

# The Discovery of New Antimalarial –Qinghaosu(Artemisinin) in China

## The Insiders\*

Since the fact that malarial parasites were resistant to frequently used antimalarials, in Vietnam War which started in 1964, the number of soldiers died of drug-resistant falciparum malaria was much higher than that of casualties from both combating sides. The then Leadership of Vietnam asked for help from China. The authorized “523 Leading Group” (523 领导小组) was inaugurated on May 23<sup>rd</sup> in 1967 which was sponsored by a consortium among the General Logistics Department of the Chinese People’s Liberation Army(中国人民解放军总后勤部), the State Science and Technology Commission of China(国家科学技术委员会), Ministry of Public Health of PRC(中华人民共和国卫生部), Ministry of Chemical Industry of PRC(中华人民共和国化工部), Commission of Science and Technology for National Defence(国防科委), Chinese Academy of Sciences(中国科学院) and General Pharmaceutical Industry Corporation (医药工业总公司). The project was named “523 Project”(523 项目), which was supervised by the “523 Leading Group”(523 领导小组) and was kindly concerned by the late premier Zhou En Lai. Even though it was at the time of “Cultural Revolution”, and normal working routines were severely interfered, the authorized “523 Leading Group” could still mobilize around five hundred scientific workers of different specialities from sixty-some institutions of the whole country, to form a closely related, united, well organized and versatile scientific troupe, which was supported by groups of various disciplines with most advanced equipments at hand.

The main task of “523 Project” was: to seek new antimalarials for the prevention and treatment of drug-resistant falciparum malaria in tropical area. The “General Leading Office of 523 Project” (全国五二三办公室) suggested the screening of new drugs to start from two aspects, one was synthesis of new drugs, and the other was investigation of anti-malarial drugs frequently used in traditional Chinese medicine and folklore medicine. Thus, two cooperative groups of the two aspects were established respectively. The Traditional Chinese Medicine and Folklore Medicine Group(TCMFM Group)(中医中药专业组) was one of the two groups, the main task of this group was attempting to search for the required new antimalarials from the traditional Chinese medicine or folklore medicine. This was the historical background and organization of the scientific troupe leading to the discovery of Qinghaosu (Artemisinin)( Zhang Jianfang, A Detailed Chronological Record of Project 523 and the Discovery and Development of Qinghaosu (Artemisinin), Yangcheng Evening News Publisher, 2006. (Hereafter it is abbreviated as “Zhang Jianfang, “Chronological Record of Project 523”) p.5-11.)

Unlike the discovery of ordinary natural products, the discovery of Qinghaosu is meaningful because it is a new type of antimalarial, its novel chemical structure brings about its advantage of

unique antimalarial efficacy without drug-resistance. In early 70s of last century, it happened that both Chinese and then Yugoslavian scientists had been engaged in the studies of natural products in *Artemisia annua* L. , and discovered the compound with the same molecular formula  $C_{15}H_{22}O_5$  and molecular weight, but the then Yugoslavian scientists gave an incorrect chemical structure to the compound (Jeremic, D., Jokic, A. and Stefanovic, M., New Type of Sesquiterpenen Lactone isolated from *Artemisia annua* L.– Ozonide of Dihydroarteannuin, *presented at the 8<sup>th</sup> Int. Symp on Chemistry of Natural Products*, New Delhi (1972) 222 (Posted by Gong Wai Lihm 江威廉 on <http://panyutiger.blogspot.com/> at the time of May 3, 2008)). Actually, *Artemisia annua* L. (黄花蒿, huanghuahao) is the plant which the Chinese antimalarial herbal drug named Qinghao(青蒿) originates from. Owing at the time of “Cultural Revolution”, Chinese scientists could not get any scientific information published outside China, they knew nothing about what was going on in then Yugoslavia. In 1986, one of the then Yugoslavian scientists visited China, he said, “Even if we gave a correct chemical structure to the compound, we could never develop the compound as an antimalarial”, because they do not have the knowledge of using *Artemisia annua* L. in the treatment of malaria in Yugoslavia. So it is Chinese scientists who not only discovered a new natural product and gave it a correct chemical structure, more important is, based on the experience of traditional Chinese medicine in treatment of malaria, they discovered a new type of antimalarial as well. So we emphasize that the discovery of Qinghaosu (Artemisinin) should not be credited only to the person who first isolated the compound as people ordinarily do for the discovery of natural products. People who are engaged in the investigation and evaluation of the history of discovery of Qinghaosu should not only concern about who is the first person who isolated this natural compound, but also those persons who had made contribution to the elucidation of the chemical structure of the compound and the demonstration of the unique antimalarial efficacy of this antimalarial through clinical trials should also be concerned about.

### **(I) Discovery of the new antimalarial Qinghaosu in China**

In 1969, Institute of Chinese Materia Medica (ICMM), Academy of Traditional Chinese Medicine (ATCM) under Ministry of Public Health(卫生部中医研究院中药研究所) in Beijing was invited by the “ General Leading Office of 523 Project” to join in TCMFM Group . Tu Youyou(屠呦呦) was designated by ICMM under ATCM as the team leader of “523 research team” in Department of Chemistry, and Yu Yagang(余亚纲) was the team member. Tu Youyou began her work at the research of pepper extract, and study on it's anti-malarial action was carried out in Academy of Military Medical Science of Chinese PLA (AMMS)(中国人民解放军军事医学科学院) , but due to its ineffectiveness the work stopped (Zhang Jianfang, “Chronological Record of Project 523”, p.16).

In 1970, Tu Youyou was asked to join in certain personnel investigation and left Yu Yagang alone. In the same year, "General Leading Office of 523 Project" dispatched Gu Guoming (顾国明) of AMMS to ICMM and worked cooperatively with Yu Yagang. They started to collect the prescriptions and single drugs of traditional and folklore medicines used in treatment of malaria. The investigation showed that the most frequently used traditional herbal drugs for treatment of malaria was Qinghao(青蒿). Yu Yagang and Gu Guoming prepared the ethyl alcohol extract from Qinghao, which was available in Beijing drug market and known as the arial part of the plant of "Huanghuahao" (植物黄花蒿, *Artemisia annua* L.), the animal experiment was carried out by scientists in AMMS, the results showed that the inhibition rate for parasites in mice was 60-80% (Zhang Jianfang, "Chronological Record of Project 523", p.16) , and according to an insider it had been as high as 90%. Since Tu Youyou did not work with them, Yu Yagang reported the results to the team leader Tu Youyou and the director of ICMM. Later, Yu Yagang was asked to leave Beijing to join in another project , so Gu Guoming was back to AMMS. This arrangement caused the suspension of Yu Yagang and Gu Guoming's work , which had not been thoroughly studied.

In 1971, Tu Youyou returned to the team, and worked with team member Zhong Yurong (钟裕蓉). Lang Lingfu(郎林福) joined the team, and was responsible for testing inhibition rate for parasites in animals. They gave up the pepper research and started to reproduce Yu Yagang and Gu Guoming's work, but the inhibition rates for parasites in mice of extracts from Qinghao were fluctuating. In comparison with different extraction methods, Tu Youyou got the clue from using of fresh juice of Qinghao, which was described by Ge Hong(葛洪, 281-341A.D.) in his "A Handbook of Prescriptions for Emergencies"(《肘后备急方》), so she modified the extraction procedure at low temperature, when they found the inhibition rate for parasites in mice of ethyl alcohol extract, which was prepared by infusion and concentrated at low temperature, was as high as 95% (Tu Youyou, "qinghao ji qinghaosulei yaowu", Printing House of Chemical Industry, 2009.01 (Hereafter it is abbreviated as Tu Youyou, "qinghao ji qinghaosulei yaowu") , p.35) . Later they found that the neutral portion of the ether extract was even more effective, the inhibition rates for parasites in mice and in monkey were as good as 100%, and the results were reproducible, it was in October ,1971 (Tu Youyou, "qinghao ji qinghaosulei yaowu", "discovery of qinghaosu" and p.34-36) .

In March 1972, Tu Youyou as a representative of ICMM under ATCM, reported the above results at the TCMFM Group meeting held by the "General Leading Office of 523 Project" in Nanjing . The report drew the attention of people who attended the meeting. On knowing the experience from ICMM under ATCM, people in Institute of Drug Research in Yunnan Province (Yunnan IDR)(云南省药物研究

所) and Institute of Traditional Chinese Medicine in Shangdong Province (Shangdong ITCM)(山东省中医药研究所), who also joined in the “523 Project”, tried to get the active ingredient by using their local plant resources respectively.

Between August and October of 1972, after finishing study on preclinical toxicity and oral administration of the ether extract-neutral portion in some healthy volunteer subjects, ICMM carried out the clinical trial of ether extract-neutral portion in 9 falciparum and 12 vivax malaria patients in Changjiang, Hainan (海南昌江), Tu Youyou joined this clinical trial (Tu Youyou, “qinghao ji qinghaosulei yaowu”, p.39-41) . Under the coordination of “General Leading Office of 523 Project”, 302 Hospital of PLA in Beijing also carried out the clinical trial of the ether extract-neutral portion in 9 vivax patients. All together 30 cases (20 cases of vivax and 10 cases of falciparum malaria patients) were observed. In her book, Tu Youyou described all these 30 cases were cured or effective (Tu Youyou “qinghao ji qinghaosulei yaowu” .p.38-39), but according to the original clinical report, among the 9 falciparum malaria patients, 7 of them were effective and 2 of them failed (523 clinical trial group of ICMM under ATCM, Clinical Summary Report of 91<sup>#</sup> (cf Zhang Jianfang, “Chronological Record of Project 523”, p.17 and Note 13).

These good antimalarial results in animal experiments and clinical trials of the ether extract –neutral portion of Qinghao which were achieved by Tu Youyou’s research team, were really an important step leading to the discovery of Qinghaosu. Ni Muyun(倪慕云) joined in Tu Youyou’s team, she designed the pre-column treatment of the ether extract-neutral portion of Qinghao, i.e., mixed the ether extract-neutral portion with polyamide, then percolated with 47% ethyl alcohol. After concentration of this ethyl alcohol solution, it was again extracted by ether, the antimalarial effectiveness of this ether extract was further improved. It was attempted to make further separation by aluminium oxide column chromatography, but failed to get any solid substance.

In December, near the end of 1972(Zhang Jianfang, “Chronological Record of Project 523”, p.18; Institute of Chinese Materia Medica under ATCM, “zhongyao qinghao de kangnue yanjiu”, “preface” ), Zhong Yurong and her assistant Cui Shulian (崔淑莲) used the pre-column treatment developed by Ni Muyun, and considered they had better use silica gel column chromatography instead of aluminium oxide for isolation of neutral substances, and used petroleum and ethyl acetate-petroleum solvent as eluent for gradient elution. The primarily eluated crystal in square-shape was high in content, and was named “crystal I “, the secondly eluated crystal in needle–shape was low in content, and was named “crystal II”, which was followed by another needle-shaped crystal named “crystal III”. After testing their inhibition rates for parasites in mice, “crystal II” was the only substance confirmed as the

antimalarial entity of Qinghao. According to their report written later to the “General Leading Office of 523 Project”, they named this “crystal II” (结晶 II) as “Qinghaosu II”(青蒿素 II). The time of discovery of “crystal II” (or “Qinghaosu II”) by Zhong Yurong was near the end of the year 1972, Tu Youyou was not in Beijing then, and Ni Muyun was the acting team leader.

The experience of traditional Chinese medicine in treatment of malaria leads to the key step taken by Yu Yagang and Gu Guomung. As the second step, based on Yu and Gu’s experiment, Tu Youyou and Zhong Yurong found the neutral portion of the ether extract of Qinghao, and demonstrated its antimalarial effect in treatment of both vivax and falciparum malaria. As the most important third step, based on the purification of the neutral portion of ether extract of Qinghao done by Ni Muyun, Zhong Yurong finally isolated the antimalarial “Qinghaosu II” by using silica gel chromatography. They are all who have made contribution to the discovery of the new antimalarial “Qinghaosu”.

In the 70’s of last century, most people in ICMM knew this story very well. Being a team leader, Tu Youyou never mentioned about the story of discovery of “Qinghaosu II” to outsiders. Outsiders only knew that Tu Youyou was the person who discovered Qinghaosu, because she was the team leader, the main person who discovered the active extract portion from ether extract, the representative of ICMM under ATCM to take part in the nation-wide meetings. Along with the years, as Qinghaosu was more and more well known by people outside China, in interview with reporters inside and outside China, and in her book , Tu Youyou simply claims that “she is the first person who discovered Qinghaosu” (Tu Youyou “qinghao ji qinghaosulei yaowu”, “preface three”), it is she, “who finally and successfully explored the antimalarial entity from traditional Chinese medicine Qinghao” (Tu Youyou “qinghao ji qinghaosulei yaowu”, “brief introduction of author”) ,and it is she, “who isolated the antimalarial entity on November 8<sup>th</sup> of 1972, and named it as Qinghaosu” (Tu Youyou “qinghao ji qinghaosulei yaowu”, “Foreword” ). As a matter of fact, in December near the end of the year 1972, Zhong Yurong and Cui Shulian ( ICMM,ATCM) isolated “Qinghaosu II” from *Artemisia annua* L. growing in Beijing; In April 1973, Luo Zeyuan(罗泽渊) (Yunnan IDR) isolated “Huanghaosu” (黄蒿素) from *A. annua* L. f. *macrocephala* Pamp. growing in Kunming, Yunnan (云南昆明), and also from *A. annua* L. growing in Chongqing, Sichuan(四川重庆); and in November 1973, Weizhenxing (魏振兴,deceased) (Shandong ITCM) isolated “Huanghuahaosu”(黄花蒿素) from *A. annua* L. growing in Taixing,Shandong (山东泰兴) (Zhang Jianfang,“Chronological Record of Project 523”, p.53). Although the isolation of the active ingredient, inhibition of parasites in mice and primary clinical trials were carried out by the three institutions respectively, crystals with different names were all isolated from *Artemisia annua* L., and was the only antimalarial substance in the plant, after the

elucidation of their chemical structure, they were accepted to be the same chemical substance, and was designated “Qinghaosu” (青蒿素) as the official name in Chinese Pharmacopoeia (edited in 2000) after the name of the herbal drug.

Tu Youyou is not the person who first discovered the antimalarial action of Qin hao extract, and not the first person who isolated the antimalarial Qinghaosu either, and these parts of work were not done under her instruction, so it was not only unfair and unreasonable, more over, it was not tally with the historical truth if Tu Youyou is the only person to be credited for.

## **(II) Demonstration of antimalarial effectiveness for Qinghaosu in clinical trials**

Between September and October of 1973, Tu Youyou’s team applied “Qinghaosu II” for the treatment of 8 cases malaria patients in Changjiang, Hainan(海南昌江), but they did not get the expected results. According to their original report, among 5 cases of falciparum malaria treated with “Qinghaosu II” tablets (in total dosage of 4.5g), 1/5 case was effective, 2/5 cases discontinued the treatment because of appearance of premature heart beat, 2/5 cases failed. Among 3 cases of vivax malaria patients treated with “Qinghaosu II “ capsules (in total dosage of 3-3.5g), 2/3 cases were cured, and 1/3 case was effective(Institute of Chinese Materia Medica under ATCM, “zhongyao qinghao de kangnue yanjiu”, p.27). Tu Youyou did not take seriously to this unexpected clinical result, and explained the reason of clinical trial failures in the 5 falciparum patients as was caused by the disintegration problem of the tablets, but did not provide any data for her explanation(Tu Youyou “qinghao ji qinghaosulei yaowu”,p.43). As a matter of fact, the content of “Qinghaosu II” was rather low in *Artemisia annua* L. growing in Beijing, and the “Qinghaosu II” sample used for clinical trails which they separated by using column chromatography was not pure enough, and was mixed with certain amount of “Qinghaosu I”, the team members all knew that. She even did not investigate the relation between the purity of “Qinghaosu II” , the poor cure rate (only 50%), and its side-effect as well. In her book, she avoided to mention about the purity of “Qinghaosu II” and the clinical results of falciparum patients, but simply asserted, “the clinical results of the Qinghaosu capsules in treatment of 3 cases of vivax malaria can fully demonstrate the effectiveness of Qinghaosu — the active ingredient in Qinghao” (Tu Youyou “qinghao ji qinghaosulei yaowu”, p.41).

In May of 1974, scientific workers of Shandong ITCM and Institute of Parasitoses in Shandong Province (Shandong IP,山东省寄生虫病研究所) carried out the treatment of 19 vivax malarial patients by using “Huanghuahaosu” . It was concluded that the efficacy of “Huanghuahaosu” in treatment of vivax malaria was promising, no significant toxicity or adverse effect were observed (Zhang Jianfang,“Chronological Record of Project 523”, p.53) .

In September of 1974, the Yunnan cooperative group of clinical trials (云南临床协作组) intended to carry out the clinical trial of “Huanghaosu” in Fengqing and Yunxian, Yunnan (云南凤庆和云县). Since it was difficult in searching of falciparum malaria patients in these areas, under coordination of the “General Leading Office of 523 Project” and the local Leading Office, Ludongwei (陆东伟) from Yunnan IDR was to be responsible for supplying “Huanghaosu”, and entrusted Li Guoqiao’s (李国桥) research group of Guangzhou University of Traditional Chinese Medicine (Guangzhou UTCM, 广州中医药大学) to carry out the clinical trials in Gengma and Cangyuan, Yunnan (云南耿马和沧源), these were the high edemic areas of falciparum malaria. Li Guoqiao was well experienced in emergent treatment of cerebral malaria. Between October and December of 1974, he worked with the Yunnan cooperative group in treatment of the first 3 falciparum malaria patients, which showed unexpected good result. Li Guoqiao’s group continued the further clinical trial, and all together 18 malarial patients, which included 14 cases of falciparum malaria (3 cases of severe malaria, one of them was pregnant) and 4 cases of vivax malaria, were cured. The efficacy of “Huanghaosu” was even better than Chloroquine, and was characterized by quick onset of action with high efficiency in short term, low toxicity and adverse effect, and without drug-resistance, but the recrudescence rates were high. The efficacy and side-effect of “Huanhaosu” in treatment of drug-resistant falciparum malaria in tropical area was basically confirmed by the said evaluation (Zhang Jianfang, “Chronological Record of Project 523”, p.27-32), this is a new generation of antimalarial which exactly is what all the malaria patients in the world are expecting for.

ICMM under ATCM had been a pioneer in isolation of the antimalarial entity, but in the clinical trials, they only got positive results in 3 cases of vivax malaria and 1 case of falciparum malaria. The characteristic effectiveness of Qinghaosu was eventually confirmed by 19 cases of vivax malaria patients treated with “Huanghuahaosu” prepared by Shandong ITCM and Shandong IP, and 14 cases of falciparum and 4 cases of vivax malaria patients treated with “Huanghaosu” prepared by Yunnan IDR and treatment carried out by Li Guoqiao’s group of Guangzhou UTCM. This was a good example of cooperative research in China that expedited the progress of antimalarial research with high speed.

### **(III) Elucidation of chemical structure of Qinghaosu**

Under the instruction of Professor Lin Qishou (林启寿, deceased) of Beijing Medical College (北京医学院) and Professor Liang Xiaotian (梁晓天, deceased) of ICMM under China Academy of Medical Science (ICMM, CAMS) (中国医学科学院药物研究所), Tu Youyou’s team carried out some experiments such as ultimate analysis, IR, <sup>1</sup>H NMR, MS spectrum, and some chemical reactions of

Qinghaosu isolated, and found that there was no nitrogen atom in its molecule, so it is assumed to be a new type of sesquiterpenoid antimalarial. Owing to having no sufficient experience and technical equipments for elucidation of chemical structure, ICMM under ATCM negotiated with specialists of Shanghai Institute of Organic Chemistry (SIOC), Academia Sinica (AS) (中国科学院上海有机化学研究所), and under the coordination of "Shanghai Leading Office of 523 Project", Professor Zhou Weishan(周维善) of SIOC supervised the research team, Wu Zhaohua(吴照华) and Wu Yulin(吴毓林) were responsible for the research. They consented that ICMM under ATCM could dispatch one person to take part in the work. From February, 1974, ICMM in succession dispatched Ni Muyun, Liu Jingming(刘静明) and Fan Jufen(樊菊芬) to work with the team in SIOC for a short duration. Tu Youyou herself had not taken part in any research work in SIOC. Even for the experiment carried out in SIOC, Professor Liang Xiaotian still contributed much to the work, and gave good advice to SIOC through communication between Tu Youyou and her team member there.

From 1974 to 1975, a series of chemical reactions of Qinghaosu were studied in SIOC, among those, four groups of reactions were valuable, one was demonstration of its **peroxyl group** by means of reacting with sodium iodide to form the colour of iodine, and reducing by triphenyl phosphine; the second one was demonstration of the **lactonyl group** by means of reacting with hydroxyl amine hydrochloride or titration with sodium hydroxide; the third one was the formation of a semiacetal by the reduction of the lactonyl group by sodium borohydride ( $\text{NaBH}_4$ ) with the peroxyl group still kept intact, this product was initially named as "reduced Qinghaosu", after the chemical structure of Qinghaosu was demonstrated, it was then named **dihydroqinghaosu (or dihydroartemisinin)**; and the fourth one was hydrogenation of Qinghaosu by using palladium-calcium carbonate as catalyst to produce the **deoxyqinghaosu (or deoxyartemisinin)**. All these reactions laid the foundation of studies on the relationship between the chemical structure and its effectiveness, and the preparation of its derivatives as well(Liu Jingming, Ni Muyun, Fan Jufen, Tu Youyou ( Institute of Chinese Materia Medica, Academy of Traditional Chinese Medicine Peking), Wu Zhaohua, Wu Yulin, Zhou Weishan (Institute of Organic Chemistry, Academia Sinica, Shanghai), Structure and Reaction of Arteannuin, Acta Chimica Sinica, 1979,37(2):129-143) .

Based on the IR spectrum,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR data, ORD spectrum and chemical reactions of Qinghaosu, scientists of SIOC had deduced certain structural fragments of the molecule. It was interesting, enlightened by the chemical structure of Yingzhaosu A (鹰爪甲素), another new antimalarial entity with a peroxyl group, reported by scientists from ICMM, CAMS (中国医学科学院药物研究所), Wu Zhaohua with Wu Yulin demonstrated the endoperoxyl group in Qinghaosu by means of chemical reactions. However, the peculiarity of the structure made it difficult to ascertain the

linkage of 15 carbon atoms and 5 oxygen atoms in the molecule. ICMM under ATCM then asked the help from Institute of Biophysics (IB), Academia Sinica(AS)(中国科学院生物物理所) in Beijing, Tu Youyou supplied them with qualified crystals of Qinghaosu for analysis, Li Pengfei(李鹏飞, deceased), Liang Li (梁丽) and their colleagues of Institute of Biophysics finally determined the chemical structure and relative configuration of Qinghaosu by means of X-ray single-crystal diffraction, and its absolute configuration was determined by means of anomalous dispersion of Cu-radiation by oxygen atoms (Qinghaosu Research Group of Institute of Biophysics, Crystal Structure and Absolute Configuration of Qinghaosu, Scientia Sinica, 1980,23(3) 380-396,in English), the time was November 30 of 1975(Tu Youyou “qinghao ji qinghaosulei yaowu”, p.44).

The results obtained from the elucidation of the chemical structure of Qinghaosu showed, Qinghaosu is so valuable in the treatment of malaria, first of all, is due to its novel and peculiar structure — a sesquiterpene lactone with no Nitrogen atom, and the endoperoxyl group links with an ethereal-like carbon and oxygen linkage in an order of O – C – O – C – O – C – O – O – C, probably is its antimalarial action site in the molecule. (Li Ying, Yu Pei-Lin, Chen Yi-Xin, Li Liang-Quan, Gai Yuan-Zhu, Wang De-Sheng, Zheng Ya-Ping. Studies on analogs of artemisinin I. The synthesis of ethers, carboxylic esters and carbonates of dihydroartemisinin. Acta Pharmaceutica Sinica, 1981, 16(6): 429-439).

In her book, Tu Youyou claimed that she “reduced Qinghaosu by using  $\text{NaBH}_4$  as a reducer to produce dihydroqinghaosu, and was the first person who created dihydroqinghaosu as early as in 1973, and the carbonyl group of Qinghaosu was demonstrated through dihydroqinghaosu”(Tu Youyou “qinghao ji qinghaosulei yaowu”, p.187). According to the description of a report with the title of “Studies on the antimalarial research of Chinese herbal drug Qinghao” written by one of her team member in November of 1975, they had reduced Qinghaosu by using  $\text{Zn}(\text{BH}_4)_2$ ,  $\text{KBH}_4$  and  $\text{AlLiH}_4$  as reducers, the products all were white crystals, in comparison with Qinghaosu, the carbonyl peak in IR spectrum disappeared and was replaced by an hydroxyl peak, and the hydroxyl group could be acetylated (Institute of Chinese Materia Medica under ATCM, “zhongyao qinghao de kangnue yanjiu”, 1975,11). So actually they had never used  $\text{NaBH}_4$  as reducer, and no further chemical elucidation had been done, and even no name had been given to any of those compounds at the time of the report was written. As a matter of fact, it was Wu Yulin of SIOC who used  $\text{NaBH}_4$  as reducer and got the said “reduced Qinghaosu” in 1975, and studied on its chemical structure as well. The chemical structure of “reduced Qinghaosu” was established after the successful elucidation of the chemical structure of Qinghaosu in 1975, and then was named as “dihydroqinghaosu” (or

dihydroartemisinin). So nothing could prove that Tu Youyou was the first person who created dihydroartemisinin in 1973.

#### **(IV) The early publication of papers concerning the studies on structure and configuration of Qinghaosu**

The early publication of papers concerning the studies on structure and configuration of Qinghaosu were as follows:

The first paper was "**A New Type of Sesquiterpene Lactone-Qinghaosu**"(in Chinese)

Cooperative Group of Qinghaosu Structural Research, A New Type of Sesquiterpene Lactone—Qinghaosu, Chinese Science Bulletin, 1977, 22(3)142) (青蒿素结构研究协作组, 一种新型的倍半萜内酯—青蒿素,科学通报, 1977, 22(3)142)

The paper was prepared by some person of ICMM by putting together all the research results of above mentioned Institutions. The publication of this paper was approved by the Ministry of Public Health of PRC, but for the sake of security, it was not allowed to reveal its anti-malarial action.

The second paper was "**Structure and Reaction of Arteannuin**" ( in Chinese, with English abstract)

Liu Jingming, Ni Muyun, Fan Jufen, Tu Youyou (Institute of Chinese Materia Medica, Academy of Traditional Chinese Medicine Peking), Wu Zhaohua , Wu Yulin , Zhou Weishan (Institute of Organic Chemistry, Academia Sinica, Shanghai), Structure and Reaction of Arteannuin, Acta Chimica Sinica, 1979,37(2):129-143 (刘静明、倪慕云、樊菊芬、屠呦呦(北京中医研究院中药研究所), 吴照华、吴毓林、周维善(中国科学院, 上海有机化学研究所), 青蒿素(Arteannuin)的结构和反应, 1979,37(2):129-143)

This paper was written by Professor Zhou Weishan.

(Note: In the reference of her book, Tu Youyou had deleted the names of Fan Jufen, Wu Zhaohua, Wu Yulin, Zhou Weishan, and left the names of Liu Jingming, Ni Muyun and Tu Youyou (Tu Youyou, "qinghao ji qinghaosulei yaowu", p.144)

The third paper was "**Crystal Structure and Absolute Configuration of Qinghaosu**"(in Chinese and English versions)

Qinghaosu Research Group of Institute of Biophysic, Crystal Structure and Absolute Configuration of Qinghaosu, *Scientia Sinica*, 1980, 23(3) 380-396 (in English)

中科院生物物理所抗疟药青蒿素协作组, 青蒿素晶体结构及其绝对构型, *中国科学*, 1979, (11): 1114-1128 (in Chinese)

The studies on relative and absolute configuration of Qinghaosu were carried out and finalized in the Institute of Biophysics, but some of the details had already been introduced in the first paper and cited in the second paper, when this paper was waiting to be published.

The fourth paper was **“Chemical Studies on Qinghaosu (Artemisinin)”** ( in English)

China cooperative Research Group on Qinghaosu and Its Derivatives as Antimalrials\*, *Chemical Studies on Qinghaosu (Artemisinin)*, *Journal of Traditional Chinese Medicine*, 1982,2(1):3-8.

\* The main research units:1.Institute of Chinese Materia Medica, Academy of Traditional Chinese Medicine; 2.Shanghai Institute of Organic Chemistry and Institute of Biophysics, Chinese Academy of Sciences.

(Note: In the reference of her book, Tu Youyou deleted the names of the main research units, and replaced with her own name as “Tu Youyou” or “屠呦呦” (Tu Youyou “qinghao ji qinghaosulei yaowu” p.69, p.140 and p.190)

In that period of time in China, Chinese scientists had to avoid putting their own names in their published paper, because it was considered as a desire for personal fame and gain, so at that time, authors who published their papers mostly used the names of the Institutions where they worked for. From 1978, people were again allowed to sign their names on the papers. But since too many people from different Institutions had taken part in the research work of Qinghaosu, so some important published papers relating to Qinghaosu were still in the name of cooperative group. Tu Youyou might have taken part in some of the work mentioned above, but certainly, she was not the only person who had done all the research work of any of the paper mentioned above.

In reviewing the history of discovery of the new antimalarial —Qinghaosu in China, people could clearly realize that not a single person or institution could fulfill the whole process of those research work mentioned above, why only one single person should be credited for? The fact was that Chinese scientists of various disciplines took part in the research work and made their own contributions at different stages like in a scientific research relay race, and finally led to the discovery of the new antimalarial Qinghaosu (Artemisinin) — an historical pioneer work in last century.

**\* This paper was written by insiders, as an important part of their investigation of the oral history relating to the discovery of the new antimalarial —Qinghaosu in China . Since most of the scientists who had joined in the research work of Qinghaosu have retired and are residing inside and outside China separately, or passed away, the writers hope that they can gain access to some of the original experimental records or related document for reference, but obstacles still exist. After almost 40 years, some insiders failed to remember things in details, some of them do not want to be disturbed. So we anxiously hope that any person in the know will help us to make this paper more tally with the historical truth.**