Zhang XP, Zhu YP, Xia XH, Li DQ. [Artesunate combined with vinorelbine plus cisplatin in treatment of advanced non-small cell lung cancer: a randomized controlled trial]. Zhong Xi Yi Jie He Xue Bao. 2008; 6(2):134-138.
61-Jansen FH, Adoubi I, J C KC, DE Cnodder T, Jansen N, Tschulakow A, Efferth T. First study of oral Artenimol-R in advanced cervical cancer: clinical benefit, tolerability and tumor markers. Anticancer Res. 2011; 31(12):4417-4422.
62-Krishna S, Ganapathi S, Ster IC, Saeed ME, Cowan M, Finlayson C, Kovacsevics H, Jansen H, Kremsner PG, Efferth T, Kumar D. A Randomised, Double Blind, Placebo-Controlled Pilot Study of Oral Artesunate Therapy for Colorectal Cancer. EBioMedicine. 2014; 15; 2(1):82-90.
63-Li Y, Shan F, Wu JM, Wu GS, Ding J, Xiao D, Yang WY, Atassi G, Léonce S, Caignard DH, Renard P. Novel antitumor artemisinin derivatives targeting G1 phase of the cell cycle. Bioorg Med Chem Lett. 2001; 11(1):5-8.
64-Wu JM, Shan F, Wu GS, Li Y, Ding J, Xiao D, Han JX, Atassi G, Leonce S, Caignard DH, Renard P. Synthesis and cytotoxicity of artemisinin derivatives containing cyanoarylmethyl group. Eur J Med Chem. 2001; 36(5):469-479.
65-Efforth T. Willmar Schwabe Award 2006: Antiplasmodial and antitumor activity of artemisinin from bench to bedside. Planta Med. 2007; 73(4): 299–309.
66-Liu Y, Lok CN, Ko BCB, Shum TYT, Wong MK, Che CM. Subcellular localization of a fluorescent artemisinin derivative to endoplasmic reticulum. Org Lett. 2010; 12: 1420–1423.
67-Morrissey C, Gallis B, Solazzi JW, Kim BJ, Gulati R, Vakar-Lopez F, Goodlett DR, Vessella RL, Sasaki T. Effect of artemisinin derivatives on apoptosis and cell cycle in prostate cancer cells. Anticancer Drugs. 2010; 21(4):423-432.
68-Lu JJ, Meng LH, Shankavaram UT, Zhu CH, Tong LJ, Chen G, Lin LP, Weinstein JN, Ding J. Dihydroartemisinin accelerates c-MYC oncoprotein degradation and induces apoptosis in c-MYC-overexpressing tumor cells. BiochemPharmacol. 2010; 80(1):22-30.
69-Lu JJ, Chen SM, Zhang XW, Ding J, Meng LH. The anti-cancer activity of dihydroartemisinin is associated with induction of iron-dependent endoplasmic reticulum stress in colorectal carcinoma HCT116 cells. Invest New Drugs. 2011; 29: 1276–1283.
70- Lu JJ, Chen SM, Ding J, Meng LH. Characterization of dihydroartemisinin-resistant colon carcinoma HCT116/R cell line. Mol Cell Biochem. 2012; 360(1-2): 329–337.
71-Yu QB, Gao YX. 56 cases of lupus erythematosus treated with artesunate. Zhonghua Pi Fu Ke Za Zhi 1997, 30: 51–52.
72-Hou LF, He SJ, Wang JX, Yang Y, Zhu FH, Zhou Y, He PL, Zhang Y, Yang YF, Li Y, Tang W, Zuo JP. SM934, a water-soluble derivative of arteminisin, exerts immunosuppressive functions in vitro and in vivo.Int Immunopharmacol. 2009; 9(13-14):1509-1517.

73-Wang Z, Qiu J, Guo TB, Liu A, Wang Y, Li Y, Zhang JZ. Anti-inflammatory properties and regulatory mechanism of a novel derivative of artemisinin in experimental autoimmune encephalomyelitis.J Immunol. 2007; 179(9):5958-5965.
74-Yang ZS, Wang JX, Zhou Y, Zuo JP, Li YSynthesis and immunosuppressive activity of new artemisinin derivatives. Part 2: 2-[12(beta or alpha)-dihydroartemisinoxymethyl(or 1'-ethyl)]phenoxyl propionic acids and esters.Bioorg Med Chem. 2006 ; 14(23):8043-8049.
75-Hou LF, He SJ, Li X, Yang Y, He PL, Zhou Y, Zhu FH, Yang YF, Li Y, Tang W, Zuo JP. Oral administration of artemisinin analog SM934 ameliorates lupus syndromes in MRL/lpr mice by inhibiting Th1 and Th17 cell responses. Arthritis Rheum. 2011;63(8):2445-2455.
76-Hou LF, He SJ, Li X, Wan CP, Yang Y, Zhang XH, He PL, Zhou Y, Zhu FH, Yang YF, Li Y, Tang W, Zuo JP. SM934 treated lupus-prone NZB × NZW F1 mice by enhancing macrophage interleukin-10 production and suppressing pathogenic T cell development. PLoS One. 2012;7(2): e32424.
77-Li H, Zuo J, Tang W. Water-soluble artemisinin derivatives as promising therapeutic immunosuppressants of autoimmune diseases. Cell Mol Immunol. 2017;14(11):887–889.
78-Wang JX, Tang W, Zhou R, Wan J, Shi LP, Zhang Y, Yang YF, Li Y, Zuo JP. The new water-soluble artemisinin derivative SM905 ameliorates collagen-induced arthritis by suppression of inflammatory and Th17 responses. Br J Pharmacol. 2008; 153(6):1303-1310.
79- Mi JQ, Li Y, Ni RM, Zhang Y, Wang J, Cai X, Wang ZY. Inventors; Qinghaosu derivative and its salt, a new type of agent for treatment of acute leukemia. Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and Shanghai Institute of Materia Medica, Chinese Academy of Sciences. Chinese Patent 201210011774.5, 2012 Jan 16.
80-Mi JQ, Li Y, Ni RM, Zhang Y, Wang J, Cai X, Wang ZY, inventors; Qinghaosu derivative and its salt, a new type of agent for treatment of leukemia. Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and Shanghai Institute of Materia Medica, Chinese Academy of Sciences. Chinese Patent 201210012386.9, 2012 Jan 16.
81-Mi JQ, Li Y, Peng Y, Zhang Y, Wang J, Cai X, Wang ZY, inventors; Qinghaosu derivative and its salt, a new type of agent for treatment of acute myelocytieleukemia. Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and Shanghai Institute of Materia Medica, Chinese Academy of Sciences. Chinese Patent 201210012204.8, 2012 Jan 16
82-Efferth, T., Romero, M. R., Wolf, D.G., Stamminger, T., Marin, J. J., Marschall, M. The anti-viral activities of Artemisinin and artesunate. Clin Infect Dis. 2008; 47(6): 804–811.
83- Cui, X., Wang, Y., Kokudo, N., Fang, D., & Tang, W. Traditional Chinese medicine and related active compounds against hepatitis B virus infection. Biosci Trends. 2010; 4 (2): 39–47.
84-Cala AC, Ferreira JF, Chagas AC, Gonzalez JM, Rodrigues RA, Foglio MA, Oliveira MC, Sousa IM, Magalhães PM, Barioni Júnior W. Anthelmintic activity of Artemisia annua L. extracts in vitro and the effect of an aqueous extract and Artemisinin in sheep naturally infected with gastrointestinal nematodes. Parasitol Res. 2014; 113(6):2345-2353.
85-Saeed ME, Krishna S, Greten HJ, Kremsner PG, Efferth T. Antischistosomal activity of artemisinin derivatives in vivo and in patients. Pharmacol. Res. 2016; 1(110):216-226.
86-Lam NS, Long X, Su XZ, Lu F. Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis. Pharmacol Res. 2018; 133:77–100.
87-Li J, Casteels T, Frogne T, Ingvorsen C, Honoré C, Courtney M, et al. Artemisinins target GABAA receptor signaling and impair a cell identity. Cell. 2017; 168(1–2):86–100.
88-Xiang, M., Chen, Z., He, L., Xiong, G., and Lu, J. Transcription profiling of artemisinin-treated diabetic nephropathy rats using high-throughput sequencing. Life Sci. 2019; 219:353–363.
89-Chen, K., Hua, H., Zhu, Z., Wu, T., Jia, Z., and Liu, Q. Artemisinin and dihydroartemisinin promote β-cell apoptosis induced by palmitate via enhancing ER stress. Apoptosis. 2020; 25 (3-4): 192–204.

90-Gao, Y., Cui, M., Zhong, S., Feng, C., Nwobodo, A. K., Chen, B., et al. Dihydroartemisinin ameliorates LPS-induced neuroinflammation by inhibiting the PI3K/AKT pathway. Metab. Brain Dis. 2020; 35 (4), 661–672.
91-Ge, P. F., Jiang, T., Zong, Y., Yang, X. J., Ma, Y. N., Wang, Y. X., et al. Effect of artesunate on the expression of ICAM-1 and MMP-9 in vascular endothelial cells under high glucose condition. Hans J. Ophthalmol. 2019; 8(1): 41–51.
92- Yu Guo, Wei Fu, Yakai Xin, Jinlei Bai, Huifang Peng, Liujun Fu, Jie Liu, Liping Li, Yuijin Ma, Hongwei Jiang. Antidiabetic and Antiobesity Effects of Artemether in db/db Mice.BioMed Research International.2018; 2018: 9.
93-Lu P, Zhang FC, Qian SW, Li X, Cui ZM, Dang YJ, Tang QQ. Artemisinin derivatives prevent obesity by inducing browning of WAT and enhancing BAT function. Cell Res. 2016; 26(10): 1169–1172.
94-B. C. Jang. Artesunate inhibits adipogenesis in 3T3-L1 preadipocytes by reducing the expression and/or phosphorylation levels of C/EBP-*α*, PPAR-*γ*, FAS, perilipin A, and STAT-3. Biochem. Biophys. Res. Commun. 2016; 474 (1): 220–225.

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