李英 编
Li Ying

Discovery and Development of New Antimalarial Drug Qinghaosu (ARTEMISININ)

青蒿素研究

本书是40年来中国在抗疟药创新研究方面的文献汇编，比较完整地反映了抗疟新药研究的各个环节，如植物化学、合成化学、分析化学、药理学、毒理学、药代动力学、临床研究等的工作。其中主要的论文是有关青蒿素的发现和发展。由于该项研究的成功，蒿甲醚、青蒿琥酯和蒿甲醚复方已被世界卫生组织列入“基本药品目录”，成为第一线的抗疟药。这是中国开发的新药走向世界的开始。

上海科学技术出版社
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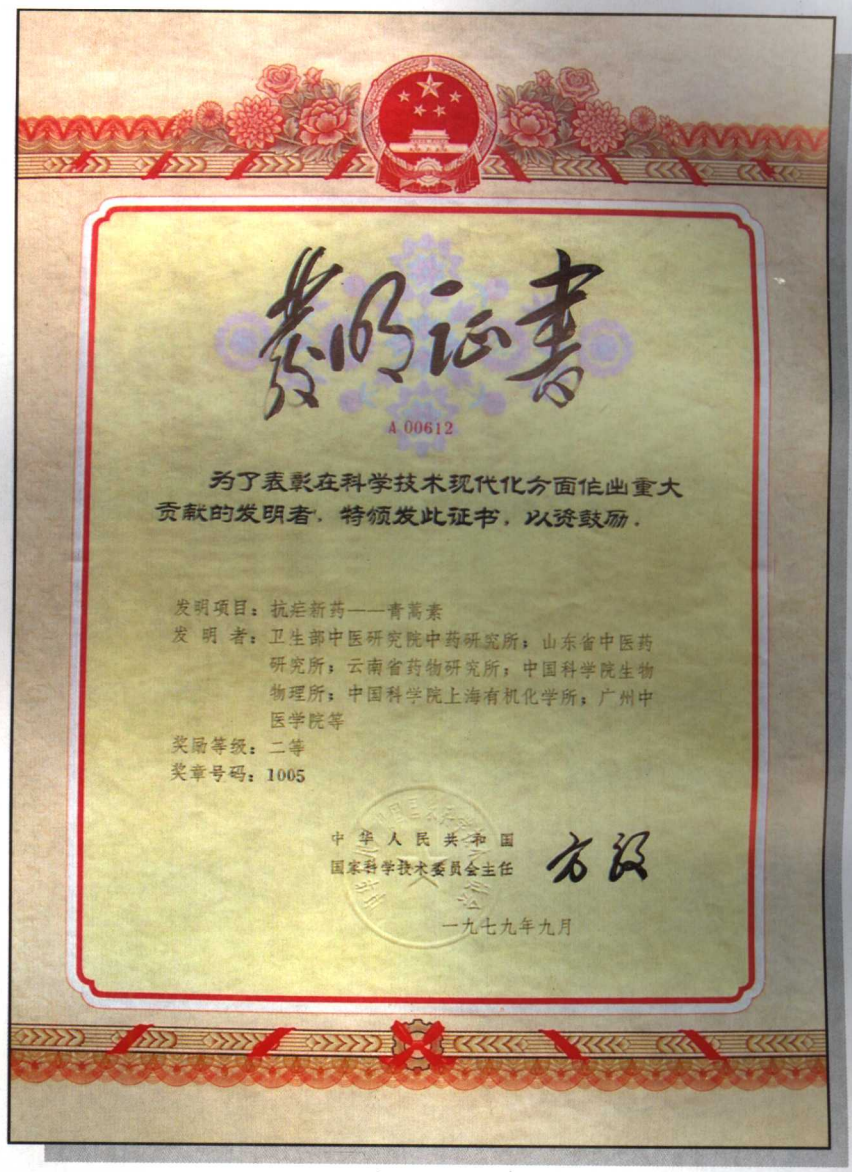
• 成长中的黄花蒿

• *Artemisia annua* L. in growth

• 收获前的黄花蒿

• *Artemisia annua* L. before harvest



发明证书

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为了表彰在科学技术现代化方面作出重大贡献的发明者，特颁发此证书，以资鼓励。

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中华人民共和国
国家科学技术委员会主任 方毅

一九七九年九月

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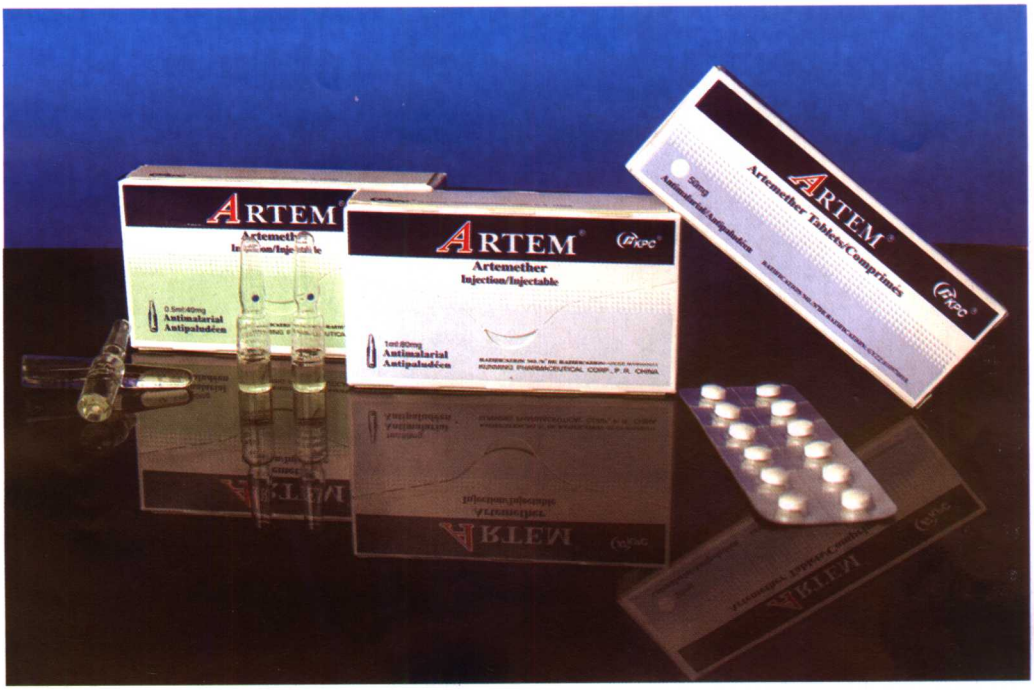
• Certificate of the National Award of Invention of new antimalarial drug Qinghaosu



• 蒿甲醚油针剂和片剂

• Artemether oil injection and tablet


新药 证书 正本

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你单位研制的新药 蒿甲醚注射液，

根据《中华人民共和国药品管理法》，经审查，符合我部颁发的《新药审批办法》的规定，特发此证。

中华人民共和国卫生部

一九八七年 九月五日

• 蒿甲醚新药证书

• Certificate of New Drug Artemether


新药证书 副本

你单位研制的新药 青蒿琥酯 ，

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中华人民共和国卫生部

• 青蒿琥酯新药证书

• Certificate of New Drug Artesunate

• 1991 年由魏振兴(右三)主持的世界上第一个吨级青蒿素的生产厂建成并投产

• Under the leading of Wei Zhen-Xing (right 3), the first worldwide 1000kg-grade Qinghaosu factory went into operation in 1991

• 抗疟新药本芴醇的两个主要发明人：邓蓉仙（中）和滕翕和（右）

• Deng Rong-Xian (middle) and Teng Xie-He (right), two main inventors of new antimalarial drug Benflumetol

• 1981 年 10 月，世界卫生组织疟疾化疗工作组第四次会议在北京召开

• "The Fourth Meeting of the Scientific Working Group, WHO on the Chemotherapy of Malaria " was held in October 1981, Beijing

• 1989 年 4 月，另一次世界卫生组织疟疾化疗工作组会议在北京召开

• Another Meeting of the Scientific Working Group on the Chemotherapy of Malaria was held in April 1989, Beijing

• 2001 年 11 月由世界卫生组织和中国卫生部主持的“抗疟药开发会议”在上海召开

• "The Meeting on Antimalarial Drug Development" organized by WHO and the Ministry of Public Health, China was held in November 2001, Shanghai

• 1998 年 4 月“青蒿素类抗疟药的合理使用讨论会”在法国 Annecy 召开

• "The Symposium on Rational Use of Qinghaosu and Its Derivatives" was held in April 1998, Annecy, France

• 青蒿素及其衍生物研究协作组获得香港求是科技基金会颁发的“杰出科技成果集体奖”（1996 年）。刘旭、李国桥、魏振兴、梁钜忠、李英（从右到左）等作为部分受奖单位代表出席 1997 年求是奖颁奖会

• "China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials" received "QiuShi" Award from Hong Kong QiuShi Foundation for Science and Technology(1996). Liu Xu, Li Guo-Qiao, Wei Zhen-Xing, Liang Ju-Zhong, Li Ying (from right to left) attended the QiuShi Award Ceremony (1977) as representatives of some research units

• 国家科技奖励办公室主任陈传宏代表中国青蒿素及其衍生物研究协作组接受泰国国王普密蓬亲自颁发的2003年度玛希敦亲王医学奖奖章

• On behalf of "China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials", Mr. Chen Chuan-Hong, Director of Office of China Awards for Science and Technology, received the 2003 Prince Mahidol Award in medicine from His Majesty King Bhumibol Adulyadej of Thailand

• 李英（右二）在泰国玛希敦大学作“中国青蒿素研究”报告后的合影

• A group picture taken the in Mahidol University, After Li Ying (right 2) gave a lecture on "Research of Qinghaosu in China"

献 给

参与创制抗疟新药的中国科技工作者与深受疟疾之苦的全球患者

To

All Chinese Participants in the Research of New Antimalarial Drugs
and
All Patients Suffering with Malaria Worldwide

内 容 提 要

本书是40年来我国在抗疟药创新研究的文献汇编，比较完整地反映了抗疟新药研究的各个环节，如植物化学、合成化学、分析化学、药理学、毒理学、药代动力学、临床研究等的工作。其中主要的论文是有关青蒿素的发现和发展。由于该项成功的研究，蒿甲醚、青蒿琥酯和蒿甲醚复方已被世界卫生组织列入“基本药品目录”，成为第一线的抗疟药。这是中国开发的新药走向世界的开始。

本书适合医药院校药学专业的师生、科研院所的研究工作者、药厂和经营单位的人员阅读、参考。

青蒿素研究大事记
A Chronological Record of Artemisinin Research

1967 年 5 月 23 日

我国政府为解决抗药性疟疾的防治问题，成立了全国疟疾防治研究领导小组及它的办事机构“五二三办公室”。先后组织全国 60 多个科研单位和 500 多个研究人员参加“五二三任务”。他们来自各个系统，各部门的研究所、大学、制药厂与医院。五二三任务包括新型的驱避剂、疟疾预防药、治疗药和根治药的研制，针灸治疟，灭蚊药械等。新药研制的策略有对已知的抗疟药结构修饰和对国外新抗疟药的仿制，从中草药中寻找新型的抗疟药和广筛等。

1967/05/23

The Anti-Malaria Drug Project, also known as Project 523, was initiated by the Chinese government in 1967 for prevention and treatment of malaria, especial drug-resistant malaria.

The National Steering Group with an executive office (coded as the “523-Office”) was established. More than 60 institutes and 500 researchers were involved in the search for new insect repellent, tissue schizontocides, blood schizontocides, gametocytocides, acupuncture treatment, and so on. The strategies included in reproduction and structure modification of known antimalarials, massive screening of Traditional Chinese Medicine and other chemicals.

1967 年 6 月～1971 年

中药常山的抗疟有效成分常山乙碱有高于奎宁的杀疟原虫的作用，但同时引起患者剧烈呕吐。改造常山乙碱的化学结构一开始就成为“五二三项目”的研究重点。不少常山乙碱衍生物和类似物被合成、筛选。之后，常山乙碱衍生物（代号 7002）和常咯啉（代号 56）进入临床试验，但未成为理想的抗疟新药。

与此同时，大量的中草药被提取、筛选。

1967/06～1971

Febrifugine, the active principle of Traditional Chinese Medicine *Dichroa febrifuga*, has a higher antimalarial effect than quinine, but is a vomitory. Its structure modification became first key program in early period. A series of derivatives and analogues were synthesized and tested in animal models. Compound 7002 and 56 were selected for clinical trial, but were discontinued due to their unsatisfied result. In the meantime, more than 5 000 samples from Traditional Chinese Medicine were screened in animal models.

1971 年

黄花蒿的乙醚提取物经动物试验证明是抗疟有效部位。

1971

The diethyl ether extract of *Artemisia annua* L. showed antimalarial activity in the animal models.

1972 年 3 月

"全国化学合成药和中草药专业组会议"在南京召开。会上报告从仙鹤草、鹰爪、黄花蒿、陵水暗罗、地耳草、鸦胆子、南天竹中分离出十余种抗疟有效部位或有效单体。

1972/03

"National Meeting on Synthetic Drug and Traditional Chinese Medicine" was held in Nanjing. More than 10 active extracts or principles from *Agrimonia pilosa*, *Artabotrys hexapetalus*, *Artemisia annua*, *Polyalthia nemoralis*, *Hypericum japonicum*, *Brucea javanica* and *Nandina domestica* were reported.

1972 年 8～10 月

黄花蒿的乙醚提取物在海南进行小型的临床试验，它的高效、速效及抢救脑型疟有效使其成为全国抗疟药研究重点。

1972/08～10

A few malaria patients were quickly cured by administration of the diethyl ether extract of *Artemisia annua* L. in Hainan. Its high effect for treatment of severe and uncomplicated malaria made it to be a new key research program.

1973 年

用乙醚提取的黄花蒿粗制剂在山东试用于间日疟，抗疟作用同样超过氯喹，且副作用小。

黄花蒿的抗疟有效单体被分离纯化，是一种白色的针状结晶。由此，开始了对它的化学结构研究。

1973

Some *vivax* malaria patients in Shangdong Province were cured by using the diethyl ether extract of *Artemisia annua* L. with better effect and less side action than quinine.

The active principle of *Artemisia annua* L. was isolated as a colorless needle crystal. Since then, the study of its chemical structure started.

1974 年

提取大量黄花蒿的抗疟有效单体，经药理、毒理试验后，在云南、山东扩大试治恶性疟和间日疟患者。它显示了作用迅速、疗效良好、毒性低，能治愈抗氯喹恶性疟，但复燃率较高。

1974

A great quantity of active principle of *Artemisia annua* L. was extracted. After further pharmacology and toxicity studies, large-scale clinical trials in Yunnan and Shangdong launched. The result demonstrated that it is a new type of antimalarial drug with rapid action, low toxicity and high effect on both drug-sensitive and chloroquine-resistant *falciparum* malaria, however, with higher recrudescence rate.

1975 年

4 月，在四川成都召开“全国五二三中草药专业会议”。组织全国大协作，全面开展黄花蒿有效单体的研究。会上对它的命名“黄花蒿素”、“黄蒿素”或“青蒿素”争论不下（以后被正式命名为青蒿素）。此外，会上报告了鹰爪甲素的过氧化合物结构，这一工作对青蒿素的结构测定有启示作用。几天后，青蒿素被证明确含有过氧基团。

通过光谱数据和化学反应，断定它是一种含有过氧基团的倍半萜内酯。青蒿素用钠硼氢还原所得的反应产物（双氢青蒿素）为以后的青蒿素衍生物制备打下了基础。

成都会议后在全国各地进行了黄花蒿野生资源的调查。溶剂汽油法提取工艺逐步成熟。

1975

“National Meeting on Traditional Chinese Medicine” was held in Chengdu in April. Summary report and further research plan about Traditional Chinese Medicine were made. At the meeting, the choice of names “huanghuahaosu”, “huanghaosu” or “qinghaosu” was in dispute, Afterwards, the active principle of *Artemisia annua* L. was named formally as qinghaosu (artemisinin). The report of structure of Yingzhaosu A being a peroxide accelerated the structure determination of artemisinin. After this meeting, it was quickly proved a peroxide too.

According to the data from spectral analysis, and chemical reactions, artemisinin is a sesquiterpene with a peroxy group. The dihydroartemisinin, reduction product of artemisinin with sodium borohydride, provided possibility for preparation of artemisinin derivatives.

After this meeting, investigation of natural resources of *Artemisia annua* L. started throughout the country. The extract process with petroleum ether was increasingly improved.

1975 年底

青蒿素的分子结构和相对构型用 X 射线晶体衍射法测定。次年，由反常 X 射线晶体衍射法完成了青蒿素绝对构型的测定。青蒿素与已知抗疟药的化学结构完全不同。

End of 1975

The molecular structure of artemisinin and its relative configuration was confirmed by X-ray diffraction. Next year, its absolute configuration was determined by abnormal X-ray diffraction. The structure of artemisinin is quite different from those of known antimalarial drugs.

1975 年 12 月

“全国五二三化学合成药评价与鉴定会议”在上海召开。会上评价了常山乙碱衍生物（代号 7002）、常咯啉（代号 56）、咯萘啶（代号 7351）、脑疟佳、硝喹（代号 CI 679）的临床试验结果。会议也介绍了青蒿素的动物试验和 900 多例的抗疟临床试验结果，效果很好，但它的溶解度小，难于制成针剂以抢救危重患者，而且复燃率高，还需改进。

1975/12

In December, “National Appraisal Meeting for Synthetic Antimalarial Drugs”

held in Shanghai. The clinical results of Febrifugine derivative 7002, Changrolin, Pyronaridine, Nitroquine and Naoyaojia were summarized and evaluated. At this meeting, the pharmacological study of artemisinin and its clinical trial of more than 900 malaria patients were also reported. It has direct parasiticidal action on plasmodium in the erythrocytic stage and powerful therapeutic effect, however, the improvement was necessary to overcome higher recrudescence rate and other difficulties encountered during the recovery of severe patients.

1976 年

2 月，青蒿素的结构改造工作开始。

12 月，制定青蒿素质量标准。

1976

In February, the structure modification of artemisinin launched.

In December, the quality standard of artemisinin was established.

1977 年

4 月，在广西南宁召开的“全国中西医结合防治疟疾药物会议”和 6 月在上海召开的“全国五二三化学合成药会议”上，报告了青蒿素的构效关系和衍生物的设计思路和第一批 20 多个青蒿素衍生物的鼠疟筛选结果，它们的抗疟效果是青蒿素的数倍。

以“青蒿素结构研究协作组”名义，在“科学通报”上发表了第一篇有关青蒿素的论文，公开了青蒿素的化学结构和相对构型。

1977

In April and June, “National Meeting of Integrated Traditional and Western Medicine” and “National Meeting of Synthetic Drugs” held in Nanning and Shanghai respectively. The structure-activity relationship of artemisinin, design of artemisinin derivatives and antimalarial activity of more 20 derivatives were reported. Most derivatives are higher active than artemisinin.

In the name of “Coordinating Research Group for the Structure of artemisinin”, the first chemical paper “A new type of sesquiterpene lactone-artemisinin” was published in Chinese Science Bulletin, it disclosed the structure and relative configuration of artemisinin.

1978 年

蒿甲醚油针剂在海南，青蒿琥酯钠盐水针剂在广西进入临床试验。它们的抗疟效果超过青蒿素，而且对危重疟疾患者的医治更迅速可靠。

11 月，在江苏扬州召开“青蒿素治疗疟疾科研成果鉴定会”，总结了青蒿素的品种资源、化学、药理、制剂、临床试验、生产工艺、质量控制等专题的科研成果。

1978

Clinical trial of artemether oil injection, sodium artesunate aqueous injection carried out in Hainan and Guangxi Province respectively. Their antimalarial effect was proved to be higher, faster and more reliable than artemisinin for treatment of severe malarial