The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine

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Joseph Goldstein has written in this journal that creation (through invention) and revelation (through discovery) are two different routes to advancement in the biomedical sciences[1]. In my work as a phytochemist, particularly during the period from the late 1960s to the 1980s, I have been fortunate enough to travel both routes.

I graduated from the Beijing Medical University School of Pharmacy in 1955. Since then, I have been involved in research on Chinese herbal medicine in the China Academy of Chinese Medical Sciences (previously known as the Academy of Traditional Chinese Medicine). From 1959 to 1962, I was released from work to participate in a training course in Chinese medicine that was especially designed for professionals with backgrounds in Western medicine. The 2.5-year training guided me to the wonderful treasure to be found in Chinese medicine and toward understanding the beauty in the philosophical thinking that underlies a holistic view of human beings and the universe.

Figure 1 *A Handbook of Prescriptions for Emergencies* by Ge Hong (284–346 CE). (**a**) Ming dynasty version (1574 CE) of the handbook. (**b**) "A handful of qinghao immersed with 2 liters of water, wring out the juice and drink it all" is printed in the fifth line from the right. (From volume 3.)

Discovery of antimalarial effect of qinghao

Malaria, caused by *Plasmodium falciparum*, has been a life-threatening disease for thousands of years. After the failure of international attempts to eradicate malaria in the 1950s, the disease rebounded, largely due to the emergence of parasites resistant to the existing antimalarial drugs of the time, such as chloroquine. This created an urgent need for new antimalarial medicines. In 1967, a national project against malaria was set up in China under the leadership of the Project 523 office. My institute quickly became involved in the project and appointed me to be the head of a malaria research group comprising both phytochemical and pharmacological researchers. Our group of young investigators started working on the extraction and isolation of constituents with possible antimalarial activities from Chinese herbal materials.

During the first stage of our work, we investigated more than 2,000 Chinese herb preparations and identified 640 hits that had possible antimalarial activities. More than 380 extracts obtained from ~200 Chinese herbs were evaluated against a mouse model of malaria. However, progress was not smooth, and no significant results emerged easily.

The turning point came when an *Artemisia annua* L. extract showed a promising degree of inhibition against parasite growth. However, this observation was not reproducible in subsequent experiments and appeared to be contradictory to what was recorded in the literature.

Seeking an explanation, we carried out an intensive review of the literature. The only reference relevant to use of qinghao (the Chinese name of *Artemisia annua* L.) for alleviating malaria symptoms appeared in Ge Hong's *A Handbook of Prescriptions for Emergencies*: "A handful of qinghao immersed with 2 liters of water, wring out the juice and drink it all" (**Fig. 1**). This sentence gave me the idea that the heating involved in the conventional extraction step we had used might have destroyed the active components, and that extraction at a lower temperature might be necessary to preserve antimalarial activity. Indeed, we obtained much better activity after switching to a lower-temperature procedure.

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Figure 2 *Artemisia annua* L. (**a**) A hand-colored drawing of qinghao in Bu Yi Lei Gong Pao Zhi Bian Lan (Ming Dynasty, 1591 CE). (**b**) *Artemisia annua* L. in the field.

We subsequently separated the extract into its acidic and neutral portions and, at long last, on 4 October 1971, we obtained a nontoxic, neutral extract that was 100% effective against parasitemia in mice infected with *Plasmodium berghei* and in monkeys infected with *Plasmodium cynomolgi*. This finding represented the breakthrough in the discovery of artemisinin.

From molecule to drug

During the Cultural Revolution, there were no practical ways to perform clinical trials of new drugs. So, in order to help patients with malaria, my colleagues and I bravely volunteered to be the first people to take the extract. After ascertaining that the extract was safe for human consumption, we went to the Hainan province to test its clinical efficacy, carrying out antimalarial trials with patients infected with both *Plasmodium vivax* and *P. falciparum*. These clinical trials produced encouraging results: patients treated with the extract experienced rapid disappearance of symptoms—namely fever and number of parasites in the blood—whereas patients receiving chloroquine did not.

Encouraged by the clinical outcome, we moved on to investigate the isolation and purification of the active components from *Artemisia* (**Fig. 2**). In 1972, we identified a colorless, crystalline substance with a molecular weight of 282 Da, a molecular formula of $C_{15}H_{22}O_5$, and a melting point of 156–157 °C as the active component of the extract. We named it qinghaosu (or artemisinin; *su* means "basic element" in Chinese).

In keeping with Goldstein's view, the discovery of artemisinin was the first step in our advancement—the revelation. We then went on to experience the second step—creation—by turning the natural molecule into a drug.

We had found that, in the genus *Artemisia*, only the species *A. annua* and its fresh leaves in the alabastrum stage contain abundant artemisinin. My team, however, used an *Artemisia* local to Beijing that contained relatively small amounts of the compound. For pharmaceutical production, we urgently required an *Artemisia* rich in artemisinin. The collaborators in the nationwide Project 523 found an *A. annua* L. native to the Sichuan province that met this requirement.

The first formulation we tested in patients was tablets, which yielded unsatisfactory results. We found out in subsequent work that this was due to the poor disintegration of an inappropriately formulated tablet produced in an old compressing machine. We shifted to a new preparation—a capsule of pure artemisinin—that had satisfactory clinical efficacy. The road leading toward the creation of a new antimalarial drug opened again.

Spreading the word

In addition to problems of production and formulation, we also faced challenges regarding the dissemination of our findings to the world. The stereo-structure of artemisinin, a sesquiterpene lactone, was determined with the assistance of a team at the Institute of Biophysics, Chinese Academy of Sciences, in 1975. The structure (**Fig. 3**) was first published in 1977 (ref. 2), and both the new molecule and the paper were immediately cited by the Chemical Abstracts Service in the same year. However, the prevailing environment in China at the time restrained the publication of any papers concerning qinghaosu, with the exception of several published in Chinese[2–20]. Fortunately, in 1979, the China National Committee of Science and Technology granted us a National Invention Certificate in recognition of the discovery of artemisinin and its antimalarial efficacy.

In 1981, the fourth meeting of the Scientific Working Group on the Chemotherapy of Malaria, sponsored by the United Nations Development Programme, the World Bank and the World Health Organization (WHO), took place in Beijing (**Fig. 4**). During a special program for research and training in tropical diseases, a series of presentations on qinghaosu and its antimalarial properties elicited enthusiastic response. As the first speaker of the meeting, I presented our report "Studies on the Chemistry of Qinghaosu." The studies disclosed on this presentation were then published in 1982 (ref. 10). The efficacy of artemisinin and its derivatives in treating several thousand patients infected with malaria in China attracted worldwide attention in the 1980s[21].

Beyond artemisinin

Dihydroartemisinin was not initially considered a useful therapeutic agent by organic chemists because of concerns about its chemical stability. During evaluation of the artemisinin

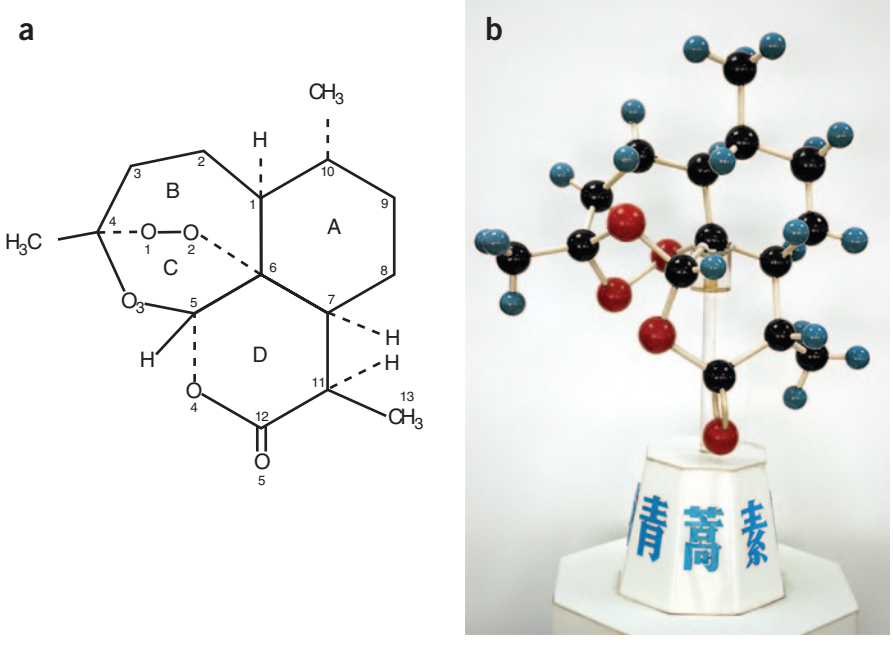

Figure 3 Artemisinin. (**a**) Molecular structure of artemisinin. (**b**) A three-dimensional model of artemisinin. Carbon atoms are represented by black balls, hydrogen atoms are blue and oxygen atoms are red. The Chinese characters underneath the model read *Qinghaosu*.

compounds, we found that dihydroartemisinin was more stable and ten times more effective than artemisinin. More importantly, there was much less disease recurrence during treatment with this derivative. Adding a hydroxyl group to the molecule also introduced more opportunities for developing new artemisinin derivatives through esterification.

My group later developed dihydroartemisinin into a new medicine. Over the past decade, my colleagues and I have explored the use of artemisinin and dihydroartemisinin for the treatment of other diseases[22–33].

The history of the discovery of qinghaosu and the knowledge we gained about the molecule and its derivatives during the course of our studies are summarized in the book *Research on Qinghaosu and Its Derivatives* (in Chinese)[34]. In 2005, the WHO announced a switch in strategy to artemisinin combination therapy (ACT). ACT is currently widely used, saving many lives, mostly those of children in Africa. The therapy markedly reduces the symptoms of malaria because of its antigametocyte activity.

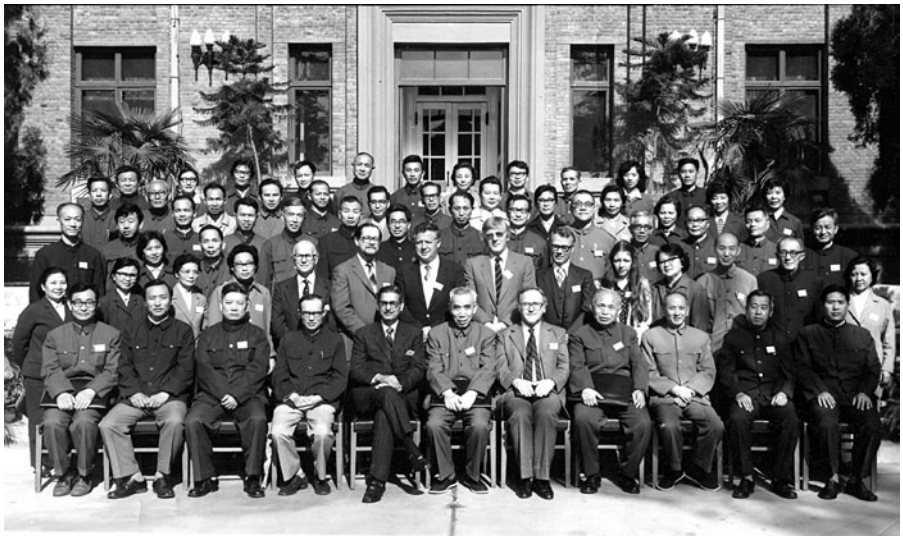

Figure 4 Delegates at the fourth meeting of the Scientific Working Group on the Chemotherapy of Malaria in Beijing in 1981. Professor Ji Zhongpu (center, first row), president of the Academy of Traditional Chinese Medicine, delivered the opening remarks to the meeting. The author is in the second row (fourth from the left).

Other gifts from Chinese medicine

Artemisinin, with its unique sesquiterpene lactone created by phytochemical evolution, is a true gift from old Chinese medicine. The route to the discovery of artemisinin was short compared with those of many other phytochemical discoveries in drug development. But this is not the only instance in which the wisdom of Chinese medicine has borne fruit. Clinical studies in China have shown that arsenic, an ancient drug used in Chinese medicine, is an effective and relatively safe drug in the treatment of acute promyelocytic leukemia (APL)[35]. Arsenic trioxide now is considered the first-line treatment for APL, exerting its therapeutic effect by promoting the degradation of promyelocytic leukemia protein (PML), which drives the growth of APL cells[36]. Huperzine A, an effective agent for treatment of memory dysfunction, is a novel acetylcholinesterase inhibitor derived from the Chinese medicinal herb *Huperzia serrata*[37], and a derivative of huperzine A is now undergoing clinical trails in Europe and the United States for the treatment of Alzheimer's disease.

However, the use of a single herb for the treatment of a specific disease is rare in Chinese medicine. Generally, the treatment is determined by a holistic characterization of the patient's syndrome, and a prescription comprises a group of herbs specifically tailored to the syndrome. The rich correlations between syndromes and prescriptions have fueled the advancement of Chinese medicine for thousands of years.

Progress in the therapy of cardiovascular and cerebrovascular diseases has also received gifts from Chinese medicine. A key therapeutic concern for Chinese medicine is the principle of activating blood circulation to remove blood stasis, and there are several examples of this principle in action in Western medicine. Compounds derived from Chinese medicinal products—the molecules chuangxiongol and paeoniflorin—have been tested for their efficacy in preventing restenosis after percutaneous coronary intervention (PCI). A multicenter, randomized, double-blind, placebo-controlled trial (335 patients, 6 months) showed that restenosis rates were significantly reduced by the medicine as compared with the placebo (26.0% versus 47.2%)[38]. Evidence supporting the therapeutic value of related strategies from Chinese medicine aimed at activating blood circulation has been obtained in the treatment of ischemic diseases[39] and in the management of myocardial ischemia-reperfusion injury[40–43].

Also in relation to cardiovascular disease, a new discipline called biomechanopharmacology aims at combining the pharmacological effects of Chinese medicine with the biomechanical properties of flowing blood[44]. The joint application of exercise (to increase the shear stress of blood flow) with extracts from shenlian, another Chinese medicine, shows promise for the prevention of atherosclerosis[45]. And recent reports have begun to provide a glimpse into the molecular mechanisms that account for the effects of Chinese remedies. For example, a recent study identified a potential mechanism to account for the effect of salvianolic acid B, a compound from the root of *Salvia miltiorrhiza*, in combination with increased shear stress, on the functions of endothelial cells[46].

The examples cited here represent only a sliver of the gifts or potential gifts Chinese medicine has to offer. It is my dream that Chinese medicine will help us conquer life-threatening diseases worldwide, and that people across the globe will enjoy its benefits for health promotion.

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COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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