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[**The Nobel Prize in Physiology or Medicine 2015**](https://www.nobelprize.org/prizes/medicine/2015/summary/)



**My Childhood**

I was born on December 30, 1930 in Ningbo, a city on the east coast of China with a rich culture and over seven thousand years of history. Although it was a tumultuous age in China when I was a child, I was lucky enough to have completed a good education from primary to middle school.

My father worked in a bank while my mother looked after my four brothers and me, the only girl in our family. According to a recently discovered family tree, my ancestors lived in Ningbo for many generations. Our family’s long history of highly valuing children’s education and always considering this as the family’s top priority allowed me to have good opportunities for attending the best schools in the region – from the private Ningbo Chongde Primary School (1936–1941) and later the private Ningbo Maoxi Primary School (1941–1943) to the private Ningbo Qizheng Middle School (1943–1945) and the private Ningbo Yongjiang Girls’ School (1945–1946).

I unfortunately contracted tuberculosis at the age of sixteen and had to take a two-year break and receive treatment at home before I resumed my study at the private Ningbo Xiaoshi High School (1948–1950) and Ningbo High School (1950–1951). This experience led me to make a decision to choose medical research for my advanced education and career – if I could learn and have (medical) skills, I could not only keep myself healthy but also cure many other patients. After graduation from high school, I attended the university entrance examination and fortunately I was accepted by the Department of Pharmacy and became a student at the Medical School of Peking University.

**My university life**

My choice of learning pharmacy was driven by my interests, curiosity, and a desire to seek new medicines for patients. In 1941, an Institute of Chinese Materia Medica was found at Peking University. The institute late developed into the Department of Pharmacy in the Medical School in 1943. In 1952, the second year of my university training, the Medical School was divided from Peking University and became the independent Beijing Medical College. By that time, significant efforts and investment were made in building the university’s infrastructure and curriculum. Most pharmacy courses such as pharmacognosy, medicinal chemistry and phytochemistry were designed and taught by returnees such as Professors Lin Qishou (林启寿) and Lou Zhicen (楼之岑) who had received educations and advanced degrees in Western countries. Although pharmacognostical study or called “crude drugs” was my major, my training was not limited to that field and I had great chances to attend all basic training in the pharmaceutical sciences. In the pharmacognosy course, Professor Lou Zhicen conveyed knowledge on the origins of medicinal plants and trained us how to classify, distinguish and identify these plants based on their botanical descriptions etc. In the phytochemistry course, Professor Lin Qishou gave a comprehensive introduction and hands-on training on how to extract active ingredients from the plants, how to select proper extraction solvents, how to carry out chemistry studies and determine the structures of the chemicals isolated from the plants etc. These courses provided scientific insights into the herbs and plants and more importantly, explained how these herbal medicines work, in a way different from traditional Chinese medicine.

**My first job and life-long commitment**

This December, we celebrated the 60th anniversary of the China Academy of Chinese Medical Sciences (CACMS). This was also the 60th anniversary of my career. After graduation from the university in 1955, I was assigned to work in the Institute of Chinese Materia Medica of the newly established Academy of Traditional Chinese Medicine under the China Ministry of Health. The academy has been growing and expanding rapidly over last sixty years along with change of its name from the Academy of Traditional Chinese Medicine to the China Academy of Traditional Chinese Medicine and now the China Academy of Chinese Medical Sciences. However, its mission of focusing on professional training, research and continuous exploring and development of Chinese medicines for human healthcare through utilization of evolving sciences and technologies has never changed. It is the academy’s mission and establishment that have provided me with good opportunities to utilize my knowledge, skills and experience while being exposed to new areas of research.

My first research project was on *Lobelia chinensis* (半边莲), an herb commonly prescribed in the traditional Chinese medicine for the treatment of *Schistosomiasis*, a disease caused by *Schistosoma*type parasitic flat worms. In fact, my first publication was on the pharmacognostical study of *Lobelia chinensis*, coauthored with my mentor, Professor Lou Zhicen, in 1958. I completed another study on pharmacognostical evaluation of *Radix Stellariae*(银 柴 胡) before I went for a full-time training program on Chinese medical theory and practice organized by the Ministry of Health for professionals with a Western (modern) medical background between 1959 and 1962. This training further added indepth knowledge on traditional Chinese medicines to my Western medical background.

Over the last sixty years, I have held different responsibilities at the academy, from head of the Chemistry Department (1973–1990) to head of the Artemisinin Research Center of the China Academy of Chinese Medical Sciences (1997–) and various academic assignments from associate professor (1979–1985), professor (1985–), and now chief professor of the China Academy of Chinese Medical Sciences.

**Western and traditional Chinese medicine – a unique combination**

China lacked medical resources in the early 1950s. There were only around twenty thousand physicians and several tens of thousands of traditional Chinese medical practitioners in the country. To fully utilize these limited resources and explore Chinese medicines, the national leadership launched programs in an effort to promote the ideas of enhancing the healthcare services through a “combination of Western and traditional Chinese medicines.” Medical school graduates or young doctors were encouraged to learn traditional Chinese medicines, while experienced traditional Chinese medical practitioners were asked to enrich their knowledge by attending training courses on Western medicine. This unique combination not only proved beneficial to patients but also enabled further exploration and development of Chinese medicine and its application through modern scientific approaches.

The Ministry of Health of China organized a number of full-time training courses in the late 1950s in which scientists with Western medical backgrounds were given opportunities for systemic training on the traditional Chinese medicine. In my two and a half year training program, I learned traditional Chinese medical theory and gained experience from clinical practice. Another training program I attended was on the processing (炮制) of Chinese Materia Medica.

This processing skill is a unique and exclusive pharmaceutical technology and has been widely used for the preparation of Chinese materia medica. The traditional way of processing was developed and summarized from thousands of years of experience in the traditional Chinese medical practices, with a belief that processing could alter the properties and functions of remedies, increase medical potency and reduce toxicity and side effects. In fact, differences in chemical compositions have been detected between herbs treated with different processes. Knowledge of such processing, in combination with the scientific explanation, benefited my work enormously.

**Assignment of the antimalarial research task**

Malaria is a life-threatening epidemic disease. It was, however, effectively treated and controlled by chloroquine and quinolines for a long period of time until the development of drug-resistant malaria *plasmodium*parasites, namely *plasmodium falciparum*, in the late 1960s following the catastrophic failure of a global attempt to eradicate malaria. Resurgence of malaria and rapidly increased mortality posed a significant global challenge, especially in the South East Asian countries. In the 1960s, the Division of Experimental Therapeutics at the Walter Reed Army Institute of Research (WRAIR) in Washington, DC launched programs to search for novel therapies to support the US military presence in South East Asia. US military force involved in the Vietnam War suffered massive casualties due to disability caused by malaria infection. Up to 1972, over 214,000 compounds were screened with no positive outcomes.

In China, the military institutes started confidential antimalarial research in 1964. In 1967, the Chinese leadership set up a group office for malaria control (abbreviated as the National 523 Office) to coordinate nationwide research. Several thousand compounds were screened between 1967 and 1969 but no useful medicines were found.

In 1969, two directors and another member from the National 523 Office visited the Academy of Traditional Chinese Medicine and the Institute of Chinese Materia Medica, seeking help in searching for novel remedies among Chinese medicines.

It was in the middle of the great cultural revolution in China. Almost every institute was impacted and all research projects were stalled. A lot of experienced experts were sidelined. After thoughtful consideration, the academy’s leadership team appointed me to head and build a Project 523 research group at the Institute of Chinese Materia Medica. My task was to search for antimalarial drugs among traditional Chinese medicines.

As a young scientist, I was so overwhelmed and motivated by this trust and responsibility. I also felt huge pressure from the high visibility, priority, challenges as well as the tight schedule of the task. The other challenge was the impact on my family life. By the time I accepted the task, my elder daughter was four years old and my younger daughter was only one. My husband had to be away from home attending a training campus. To focus on research, I left my younger daughter with my parents in Ningbo and sent my elder daughter to a full-time nursery where she had to live with her teacher’s family while I was away from home for the project. This continued for several years. My younger daughter couldn’t recognize me when I visited my parents three years later, and my elder daughter hid behind her teacher when I picked her up upon returning to Beijing after a clinical investigation.

**Traditional Chinese medicine and its relevance to malaria**

Our long journey searching for antimalarial drugs began with collection of relevant information and recipes from traditional Chinese medicine.

Malaria was one of the epidemic diseases with the most comprehensive records in traditional Chinese medical literature, such as *Zhou Li*(周礼), a classical book in ancient China published in the Zhou Dynasty (1046–256 B.C.). Other literature includes the *Inner Canon of the Yellow Emperor*(黄帝内经) published around the time of the Chun Qiu and Qin Dynasties (770–207 B.C.), the *Synopsis of Prescriptions of the Golden Chamber*(金匮要略) published in the Han Dynasty (206 B.C–220 A.D.), the *General Treatise on the Causes and Symptoms of Diseases*(诸病源候论) published in the Sui Dynasty (581–618 A.D.), the Qian Jin Fang or *Prescriptions Worth a Thousand Pieces of Gold*(千金方) and the Wai Tai Mi Yao or *Secret Medical Essentials of a Provincial Governor*(外台密要) published in the Tang Dynasty (618–907 A.D.), a book on malaria (痎疟论疏) published in the Ming Dynasty (1368–1644 A.D.) and the *Malignant Malaria Guide* (瘴疟指南) published in the Qing Dynasty (1644–1911 A.D.), the *Prescription for Universal Relief*(普济方) published in the Ming Dynasty, 1368–1644 A.D.), *etc*.

After thoroughly reviewing the traditional Chinese medical literature and folk recipes and interviewing experienced Chinese medical practitioners, I collected over two thousand herbal, animal and mineral prescriptions within three months after initiation of the project. From these two thousand recipes, I summarized 640 prescriptions in a brochure entitled “Antimalarial Collections of Recipes and Prescriptions” (抗疟单秘验方集). I circulated copies of the brochure to other research groups outside the institute for reference through the national project 523 office in April 1969.

**A handful of qinghao immersed in two liters of water, wring out the juice and drink it all (青蒿一握, 以水二升渍, 绞取汁, 尽服之)**

We started our experiments on dichroine using animal models. The study was soon stopped due to its severe side effects. From May 1969, extracts of over hundred herbs were prepared and tested in rodent malaria, with few promising results found up to June 1971.

After multiple experiments and failures, I re-focused on reviewing the traditional Chinese medical literature. One of the herbs, Qinghao (青蒿) (the Chinese name for the herbs in the *Artemisia*family), showed some effects in inhibiting malaria parasites during initial screening, but the result was inconsistent and not reproducible. I repeatedly read relevant paragraphs in the literature where the use of Qinghao was recorded as relieving malaria symptoms.

In Ge Hong’s *A Handbook of Prescriptions for Emergencies* (肘后备急方), I noticed one sentence “A handful of Qinghao immersed in two liters of water, wring out the juice and drink it all” (青蒿一握, 以水二升渍, 绞取汁, 尽服之) when Qinghao was mentioned for alleviating malaria fevers. Most herbs were typically boiled in water and made into a decoction before taken by the patients.

This unique way of using Qinghao gave me the idea that heating during extraction might have destroyed the active components and the high temperature might need to be avoided in order to preserve the herb’s activity. Ge Hong’s handbook also mentioned “wring out the juice.” This reminded me that the leaf of Qinghao might be one of the main components prescribed. I redesigned experiments in which the stems and leaves of Qinghao were extracted separately at a reduced temperature using water, ethanol and ethyl ether.

**Sample no. 191, a symbolic breakthrough in artemisinin discovery**

We produced extracts from different herbs including Qinghao using the modified process and subsequently tested those ethyl ether, ethanol and aqueous extracts on rodent malaria. On October 4, 1971, we observed that sample number 191 of the Qinghao ethyl ether extract showed 100% effectiveness in inhibiting malaria parasites in rodent malaria. In subsequent experiments, we separated the extracts into a neutral portion and a toxic acidic portion. The neutral portion showed the same effect when tested in malaria-infected monkeys between December 1971 and January 1972.

On March 8, 1972, I reported these findings at the National Project 523 meeting held in Nanjing. This encouraging news evoked overwhelming interest from antimalarial drug research teams across the country.

**“Shen Nong tasted hundred herbs,” why couldn’t we?**

Starting in March 1972, the team started to produce large quantities of Qinghao extract in preparation for clinical studies. Most pharmaceutical workshops were shut down during the great cultural revolution. Without manufacturing support, we had to extract herbs ourselves using household vats etc. The team worked very long hours every day including the weekends. Due to lack of proper equipment and ventilation, and long-term exposure to the organic solvents, some of my team members included myself started to show unhealthy symptoms. This, however, did not stop our efforts.

Some conflicting information was seen from the animal toxicological studies. It was already in the middle of the summer and very limited time was available to us before the malaria epidemic season would end. We would have to delay the study for at least a year if we continued our debate on toxicity. To expedite the safety evaluation, I asked to take the extracts voluntarily. The leaders at the institute approved my request. In July 1972, two other team members and myself took the extracts under close monitoring in the hospital. No side effect was observed in the one-week test window. Following the trial, another five members volunteered in the dose escalation study. This safety evaluation won us precious time and allowed us to start and complete the clinical trial in time.

Traditional Chinese medicine started with a story: “Shen Nong tasted a hundred herbs.” Shen Nong was an ancient Chinese medical practitioner. To understand the efficacy and toxicity of the herbs, he tasted over a hundred herbs himself and recorded all the details, which left us with a lot of precious information. Although Qinghao was prescribed as an herbal medicine for thousands of years, the dose of the active ingredients in these prescriptions was much lower than that in the Qinghao extract we tested. Our desire to get the clinical trial completed and have the medicine for our patients as soon as possible was the real driving force behind our action.

**Success in the first clinical trial**

The first clinical trial on the Qinghao extract was carried out in Hainan province between August and October 1972. We treated a total of twenty-one local and migrant malaria patients, nine infected by *Plasmodium falciparum*, eleven infected by *Plasmodium vivax*and one with mixed malaria infections.

The patients were divided into three groups with different dose regimens. We closely monitored the patients’ body temperature and the changes in the numbers of parasites in their blood specimens. The trial was successful: all patients recovered from the fevers and no malaria parasites were detected after treatment. Nine malaria patients were also successfully treated with the Qinghao extract in Beijing No. 302 hospital.

The results from the first clinical trial in Hainan and Beijing No. 302 hospital were reported in the National Project 523 meeting held in Beijing in November 1972. The success of the first clinical trial and previous evidence observed in rodent malaria and monkey studies steered nationwide antimalarial drug research toward Qinghao.

**Artemisinin and dihydroartemisinin**

We started isolation and purification of neutral Qinghao ethyl ether extract parallel with the clinical trial in 1972. Between April and June of 1972, a few crystals were isolated from the extract. The team finally isolated several crystals using silica gel column chromatography in November 1972, of which one showed effectiveness against malaria. The compound was later named artemisinin, or Qinghaosu (青蒿素) in Chinese.

We carried out a clinical trial of artemisinin between August and October 1973 using artemisinin tablets, which however did not yield the desired results. We examined the tablets returned from the clinical center and found that the tablets were too hard to disintegrate. We resumed the study using artemisinin capsules at the end of September 1973. Since it was already toward the end of the epidemic season, we only treated three patients and all of them recovered after administration of artemisinin capsules.

Dihydroartemisinin was found in September 1973 in an experiment where I tried to derivatize artemisinin for a structural activity relationship evaluation. The carboxyl group related peak disappeared and was replaced by the hydroxyl group related peak in the IR spectrum after a reduction reaction using sodium borohydride. This experimental result was verified in a repeat experiment carried out by team members. In a subsequent test in rodent malaria, we noticed that a significantly reduced dose was sufficient to achieve the same efficacy as artemisinin when dihydroartemisinin was administered.

We completed a series of development activities on the chemistry, pharmacology, pharmacokinetics, stability, and clinical trials on artemisinin and dihydroartemisinin according to regulatory requirements. The China Ministry of Health granted an Artemisinin New Drug Certificate to the Institute of Chinese Materia Medica in 1986 and a Dihydroartemisinin New Drug Certificate in 1992, respectively. Dihydroartemisinin is ten times more potent than artemisinin clinically, again demonstrating the “high efficacy, rapid action and low toxicity” of the drugs in the artemisinin category.

**“Bench to bedside” – collaboration expedited translation from a discovery to a medicine**

We started to determine the chemical structure of artemisinin in December 1972. The first thing we verified was that the compound did not contain nitrogen. This gave us a hint that the compound we found could be a new chemical different from quinolines. The team late confirmed that the compound was a new sesquiterpene lactone containing a peroxy group with a formula of C15H22O5 and a molecular weight of 282.

In the 1970s, instruments and capabilities were very limited at each individual institute. The team at the Institute of Chinese Materia Medica collaborated with the Institute of Materia Medica, China Academy of Medical Sciences, who confirmed the formula of the artemisinin molecule. We started collaboration with the Shanghai Institute of Organic Chemistry and the Institute of Biophysics of the Chinese Academy of Sciences on artemisinin chemical structure analysis in 1974. The stereo structure was finally determined using X-ray crystallography at the Institute of Biophysics. This was one of the first applications reported in China in determining an absolute molecular configuration utilizing the scattering effects of oxygen atoms by X-ray diffraction technique.

No doubt, collaboration and collective efforts expedited the translation from discovery to new medicine. Colleagues from the Academy of Traditional Chinese Medicine, the Shangdong Provincial Institute of Chinese Medicine, the Yunnan Provincial Institute of Materia Medica, the Institute of Biophysics of the Chinese Academy of Sciences, the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences, the Guangzhou University of Chinese Medicine, the Academy of Military Medical Sciences and many other institutes made significant contributions in their respective areas of responsibility during the development process. The leadership team from the National 523 Office played an important role in ensuring logistic support and coordinating nationwide collaboration.

**Qinghao and artemisia annua l.**

The herb Qinghao was frequently mentioned in the traditional Chinese medical literature for various clinical applications besides alleviating malaria symptoms. These applications include relieving itches caused by scabies and scabs, treating malignant sores, killing lice, retaining warmth in joints, improving visual acuity, etc. However, little explanation was given on either the species or effective parts of the plant in the traditional Chinese medical literature.

According to plant taxonomy, there are at least six species in the *Artemisia*family: *Artemisia annua*L., *Artemisia apiacea*Hance, *Artemisia scoparia*Waldst. et kit., *Artemisia capillaries*Thunb., *Artemisia japonica*Thunb., and *Artemisia eriopoda*Bunge. The traditional Chinese medical literature only mentioned Qinghao (the general name of *Artemisia*in Chinese). By the time that our research on artemisinin was being carried out, two Qinghao (*Artemisia*) species were listed in the Chinese Pharmacopoeia and four others were also being prescribed.

We carried out a thorough investigation and confirmed that only *Artemisia annua*L. (sweet wormwood) contains artemisinin. In addition to identification of the right species, we also verified the best regions for growing Qinghao, the best collection season and the officinal part of the plant.

**Our discovery saves patients’ lives while scientific communities recognize our contributions**

I always feel that nothing can be more rewarding than the fact that artemisinin, since its discovery, has saved many malaria patients’ lives. Over the past several decades, more than two hundred million malaria patients have received artemisinin or artemisinin combination therapies.

The scientific community never forgets any significant contribution to healthcare. I appreciate the numerous awards granted by the government and organizations in China. This includes the Award for Progress in Antimalarial Research Achieved by the Project 523 Scientific Team by the China National Science Conference in 1978, the National Scientific Discovery Award for the Antimalarial Drug Qinghaosu by the China Ministry of Science and Technology in 1979, the Invention Award (as the first inventor) by the China National Congress for Science and Technology in 1982, the Award for Young and Middleaged Experts with Outstanding Contributions by the China State Council in 1984, the Highest Honorary Award of the China Academy of Traditional Chinese Medicine in 1992, the Top Ten National Achievements for Progress in Science and Technology award from the China State Scientific and Technological Commission in 1992, the First-rate Award of National Achievements in Science and Technology by the National Award Committee for Advances in Science and Technology in 1992, the National Model Worker award from the China State Council in 1995, the Award for Outstanding Achievement in Traditional Chinese Medicine by the Guangzhou Zhongjing Award Foundation for Traditional Chinese Medicine in 1995, the Outstanding Scientific Achievement Award by the Hong Kong Qiu Shi Science and Technologies Foundation in 1996, the Top Ten Healthcare Achievements in New China by the China Ministry of Health in 1997, the Woman Inventor of the New Century award by the China National Bureau of Intellectual Property in 2002, the Golden Medal of the 14th National Invention Exhibition by the China National Bureau of Intellectual Property in 2003, the Award for Development of Chinese Materia Medica by the Cyrus Chung Ying Tang Foundation in 2009 and the China GlaxoSmithKline Award for Outstanding Achievements in Life Science in 2011.

I sincerely thank the Prince Mahidol Award Foundation (Thailand) for presenting me with the 2003 Prince Mahidol Award, the Albert and Mary Lasker Foundation (USA) for presenting me with the 2011 Lasker-DeBakey Clinical Medical Research Award and the Warren Alpert Foundation and Harvard Medical School (USA) for awarding me the 2015 Warren Alpert Foundation Prize (co-recipient). I am, once again, sincerely grateful to the Nobel Foundation (Sweden) for awarding me the 2015 Nobel Prize in Physiology or Medicine as a co-recipient.

**Research efforts continue**

The discovery of artemisinin inspires us to approach research through the integration of diversified disciplines. Exploring the treasury of traditional Chinese medicine has provided us with a unique path leading to success, while utilizing modern scientific techniques and approaches are no doubt an effective and efficient way of realizing and expediting discoveries.

We are continuing our research efforts on artemisinin to understand its action mechanisms and to prevent or delay the development of artemisinintolerant or -resistant malaria. Expanding the clinical applications of artimisinin is also of interest to public health. We know what it can do, but we need to know why and how it does this, what else it can do and how it can do better …