



**HAL**  
open science

# The Vietnamese pharmaceutical expertise in the era of drug globalization: the case of artemisinin

Annick Guénel

► **To cite this version:**

Annick Guénel. The Vietnamese pharmaceutical expertise in the era of drug globalization: the case of artemisinin. 14th International Conference on the History of Science in East Asia, Jul 2015, Paris, France. halshs-03284414

**HAL Id: halshs-03284414**

**<https://shs.hal.science/halshs-03284414>**

Submitted on 12 Jul 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# The Vietnamese pharmaceutical expertise in the era of drug globalization: the case of artemisinin

Annick Guénel

At the 2011 International Artemisinin Conference in Hanoi, the Vietnamese Vice-Minister of Health pointed out the role played by the country in the production and supply of antimalarial drugs. Artemisinin-based therapy has gained widespread use since its recommendation for the national malaria programs of endemic countries by the WHO in the early 2000s. Vietnam is now the world's second largest producer of artemisinin, a plant extract drawn from *Artemisia annua*, or annual sweet wormwood, which Nguyễn Văn Đán, former director at the Institute of Materia Medica in Hanoi, hailed as “the first international scientific and industrial success for the country”.

Despite this statement, the pioneering work of a Chinese team responsible for the discovery of artemisinin antimalarial properties is fully recognized. The discovery resulted from a vast project launched in the midst of the US-Vietnam war, called project 523, for the day it was announced, May 23 1967. According to retrospective reports, it followed an initial appeal for help from Hô Chi Minh to Zhou En Lai.<sup>1</sup> We have no document on the Vietnamese leader's personal role. But in any event, around that year, first cases of *P. falciparum* resistance to chloroquin were detected on the famous Hô Chi Minh trail, which was actually a devastating issue for the North Vietnamese Army.<sup>2</sup> The Chinese provided substantial aid with combinations of existing drugs that they developed at this time, drugs called V1, V2 and V3 by the Vietnamese doctors.<sup>3</sup>

The research on a new effective drug was a long and laborious process, as it went through a systematic screening of medicinal plants and the extraction of the active component of *Artemisia* whose antimalarial effects could not be demonstrated until 1972. Sino-Vietnamese relationships were already deteriorating, while Chinese scientists, in the course of the

---

1 Kenneth J. Arrow, Claire Panosian and Hellen Gelband, eds., *Saving lives, buying times : Economies of malaria drugs in an age of resistance*, The National Academies Press, 2004, p. 133, [http://books.nap.edu/catalog.php?record\\_id=11017](http://books.nap.edu/catalog.php?record_id=11017); Richard J Maude, Charles J Woodrow, and Lisa J White, *Artemisinin Antimalarials: Preserving the “Magic Bullet”*, *Drug Dev Res.* 2010 February; 71(1): 12–19 ; Weina PJ. *Artemisinins from folklore to modern medicine—transforming an herbal extract to life-saving drugs.* *Parasitologia.* 2008;50:25–29.

<sup>2</sup> Interview with Dr Phạm Huy Tiến who was head of a medical team in the Nghê An province in 1967, October 2012.

<sup>3</sup> The drugs were in the form of tablets (Viên, in Vietnamese). Pyrimethamine is a component of V1 and V2, while V3 contains piperazine.

determination of the molecular structure of artemisinin, developed derivatives more stable and effective than the natural product. Ironically, these artemisinin-based antimalarial drugs were first used by the Chinese army during the Sino-Vietnamese War in 1979.<sup>4</sup>

How, less a decade after this final breaking-off, the Vietnamese developed their own artemisinin production technology, and how the rise of artemisinin globalization has brought new objectives and new challenges for the country, is the story I'm telling here.

A large part of my data is based on interviews with scientists. I have also used some reports and articles, most of them published after 1990. Before this date the publications dealing with the ongoing Vietnamese scientific work on *Artemisia annua* and artemisinin are rare or not yet available. But I do not rule out that scientist' notebooks or other archival records will be accessible in the near future.

First, I give a brief overview of the malaria situation in the years following the Vietnam war.

### Malaria epidemiology and control in the 1980s

After the reunification of Vietnam in 1975, the control of malaria was one of the biggest challenges for the health authorities due to the accumulation of unfavourable factors. There were not only intense population movements - notably people having lost their immunity to malaria who went back to their villages - but also environmental changes. The main vectors were or had become exophilic, reducing the effectiveness of DDT spraying. Socio-economic problems were very hard to solve too: the South was nearly deprived of malaria specialized staff and equipment, while the Northern teams had been disorganized. Last but not least, in the South, the chloroquin resistance, documented in NhaTrang, Central Vietnam, as soon as 1965, had become widespread and *falciparum* malaria was predominant.<sup>5</sup> Resistance to chloroquin was also growing in the North, while some areas which had reached a near malaria-eradication state in the 1960s, saw a new vector proliferation because of the discontinuation of DDT. In addition, malaria was increasingly resistant both to quinine, the most available alternative drug and to newly developed Western antimalarials, such as

---

<sup>4</sup>"Ancient Chinese anti-fever cure becomes panacea for malaria. An interview with Zhou Yiqing", *Bulletin of the World Health Organization*, <http://www.who.int.bulletin/volumes/87/10/09-051009/en/index.html>

<sup>5</sup> It is now fully accepted that drug-resistant malaria was on the rise in Southeast Asia before the 1960s, see Helen Power, "Drug-resistant malaria: a global problem and the Thai response", in Andrew Cunningham and Bridie Andrews, *Western Medicine as contested knowledge*, Manchester University Press, 1997, pp. 262-286. As soon as 1965, US troops stationed in Central Vietnam experienced chloroquin-resistance

Fansidar<sup>6</sup>

With the development of new economic areas encouraged by the government, population migration principally to the south did not stop, and the situation worsened beginning in the early 1980s. It was at that time that the WHO operated a shift in malaria control strategy, abandoning its eradication program to promote an integrated approach based on primary health care, an approach that the Vietnamese health authorities tried to adapt to the country's situation, under the technical guidance of the National Institute of Malariology. While the systematic DDT spraying of houses was progressively abandoned, especially since the Soviet Union stopped supplying insecticide, more emphasis had to be given, to early diagnosis and treatment. A major point at issue was the crucial lack of cheap, effective drugs.

#### Artemisia annua, artemisinin...

In mid-1980, the slogan coming from the National Institute of Malariology under the Communist party auspices was "to promote technical innovations". One of the main incentives was to explore the potential drug production from the country natural resources. In this vein, an official research program on *Artemisia annua* was launched, with the collaboration of two other Institutes: the Institute of Materia Medica<sup>7</sup> and the Institute of Science and Technology, both located in Hanoi<sup>8</sup>

What were the extent and sources of the Vietnamese scientists' knowledge about the *Artemisia annua* species and the Chinese drug at this time? Plants of the genus *Artemisia* which grow wild in the north of the country were probably known for a long time. The variability of given names suggests that there was some confusion between the different species. Thanh hao hoa vàng (or simply Thanh hao) is now the most commonly used name for *A. a.* in scientific reports. As the plant was used for the treatment of fevers for a couple of millennia in China, it could be assumed that it was also known to Vietnamese traditional practitioners, due to the medical exchanges in the past between the two countries.<sup>9</sup>

---

<sup>6</sup> Vu Thi Phan, *Epidémiologie du paludisme et lutte antipaludique au Vietnam*, Hanoi, Editions Médicales Vietnam, 1998

<sup>7</sup> The IMM is one of the institutions which had been created in North Vietnam in the post-Independence period, working for the integration of traditional and modern medicine. Its research mission was reinforced in 1981.

<sup>8</sup> In Vietnamese: "phát huy sáng kiến cải tiến kỹ thuật". In *Lịch sử Viện sốt rét ký sinh trùng và côn trùng (1957-1997)* [Histoire de l'Institut de malariologie, de parasitologie et d'entomologie], Nhà Xuất Bản Chính Trị Quốc gia, Hà Nội, 1998, p. 219.

<sup>9</sup> In some articles, there are references to Tuê Tinh and Lan Ong's writings, the two most ancient medical practitioners in Vietnam, to claim a several century old knowledge. of Vu Thi Phan, "L'artémisinine et l'artésunate dans le traitement du paludisme au Vietnam (1984-1999)", *Thérapeutique*, 2001, Manuscrit n°2252, 86-88 ; Nguyen Duy Sy et al., "Treatment of malaria in Vietnam with oral artemisinin", *Am. J. Trop. Med. Hyg.*, 1993, 398-402.

Nevertheless, in the early 1980s it seems that there were few available scientific documents in Vietnam concerning the plant's ecology, its botanical and pharmaceutical characteristics, or other things. Pr Lê Kim Biên, has been quoted by one of my informants, as the rare, if not the only, Vietnamese botanist to have acquired an useful knowledge of the plant, most likely through direct contacts with Chinese specialists.

The Institute of Materia Medica's first mission was to carry out an inventory of wild Artemisia resources in the country and to collect documentation. Thus, it was confirmed that the plant distribution area was relatively wide, covering five northeastern provinces, close to the Chinese border.<sup>10</sup> The next studies were conducted abroad : they started in 1985, a time of a close scientific collaboration with the Soviet bloc countries. Phạm Gia Điền, then a young chemist, was sent to the Academy of Science of Bulgaria where he worked for 4 years.

First, in collaboration with Pr Ilia Ognianov, he developed an extraction process of artemisinin from Artemisia leaf samples harvested both in Lang Son province, and in Bulgaria. Then he experimented the process at the pilot stage, which produced promising results with plants from Vietnam (200g artemisinin from 70kg Artemisia dry leaves). The synthesis of two derivatives, Artesunat and Arthemether, was also performed in Bulgaria. The two chemists registered a patent for the artemisinin extraction process with the Bulgarian Intellectual Property Office in 1987. One year later, Điền defended his thesis written in Bulgarian, entitled "Comparative chemical study of the Artemisia annua plants native to Bulgaria and Vietnam". According to the agreement with the Academy of Science in Bulgaria, the work's results could not be published for many years (as indicated on the cover of the thesis).

The cooperation with Bulgaria did not stop immediately and some chemistry students were sent there for training. But the next steps were carried out in Vietnam, where Pr Điền first created a special Unit inside the Institute for the Chemistry of Natural Products, and developed a system of large scale production. Since the early 1990s, due the very concerning malaria situation, and under the government pressure, artemisinin production was accelerated . The extraction technology was first transferred to public scientific services and State pharmaceutical companies in central and northern provinces where malaria epidemics were breaking out. The first Artemisia plantations were also created in the North. According to Pr Điền, in 1992, 3 tons of artemisinin were produced, a quantity judged sufficient for the country's needs.

---

<sup>10</sup> Cao Bang, Lang Son, Thai Nguyen, Bac Giang and Quang Ninh provinces.

### Clinical trials and implementation of artemisinin as a first line therapy in Vietnam

Nevertheless, it would take another few years before the clinical trials of drugs prepared from the Vietnamese artemisinin raw material and their mode of administration produced really satisfactory results.<sup>11</sup> It should be noted that in China the clinical trials of artemisinin and derivatives to evaluate toxicity, mode of administration, dosage, resistance, interaction with other drugs, and so on, lasted at least until the early 1990s before studies for international registration began. Interestingly, several trials of made in China artemisinin were even conducted in the Cho Quan hospital at Ho Chi Minh-city from 1989 on. This was due to the initiative of Dr Keith Arnold, the first Westerner introduced to the Chinese work, and to his personal relationships with Pr Tran Tinh Hien, head of malaria service at the hospital.<sup>12</sup>

Despite the lack of official cooperation with China, the clinical trials of the artemisinin based drugs made in Vietnam probably benefited from these experiments. In the 1990s, the scientists of the National Institute of Malariology who supervised the trials had also a better access to the scientific literature than before and received advice from WHO consultants and other foreign institutions. Besides the effectiveness of locally produced drugs, the success of the national malaria program also required an adequate health system, so that the population living in endemic areas could have rapid access to these drugs as a first line therapy.

Combined with preventive measures, especially insecticide impregnated bednets, the mass use of Artemisinin in some regions started in 1993. From this date, malaria morbidity and mortality rates did not always fall in a linear fashion. They were slower in the South than in the North. Nonetheless, there was a global rather rapid decline before the end of the century. For example, between 1991 and 1997, the morbidity rate decrease was nearly 60%, and the mortality 97%. Although malaria has not completely disappeared from Vietnam, this trend has continued in the years after 2000.<sup>13</sup>

---

<sup>11</sup> Nguyen Tang Am, Le paludisme au Viet-Nam. Environnement, prévention et traitement, *Bull. Soc. Path. Exo.*, 1993, 86, 494-499 ; Nguyen Duy Sy and *al.*, Treatment of malaria in Vietnam with oral artemisin, *Am. J. Trop. Med. Hyg.*, 1993, 48 (3), 398-402; Tran Tinh Hien, An overview of the clinical use of artemisinin and its derivatives in the treatment of falciparum malaria in Viet Nam, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, 36 (Suppl. 1), 7-8; M. Morillon, D. Baudon, Bui Dai, Les paludismes Au Viet-Nam en 1996. Brève synthèse des connaissances épidémiologiques, *Med. Trop.*, 1996, 56, 197-200 ;

<sup>12</sup> Keith Arnold, Tran Tinh Hien et al., A randomized comparative study of artemisinine (qinghaosu) suppositories and oral quinine in acute falciparum malaria, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1990, 84, 499-502.

<sup>13</sup> Vu Thi Phan, L'artémisinine et l'artésunate dans le traitement du paludisme au Vietnam (1984-1999), *Bull. Soc. Path. Exo.*, 2002, 95 (2), 86-88; Le Q. Hung et al., Control of malaria: a successful experience from Viet Nam, *Bulletin of the WHO*, 2002, 80 (8), 660-666.

## The artemisinin industry

Due to this success, only a small proportion of the artemisinin produced in Vietnam is designed to meet national needs. But other outlets have been easily found thanks to the globalization of the drug. According to Pr Dien, as early as 1994, excess production allowed exports to the neighboring countries. Furthermore, as Vietnam has entered the Doi Moi era since 1986, artemisinin extraction technology was rapidly transferred to private or joint-venture pharmaceutical companies, or even not pharmaceutical ones. A 2007 report estimated the number of extractor/producer units in Vietnam at 20, but it is difficult to know the present situation, this number could have been reduced, due to the growth of large companies.

All the large companies are concentrated in the north, because of the higher artemisinin content of the plant growing in the north than in the south where there were some plantation trials. Among the biggest companies is Mediplantex whose head office is located in Hanoi and which had 2 factories. Mediplantex originated as a State Company founded in 1971, and was transformed in a joint-stock company in 2004. It produces various artemisinin-combined drugs, as well as many other medicines including medicinal plants, or else cosmetics. A small part of its artemisinin-combined drugs is for the national use, while the biggest part is exported to Asian countries, Cambodia and Burma, as well as to Papua New Guinea. It also exports artemisinin raw material to India where the drug is formulated.

Presently, the biggest company is a private company, created in 1999, called Sao Kim Pharma. It originates from the first Artemisia plantation established to provide the Chemistry Institute when Pr Dien worked on the industrial development of artemisinin production. Now the company owns several plantations. The most recent one associated with a production plant, is located in the Hanoi industrial area, Mê Linh. The company's artemisinin production is exclusively for export and remains its main activity. 10 to 20 tons per year of raw material are produced in its extraction factories, 99% of which exported to India and some European countries (Germany, Belgium, Italy). However, the company also produces several formulated artemisinin-based drugs : its present flagship product being Co-Lutem (Arthemether + Lumefantrin), which is exported to Cambodia, Laos as well as to Nigeria.

To-day, Sao Kim is the only Vietnamese company eligible for the WHO pre-qualification. This pre-qualification allows that essential medicines are procured using international funds

(the Global Fund for TAM). It is a rather complex procedure, including not only pharmacological and therapeutical, but also economic criteria. Despite its high artemisinin production capacity, and the high content of raw material from *Artemisia* cultivated in the country (higher than in China, according to Vietnamese scientists), pharmaceutical companies face stiff competition to export Artemisinin-combined drugs, the only antimalarials now recommended by the WHO. According to company managers and to some officials, the few investment to improve technology and the lack of foreign aid do not allow undertakings to charge competitive prices on the market, especially the largest one, the African market.

In the 1980s-1990s, Vietnam succeeded to produce low price drugs aimed to their national control program so that the disease has decreased dramatically. They adopted a pragmatic approach, mobilizing their national scientific institutions, while using support of their political allies then. With the globalization of the drugs, new issues have appeared. It is a new challenge for Vietnam which put globalization at the center of its policy agenda.