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The discovery of Qinghaosu (artemisinin) as an effective anti-malaria drug: A unique China story

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In a collective effort to find new drugs for killing the malaria parasites (plasmodium) that became resistant to the conventional drugs such as chloroquine, scientists in China not only rediscovered the anti-malaria effect of the Chinese herb Qinghao (*Artemesia annua* L.), but also isolated the single active ingredient Qinghaosu (artemisinin in English) in crystal form. They subsequently conducted very systematic studies on the pharmacological properties of qinghaosu and its derivatives, and determined the unusual chemical structure of Qinghaosu. These anti-malaria drugs have saved countless lives, especially in the developing countries. Due to her key role in achieving these remarkable discoveries, Prof. Youyou Tu was awarded the 2015 Nobel Prize in Physiology or Medicine *"for her discoveries concerning a novel therapy against Malaria*". Here I will try to tell this fascinating China story based on what have been recorded in the peer-reviewed papers that were published in Chinese or English and largely in journals published in China.

Malaria has been a devastating infectious disease caused by parasites and especially common in the tropical area of the world, killing about one million children each year in Africa alone (Miller et al., 2013). Scientists in China rediscovered the anti-malaria effect of the leave extract of the Chinese herb Qinghao (English name: *Artemisia annua* L., commonly called the sweet wormwood) in 1971, identified Qinghaosu (meaning the "active principle of Qinghao"; later translated as "artemisinin" in English) as the active principle in 1972, characterized its full chemical and three-dimensional structure by 1978, developed more potent and also oil or water soluble derivatives in 1979. All these remarkable scientific discoveries were achieved within about ten years, making an extraordinary and unique China story that is worth to be told to the world community (Su and Miller, 2015).

Despite their great power in killing the malaria parasites, Qinghaosu derivatives such as the dihydro-qinghaosu, artemether and artesunate, possess a short elimination half-life in patients. When used in combination with other types of anti-malaria drugs of longer half-life (thus designated as Artimesinin-Combination Therapy, or ACT in short), it makes the most effective recipe for treating malaria worldwide and was thus officially recommended by the World Health Organization (WHO) (Eastman and Fidock, 2009). The development of the qinghaosu family anti-malaria drugs undoubtedly represents an outstanding contribution to human health. Due to this, Prof. YouYou Tu, as the major player in this unique story, was awarded half of the 2015 Nobel Prize in Physiology or Medicine *"for her discoveries concerning a novel therapy against Malaria"* (and the other half to professors William Campbell and Satoshi Omura "*for their discoveries concerning a novel therapy against infections caused by roundworm parasites*").

The discovery of Qinghaosu and its derivatives as effective drugs for treating malaria was a result of a collective research effort of the so-called "523 Project" organized by

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the Chinese government, so designated because it was started on May 23rd, 1967. The mission of this project was to find new drugs for patients who were infected by parasites that became resistant to the conventional drugs such as chloroquine, involving over 500 scientists from about 60 institutions all over China. Early research results of this project were either not published or published in peer-reviewed journals published in China, either in Chinese, or in English, or in both, often in a delayed and unusual manner, such that no names of authors or even no names of research institutions listed, except indicating that it was contributed by a particular "coordination group". Nevertheless, a systematic retrospective analysis of both the published and unpublished records did reveal undoubtedly that Prof. YouYou Tu played a key role at most of the stages in this work. Here I will try to tell these amazing discoveries according to what were recorded by the peer-reviewed papers published in 1970s and early 1980s, and largely in journals published in China. But for the descriptions of the procedures through which qinghaosu was initially extracted and isolated, I have to rely on the book entitled "Qinghao and Qinghaosu Family of Drugs" authored by Prof. Tu and published in Chinese in 2009, because I could find such descriptions nowhere in the peer-reviewed papers published (in Chinese or English).

MALARIA HAS BEEN A DEVASTATING PARASITE DISEASE THAT HAS LIKELY KILLED ONE HALF OF ALL THE HUMAN BEINGS EVER LIVED ON THE EARTH

The saga of the disease called malaria (meaning 'bad air', because it was believed to be caused by the miasmas rising from the swamps of stagnant water), as characterized by intermittent chills and fever, precedes the history of humans and has been recorded in the literatures of all the major civilizations since the ancient time. Descriptions of such malaria-specific symptoms are found in ancient Chinese literatures compiled thousands of years ago. Although countless ways of treatments were tested over the thousands of years, success was occasional and failure was common. Historically, the epidemic of malaria has been considered as the likely cause for the fall of many major powers (including the Roman Empire) and defeat in wars. Medical historians estimated that malaria has killed around half of all humans who have ever lived on the earth!

The modern elucidation on the cause of malaria

A scientific understanding of malaria became possible only till the end of the 19th century, with the establishment of the germ theory of infectious diseases due to the effort of such scientists as Louis Pasteur and Robert Kochin1870s. A painstaking search for a bacterial cause of malaria in the 1880s ended with the surprising discovery of the single-celled protozoan parasite, belonging to the genus *Plasmodium*, as the pathogen. The elucidation of its way of transmission was considered as one of the most exciting events for humankind to understand infectious diseases.

The initial breakthrough in identifying the pathogen of malaria came from the French army surgeon Alphonse Laveran, who, while working in Algeria, observed in 1880 the parasite in the blood of malarial patients but not in normal healthy people and immediately realized its relation to the disease (Laveran, 1907). Further research by people like Patrick Manson, Ronald Ross and others in the 1890s unveiled first in birds and then in humans that female mosquitoes act as the vector to transmit the malaria parasites from one individual to another (Ross and Smyth, 1897; Ross, 1898; Ross, 1902). Much later, it was discovered first in monkeys, remarkably, that the parasites injected by the mosquito first live in the human liver cells for about one week before moving into the red blood cells, explaining a long-puzzled phenomenon that the parasites could only be detected in the red blood cells about one week after the mosquito biting (Shortt and Garham, 1948).

Ronald Ross was awarded the 1902 Nobel Prize in Physiology or Medicine (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1902/ross-lecture.pdf) "*for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it*." Alphonse Laveran was awarded the 1907 Nobel Prize in Physiology or Medicine (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1907/laveran-lecture.html) *"in recognition of his work on the role played by protozoa in causing diseases"*.

The unusual life cycle of the malaria parasite

The malaria parasites possess an unusual life cycle by living in both female mosquitos and individuals of human or other animals (Thera and Plowe, 2012; Miller et al., 2013; Winzeler, 2008), as briefly summarized here (Figure 1). We may start from the gut (stomach) of a female mosquito, where each *Plasmodium* oocyst (i.e., encysted zygote) divides to form thousands of sporozoites (i.e., the spores). The latter then migrates and infects the mosquito's salivary gland before being injected into the bloodstream of an animal (or human) individual through biting. The sporozoites then start their pre-erythrocyte stage of life by invading the victim's heptocytes (i.e., liver cells), where, after several days, they undergo multiple asexual divisions to produce merozoites (one sporozoite may develop into many thousands of merozoites). When an infected liver cell bursts, the merozoites will be released into the blood and then invade the red blood cells (merozoites cannot re-infect other liver cells). In the liver cells, some sporozoites may differentiate into hypnozoites that remain dormant in the liver for months to years before waking up to undergo division and development into merozoites (causing the recurrence of the

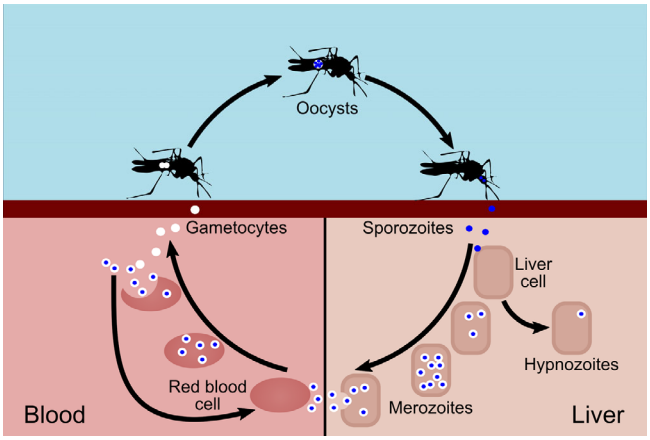

Figure 1 (color online) The life cycle of the malaria parasites (*Plasmodium*).

symptoms in individuals sometime after an effective drug treatment of malaria).

Inside the red blood cells, the merozoites grow and divide asexually into a great number of new merozoites. In the red blood cells, themerozoites divide either to form the parasite's sexual form known as gametocyte or the asexual form called trophozoite. When the red blood cells rupture, which occurs every 48 or 72 hours (depending on the parasite species), the trophozoites will invade more red blood cells, repeating indefinitely, causing the periodic chills and fever. The gametocytes from the blood may enter another mosquito which bites such an infected patient. Once inside a mosquito, the gametocytes will develop into mature sex cells, the male and female gametes, which may undergo fertilization to form the oocysts again in the gut before dividing to form the sporozoites, which may start a new cycle of the parasite's life (Figure 1).

The malaria parasite's evasive and complex life cycle makes it rather difficult to develop effective vaccines or drugs (Thera and Plowe; 2012; Winzeler, 2008; Miller et al., 2013). The fact that the malaria parasites spend most of their time hiding either inside the liver cells or the red blood cells makes it difficult for the host to elicit an efficient immune attack or for scientists to develop an effective vaccine. Adding to this difficulty is the genetic mutation occurring during the mitotic reproduction in the malaria parasite's haploid stages in the liver and blood, as well as genetic recombination during the diploid sexual reproductive stages in the mosquito. Both of these generate an extensive genetic diversity, such that their surface proteins keep changing their "faces", efficiently escaping the host's immune attack. Another challenge is that some malaria parasites in the liver cells may enter a dormant state, towards which drugs become powerless, as true for all types of pathogens that have entered their dormant states (Wang et al., 2009; Liu et al., 2015).

ANTI-MALARIA DRUGS BEFORE QINGHAOSU (ARTEMISININ)

To the humankind, the first effective drug for treating malaria was the alkaloid-type of compound quinine isolated from the bark of cinchona tree. Similar to the story of Qinghao, the powdered bark of the cinchona tree was initially used to treat fever in South America, and then to treat malaria in the 17th century. Subsequently, quinine was isolated as the active principle to treat malaria in the 1820s by French pharmacists, Pierre-Joseph Pelletier and Joseph-Bienaimé Caventou (Kaufman and Ruveda, 2005). Similar to the case of qinghaosu, the action mechanism of quinine remains to be defined, one of the explanations is that quinine suppresses the biocrystallization and detoxification of the heme group in the red blood cells, thus enabling the free and toxic heme groups to accumulate in the red blood cells and eventually kill the malaria parasites themselves. Apparently, quinine is unable to eradicate the malaria disease.

Quinine was used as the only effective drug against malaria until the 1920s, but resistant strains appeared. In 1934, German chemists developed a new anti-malaria quinine derivative, chloroquine, which became a dominant anti-malaria drug because it is able to kill several *Plasmodium* species at most stages of the parasite's life cycle. By the end of the Second World War, pharmacists had devised drugs effective against parasites at all stages of their life cycles. In addition, there was a powerful insecticide called DDT that was used to suppress the spread of mosquitos, thus blocking them from transmitting the parasite from patients to health individuals.

For a while, it looked as if this combination of mosquito control and drug treatment might help the humankind to defeat malaria, a disease that has harmed the humankind for thousands of years. In 1956, this optimism became the official policy of the World Health Organization (WHO), who launched a global campaign to eradicate malaria. But in the 1960s, chloroquine-resistant strains of the parasite and DDT-resistant mosquitoes became increasingly common. By the end of the 1960s, the WHO had to admit that eradicating malaria was impossible, and switched its goal to controlling the disease.

QINGHAOSU WAS DISCOVERED AS THE ANTI-MALARIA PRINCIPLE PRESENT IN THE CHINESE HERB QINGHAO

It seems to be imperative to develop new drugs once a while in order to keep pace with mutations occurring in the malaria parasites. Since the late 1960s, The Chinese government started a massive effort to search for new drugs that are effective in treating the malaria resistant to such conventional drugs as chloroquine. One approach was to screen the available chemical compound libraries, but ended

with no luck. The other approach was to look into the treasure of the traditional Chinese medicine, which，as common in scientific research, resulted in at least one success after countless failures. Professor YouYou Tu was a key figure in this second venture of eventual success.

Qinghao extract only when prepared in a proper way was effective in treating malaria

Although Qinghao has been recorded in Chinese medical books compiled about 1500 years ago for its effectiveness in treating malaria, those early practices were based on experiences instead of strict scientific tests. Its therapeutic efficacy was unavoidably neither consistent nor pronounced. Prof. YouYou Tu studied modern medicine in Beijing Medical College, which was Peking University Medical School when she enrolled in 1951, and one year later in 1952, it became an independent medical college and later a medical university, which was reincorporated into Peking University in 2000 and is currently Peking University Health Science Center. After graduation from college, Tu was chosen to study Chinese medicine for two full years. This allowed her to make the unique contribution in rediscovering the anti-malaria effect of the Chinese herb Qinghao and subsequently isolate the active principle. This all started with her deeper understanding on the sentence "take one bunch of Qinghao, soak in two sheng (~0.4 liter) of water, wring it out to obtain the juice and ingest it in its entirety" from a Chinese medical book compiled about 1500 years ago. She realized that, in contrast to the way of preparing most Chinese medicine which commonly requires boiling, in preparing Qinghao extract for treating malaria, boiling should be avoided instead (Klayman, 1985; Miller and Su, 2011; White, 2008; Tu, 2011).

The group led by Prof. Tu then painstakingly tried to extract the active anti-malaria components in Qinghao. For this, they tested various solvents (including water, oil, alcohol and diethyl ether), different temperatures, different parts of the plant, the plant of different developing stages, etc (Tu, 2009). As a result, they demonstrated that the effective components are mainly found in the leaves of mature plants and can be effectively extracted with diethyl ether or alcohol as solvent but have to operate at a temperature below 60^{o}C (Tu, 2009; Miller and Su, 2011; Su and Miller, 2015). Interestingly, the active anti-malaria components after such diethyl ether or alcohol extraction were found to be rather stable, with the anti-malaria activity almost unaltered even after being boiled for 30 minutes. It awaits further clarification on why heating on the initial mixture destroyed but heating on the solvent-extracted mixture did not affect the anti-malaria activity.

Those components that exhibit toxicity but no anti-malaria activity could be effectively removed by a sodium hydroxide extraction step

In an attempt to reduce the toxicity of the diethyl ether extract of Qinghao, Tu et al. tried to further separate the active ingredients from those inactive components. For that, they found, in 1971, that treating the diethyl ether extract of Qinghao (active but toxic) with 2% NaOH removed those acidic components that are toxic but exhibiting no anti-malaria effect, while the leftover neutral part in the diethyl ether solvent was found to exhibit little toxicity but high anti-malaria activity (Tu, 2009; Miller and Su, 2011; Su and Miller, 2015). This fraction with high anti-malaria activity was again concentrated before being utilized for further purification of the active ingredient.

Qinghaosu was successfully purified as a single crystallizable ingredient by using silica gel column chromatography

The concentrated sample of the Qinghao extract that exhibited high anti-malaria activity but little toxicity was then used for further purification of the active ingredients. For this purpose, polyamide was first added into this concentrated extractum, being shaken by votexing, before percolated with 47% alcohol. The diluted alcohol percolated extract was then subject to another round of diethyl ether extraction, with the extracted components being separated by silica gel column chromatography. The fraction eluted with 10% acetyl ester from the silicon column was able to form needle-like crystals and exhibited the full anti-malaria activity when tested with mice of malaria, while those eluted with other petroleum ether or 15% acetyl ester did not show any anti-malaria activity (Tu, 2009).

The systematic data of the anti-malaria activity of Qinghaosu was first published in 1979

Although Qinghaosu was first isolated in crystal form as the active anti-malaria ingredient in 1972 (by Prof. Tu et al.) and systematic structural and pharmacological studies were performed since then, the publication of these novel research data was years delayed. The first paper on Qinghaosu was published in 1977, but only reporting its structure, without mentioning anything about its anti-malaria activity (Qinghaosu Coordinating Research Group, 1977). The two papers (they were actually one paper published in Chinese and English) reporting about the anti-malaria activity of Qinghaosu were published two years later (Qinghaosu Antimalaria Coordinating Research Group, 1979a, 1979b].

Although there was no description in these early papers and others published later on how Qinghaosu was isolated, its chemical structure, its efficacy in treating animal (mice, monkey, chicken) malaria, its toxicity, its clinical trial results (among the 2,099 malaria patients tested from all over China between 1973–1978, covering all types of malaria including choroquine-resistant and brain malaria, all were effective except about 10 people who died due to other complications) and its pharmacokinetics (absorption, organ distribution, biotransformation and excretion, by administering radio-labeled Qinghaosu to the animals)，one-month

recrudescent rate were all described in detail (Qinghaosu Antimalaria Coordinating Research Group, 1979a, 1979b; China Cooperative Research Group on Qinghaosu and Its Derivatives as Antimalarials, 1982a, b, c, d, e, f). These results demonstrated that Qinghaosu is an anti-malaria drug of rapid action, high efficiency and low toxicity but also of a short elimination half-life in the body and a rather high one-month recrudescence rate after a three-day treatment.

Remarkably, Qinghaosu apparently cleared the parasite from the blood and relieved the fever symptoms within a time period that was significantly shorter than chloroquine did in addition to its efficiency in curing cerebral and chloroquine-resistant malaria. Further analysis demonstrated that Qinghaosu exhibited direct killing effect only on the parasites living in erythrocytes but not on those living the heptocytes. Studies with electron microscopy revealed that Qinghaosu apparently directly damaged the membrane system in the parasite cell, leading to the formation of autophagic vacuoles and eventual death of the parasites (QinghaosuAntimalaria Coordinating Research Group, 1979a, 1979b; Tu, 2009; Zhou, 2015). The recrudescent parasites were apparently generated from those dormant forms of the parasites hiding in the liver cells, instead of due to any mutations of the parasite. In view of these advantages and disadvantages of Qinghaosu (or its derivatives) treatment, WHO suggested admisinin combination therapy (ACT) as a standard treatment for malaria, with an additional drug of longer elimination half-life being used together with Qinghaosu. The practice of ACT has significantly lowered the recrudescent rate of Qinghaosu.

QINGHAOSU POSSESSES AN UNUSUAL MULTI-RING AND NITROGEN-FREE CHEMICAL STRUCTURE

The first publication on Qinghaosu focused on its unique structure (Qinghaosu Coordinating Research Group, 1977) (*the manuscript was submitted on Feb. 20, 1976*). "The Qinghaosu Structure Study Coordinating Group" was listed as the "author", with names of neither authors nor institutions indicated. Although there was no description on how this material named as Qinghaosu was isolated (except indicating that it was a colorless crystalline isolated from the plant Qinghao, its chemical structure was claimed to be comprehensively examined using all types of modern techniques).

Qinghaosu was characterized as a new type of sesquiterpene lactone containing a key peroxide group

Through comprehensive chemical and physical analyses, it was demonstrated that Qinghaosu is a new type of sesquiterpene lactone (meaning that the molecule contains three molecules of isoprene units and a lactone ring). It differs from another sesquiterpene lactone that was recently isolated from *Artimisia Annua L.* (named as arteannuin B, with a molecular formula of $C_{15}H_{20}O_3$ (Jeremic et al., 1973)) by containing an additional unique peroxide group (Qinghaosu Coordinating Research Group, 1977; China Cooperative Research Group on Qinghaosu and Its Derivatives as Antimalarials, 1982a). In these characterizations on Qinghaosu, types of methods used include element analysis, high reso-

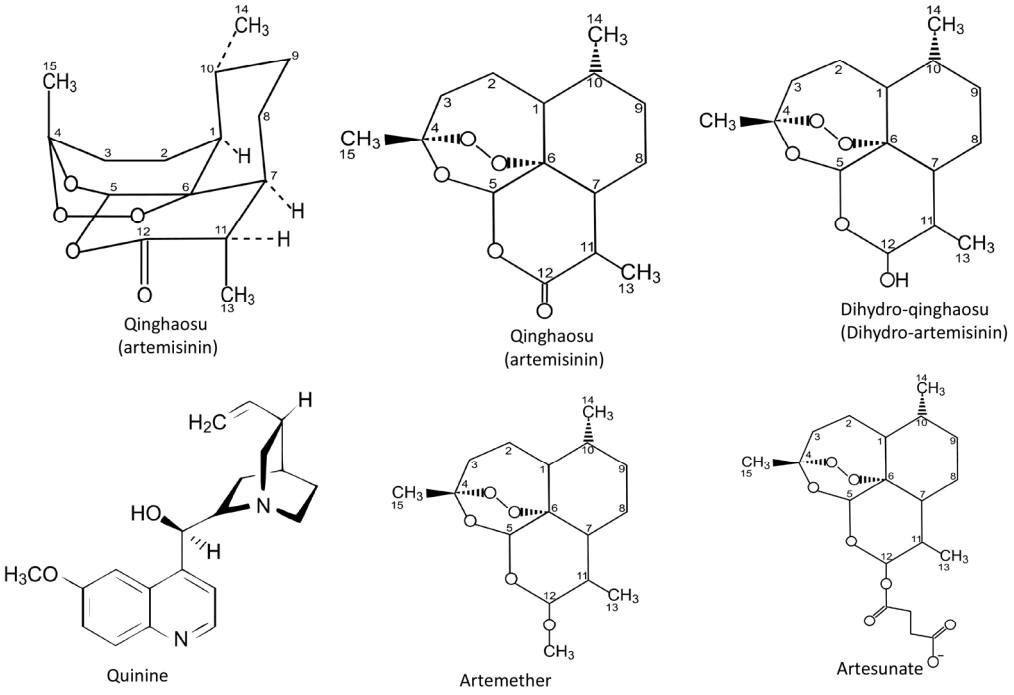

Figure 2 Structure of Qinghaosu (artemisinin), dihydro-qinghaosu, artemether, artesunate and quinine.

lution mass spectrometry, infrared spectroscopy, ^{1}H and ^{13}C NMR (with almost all the different types of hydrogen atoms and all the 15 carbon atoms clearly identified using a 100 MHz machine), chemical reaction analysis and X-ray crystallography, and others. The properties of this molecule were characterized as possessing a melting point of 156−157°C, an optical activity of +66.3°, a molecular formula of $C_{15}H_{22}O_5$, a lactone (i.e., with an IR absorption peak at 1745 cm^{-1}) and a peroxide group (i.e., with IR absorption peaks at 831, 881 and 1115 cm^{-1}), but containing no carbon-carbon double bond (Qinghaosu Coordinating Research Group, 1977; Liu et al., 1979; China Cooperative Research Group on Qinghaosu and Its Derivatives as Antimalarials, 1982a).Although the three-dimen- sional structure of Qinghaosu was displayed and described in these early papers (Qinghaosu Coordinating Research Group, 1977; Qinghaosu Antimalaria Coordinating Research Group, 1979a; Qinghaosu Antimalaria Coordinating Research Group, 1979b), detail reports on the X-ray crystallography studies on Qinghaosu appeared later (see below).

The three dimensional structure of Qinghaosu was determined by X-ray crystallography

The X-ray single crystal diffraction studies, with the crystals provided by the Qinghao Research Group of the Institute of Chinese Materia Medica, Academy of Traditional Chinese Medicine, elucidated the three dimensional structure of the Qinghaosu molecule, including the absolute configuration of the 7 asymmetric carbons (Qinghaosu Research Group of the Institute of Biophysics of the Chinese Academy of Sciences, 1979; 1980; *both papers had the identical contents, but the former was published in Chinese and the latter in English, and both submitted on May 9, 1978*). In this work, the diffraction studies were performed using a four-circle diffractometer PW-1100 (using CuK_a radiation). The structure was resolved by the symbolic addition procedure and refined by full-matrix least-square method to a final R index of 0.085 for 1553 reflections and 0.074 for 1299 observed reflections. The absolute configurations of all the asymmetric carbons in the Qinghaosu molecule were determined. It was revealed that the 15 carbon atoms and 5 oxygen atoms in the Qinghaosu molecule are linked into a structure of four rings (designated as ring A, B, C or D; as displayed in Figure 2). In particular, ring A is a chair-shaped cyclohexane, rings B and C are both saturated oxyheterocycles, while ring D is a delta-lactone (i.e., an intra-molecular ester). Remarkably, all the five oxygen atoms are allocated on one side of the molecule (Figure 2) forming a unique carbon-oxygen chain (made of O-C_{12}-O-C_5-O-C_4-O-O-C_6). Apparently, this unique carbon-oxygen chain makes the peroxide group unusually stable towards both heat and light. How the unique chemical properties of this chain of carbon-oxygen enable Qinghaosu to exhibit the anti-malaria activity remains to be clarified.

DIHYDRO-QINGHAOSU AND OTHER DERIVATIVES OF QINGHAOSU WERE FOUND TO EXHIBIT A MORE POTENT ANTI-MALARIA EFFECT THAN QINGHAOSU

Such undesired properties as low water solubility and high recrudescence rate of Qinghaosu prompted scientists in China to try to develop derivatives of Qinghaosu (as similarly done on quinine). For this, they found that treating Qinghaosu with sodium borohydride ($NaBH_4$) generated dihydro-qinghaosu (whose structure is shown in Figure 2). This resulted in the reduction of the only carbonyl group in the Qinghaosu molecule to a hydroxyl group, to which (and only to which) many chemical groups were subsequently covalently linked, generating a great number of derivatives that included ethers, esters and carbonates (Li et al., 1979; China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials, 1982b). When applied to treat mice infected with chloroquine resistant *P. berghei*, dihydro-qinghaosu and many of these dihydro-qinghaosu derivatives were found to exhibit a much more potent anti-malaria effect than Qinghaosu itself (Gu et al., 1980; China Cooperative Research Group on Qinghaosu and Its Derivatives as Antimalarials, 1982c). These studies meanwhile demonstrated that the peroxide group in Qinghaosu has to be maintained for any derivative to exhibit an anti-malaria effect. In other words, the peroxide group is essential for Qinghaosu to exhibit the anti-malaria effect (Gu et al., 1980). Among these synthesized and tested Qinghaosu derivatives were those that were developed into commonly used anti-malaria drugs, such as artemether (Figure 2; i.e., having a methyl group linked to the hydroxyl group, thus of high oil solubility, and thus proper for oral administration) (Gu et al., 1980, 1981; China Cooperative Research group on Qinghaosu and Its Derivatives as Antimalarials, 1982b, 1982c, 1982f). Another derivative of high water solubility and anti-malaria efficiency is artesunate (Figure 2; i.e., having a succinate linked in its monoester-form, thus of high water solubility and proper for intravenous injection) (China Cooperative Research group on Qinghaosu and Its Derivatives as Antimalarials, 1982b, 1982c, 1982f).

THE OUTSIDE WORLD LEARNED AND CONFIRMED THE ANTI-MALARIA EFFECT OF QINGHAOSU (ARTEMISININ)

Although the chemical structure of Qinghaosu was first published in 1977 (Qinghaosu Coordinating Research Group, 1977), its anti-malaria effect was first announced to the general public (including in China) only in papers published two years later (Qinghaosu Antimalaria Coordinating Research Group, 1979, 1979b), it immediately caused the attention of the outside world. Two more years later, WHO,

together with the United Nations Development Program and World Bank, organized a special conference "the Fourth Meeting of the Scientific Working Group on the Chemotherapy of Malaria", October 6–10, 1981 in Beijing (The 4th meeting of the SWG-CHEMAL, 1981; Bruce-Chwatt, 1982; Klayman, 1985; Miller and Su, 2011; Tu, 2011). Qinghaosu's outstanding anti-malaria activity and unusual nitrogen-free chemical structure, all unveiled for the first time and completely characterized by scientists in China during a chaotic period of time (i.e., the so-called Culture Revolution), were intriguing (or even shocking) to the outside world (Bruce-Chwatt, 1982; Klayman, 1985; White, 2008; Miller and Su, 2011). The correctness of such a hitherto unknown unique structure was further proved by its full chemical synthesis. This outstanding work was painstakingly and almost simultaneously accomplished by scientists both in China (Xu et al., 1983) and in Switzland (Schmid and Hofheinz, 1983). Nevertheless, such chemical synthesis procedures remain too complex and too expensive for producing Qinghaosu this way for commercial applications (in other words, we have to still rely on the plant Qinghao to produce Qinghaosu for us).

When the Chinese scientists developed artemether (for oral administration) and artesunate (for intravenous injection) as the common anti-malaria drug (Gu et al., 1980, 1981; China Cooperative Research Group on Qinghaosu and Its Derivatives as Antimalarials, 1982c), it was almost entirely ignored outside China. Nevertheless, on the one hand, the situation of parasite resistance to the available anti-malaria drugs (e.g., quinine, chloroquine and mefloquine) was worsening, and on the other hand, the accumulating evidences supported the rapidity, reliability and safety of the Qinghaosu family drugs. These facts forced colleagues outside China to change their mind and switched to the drugs discovered and developed by scientists in China (Klayman, 1985; White, 2008; Miller and Su, 2011). The first non-Chinese journal that reported about the better anti-malaria efficacy of Qinghaosu over the conventional drugs was *Lancet* (Jiang et al., 1982). Revelations on the outstanding anti-malaria effect of Qinghaosu was later confirmed by scientists in the United States (Klayman et al., 1984). After these, Qinghaosu and its derivatives (including dihydro-qinghaosu, artemether, artesunate and others) became first choice anti-malaria drugs by physicians worldwide (Bruce-Chwatt, 1982; Klayman, 1985; White, 2008; Miller and Su, 2011).

SUMMARY AND PERSPECTIVES

The discovery of the anti-malaria effect of the Chinese herb Qinghao had been a long and tortuous China story, in which scientists in China initially extracted the active mixture and subsequently purified the active ingredient Qinghaosu, characterized the unusual structure of Qinghaosu, prepared derivatives that retain the anti-malaria effect but are more potent in eliminating the parasite and more convenient for administration to the patients (i.e., soluble either in water or oil), among others. The discovery of Qinghaosu as an anti-malaria drug that is more effective than the other drugs, and importantly more efficient in killing the malaria parasites that have become resistant to the other drugs represented a major contribution of scientists in China to the world. We expect more such treasures to be dug out from the Chinese traditional medicine, which has a recorded history of thousands of years.

As usual in scientific research, many questions remain on Qinghaosu and its derivatives. For example, what they exact do in killing the parasites (Zhou, 2015)? Why do they exhibit a killing effect only on the parasites living in the red blood cells but exhibit no effect on the parasite living in the liver cells? Why do the plants synthesize such an unusual molecule by spending much energy and via a multistep biosynthetic pathway? What does it do for the plants? Do plants other than Qinghao also synthesize it and again for what purposes (If Qinghaosu is synthesized in other plants, it should play role similar as in Qinghao)?

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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