THE DEVELOPMENT OF THE ANTIMALARIAL DRUGS WITH NEW TYPE OF CHEMICAL STRUCTURE - QINGHAOSU AND DIHYDROQINGHAOSU

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Malaria is a hazardous epidemic to human health. As estimated by WHO, some 500 million infections kill up to 2.7 million people each year. So, malaria is one of the key targets selected by WHO. Chloroquine is the first choice among the popular therapeutics, quine, primaquine and chloroquine. There has been an urgent need for new antimalarial drugs due to the problem of chloroquine-resistant strains of *P. falciparum* since 1960s. A large scale screening for antimalarials was carried out at home and abroad at that time, without satisfactory results. *Artemisia annua* L was screened without success.

Our project for developing new antimalarials was set up under the above mentioned situation in 1969. I graduated from the Department of Pharmacy, Beijing Medical College, studied systematically traditional Chinese medicine after graduation, and based on the 'modern medicine learned from traditional Chinese medicine' background, it was my firm belief that traditional Chinese medicine with this long history is a great treasure-house, and efforts should be made to explore its essence. On the basis of collection and analysis of traditional prescriptions, my research group screened over two hundred herbs and three hundred and eighty extracts from them using malarial models of mouse or monkey. I was enlightened by the description, 'a handful of Qinghao immersed with 2 liters of water, get juice and drink it' (Gehoung, 1956). The antimalarial effect of Qinghao was gradually cleared up when temperature, enzymolysis, solvents, species, portions and collecting season of the herb were systematically considered. A new antimalarial was developed in 1971, based on scientific analysis of antimalarial nature of Qinghao with its history of over one thousand years. The new drug won the national award of invention, and brings benefit to the people of the world.

The new compound, isolated from *Artemisia annua* L, is titled Qinghaosu. Its structure established by spectral data, chemical reactions, and x-ray diffraction in Beijing was firstly published in 1977 (Qinghaosu RCRG, 1977). It is a sesquiterpene lactone with a peroxide, and a breakthrough in the antimalarial history chemically and pharmacologically. It provides a partial solution to the international difficulty of antimalarial drug-resistance. The statement that 'antimalarial drugs should be compounds containing N' is defeated by the fact of Qinghaosu's molecular formula is $C_{15}H_{22}O_5$ (Tu, 1981; 1982) (Fig 1). Clinical trials show that Qinghaosu is effective for various types of malaria, especially chloroquine-resistant, primaquine-resistant and some other life-threatening malaria. It is a drug of high efficacy, fast-action and safe.

Pharmacodynamics showed that Qinghaosu had a direct lethal effect on *Plasmodium* (Qinghaosu RCRG, 1979). The main action is targeted at the plasmodial membrane, interfering with mitochondrion functions. The accumulation of autophagic vacuoles in *Plasmodium* was significant after 20 hours of administration, resulting in destruction of the parasite. It was different from the autophagic vacuole containing pigmentogenesis induced by chloroquine. Pharmacokinetics showed that the drug's absorption, distribution, metabolism and excretion were fast. The acute and chronic toxicity tests showed that LD_{50} was 4,223 mg/kg, SD_{50} 89.4 mg/kg and the therapeutic index 47.1. The clinical trials showed the drug was safe and low in side effects.

On behalf of the 4th Conference of Tropical Diseases and Chemotherapy for Malaria sponsored by UNDB, World Bank and WHO, an International, Qinghaosu symposium was held in Beijing in October 1981. My report- 'Chemical studies on Qinghaosu' as the keynote speech, was highly appreciated by the symposium, which considered that 'Qinghaosu was developed as a new antimalarial based on direction for drug synthesis and design'. 'Qinghaosu promotes new international antimalarial development' (Tu, 1981). Qinghaosu and its family of drugs are employed for antimalarial therapy in many countries. Based on our Qinghaosu and Dihydroquinghaosu, new derivatives, various prepa-

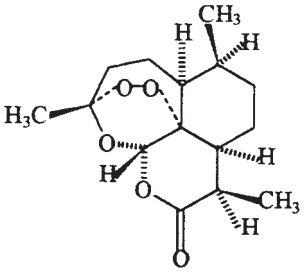

Fig 1–The structure of Qinghaosu.

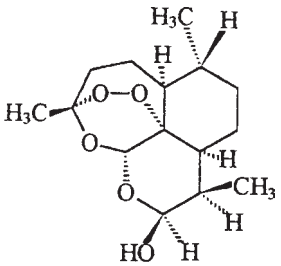

Fig 2–The structure of dihydroqinghaosu.

rations aznd improvement in efficacy have been developed by scholars at home and abroad. It indicates the strong vitality for enriching world medicine contributed by natural compounds originated from traditional Chinese medicine.

Dihydroqinghaosu (Fig 2) is the first generation of derivatives of Qinghaosu. It was derived from Qinghaosu by modifying carbonyl groups into hydroxyl groups in 1973. The significance of it lies in the following: 1) the existence of carbonyl groups was first confirmed before the structure of Qinghaosu was determined; 2) the hydroxyl groups in Dihydroqinghaosu led to the preparation of the second generation of Qinghaosu derivatives, *ie* Artemether, Artesunate in China, and Arteether in USA; 3) compared with Qinghaosu, they are ten times effective, low in malaria recurrence (as low as 1.95%). Additionally, its production process is simple.

Pharmacodynamics studies showed that a small dose of 1 mg/kg of Dihydroqinghaosu could clear up *Plasmodium (P. knowlesi)* in the monkey. At the dosage of 3.16 MKD, for 50%, 90% or total clearance of *Plasmodium*, oral Dihydroquinghaosu was better than intravenous Artesunate. At single dose of 120 mg, for 95% clearance of *Plasmodium*, the required time was 16 hours for oral Dihydroqinghaosu, 16 hours for intravenous infection of Artesunate, 20 hours for intramuscular Artemether, and 28 hours for intravenous Dihydrochlorid-quinine. It indicates the action of Dihydroqinghaosu is fast and effective, even it is oral administration instead of infection. The safety of the drug is also good. The chemotherapeutic indexes (LD_{50}/SD_{50}) are 834.0 for Dihydroqinghaosu, 792.8 for Artesunate and 447.0 for Artemether. Dihydroqinghaosu is regarded as the first choice in the Qinghaosu family. When we compare the Dihydroqinghaosu tablet with positive control of Piperaquine phosphate, the benefits of the drug are clear cut in dose, abatement of fever, clearance of *Plasmodium*, and recurrence rate (Table 1). For fulfilling needs of different sufferers, Dihydroqinghaosu is available in the form of tablet and suppository (convenient for children or patients in coma or vomiting).

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Table 1
Comparison in efficacy between Dihydroqinghaosu tablet and Piperaquine phosphate.

Group	Dose (mg)	Cases	Abatement of fever (hrs)	Clearance of Plasmodium (hrs)	Recurrence rate (%)
Dihydroqinghaosu	360	50	16.3±6.6	64.0±12.0	6.3 (2/32)
	480	50	19.7±13.2	66.5±12.0	0 (0/42)
Piperaquing phosphate	1,500	51	37.3±16.3	104±16.8	55.31 (21/38)