East meets West: how China almost cured malaria

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With the isolation of quinine from Cinchona in 1820, an ancient herbal cure was transformed into a chemical drug. This was the inspiration for a new scientific discipline – ethnopharmacology – as Western scientists began to reinvent traditional herbal cures by extracting their active principles to make new and profitable drugs. The Chinese government may claim many such success stories as their own, but such triumphant narratives only reveal part of the story. The draw-out hunt for the active principle of another anti-malarial herb, changshan, or Dichroa febrifuga, offers a more nuanced narrative that captures the complex interplay between traditional Chinese and Western medicine.

Mao’s treasure house

In the hot, dry, summer of 1941, malaria broke out at a cotton mill on China’s south coast. A 35-year old doctor, Zhang Changshao, chose 13 feverish workers to be guinea pigs in an experiment [1].

He pricked each patient’s finger with a needle and squeezed a drop of blood onto a glass microscope slide. He pressed the edge of another slide against the drop and smeared the blood into a thin, comet-shaped film that he stained with a mix of methylene blue and eosin. The mix, called Giemsa’s stain after its German inventor, dyed the malaria parasites purple, revealing them under the microscope.

The mill workers were infected with Plasmodium vivax, a type of malaria that does not kill but drives the patient from hot to cold and back again, and then subsides only to strike a second time after a month or a year. Then, as now, P. vivax malaria can be cured with quinine. But China was short of the drug because the ongoing war with Japan had cut off supplies.

Zhang was therefore trying something completely different on the 13 patients: an ancient Chinese fever remedy called changshan made from a Chinese hydrangea. He drew blood from each patient four times a day: at 8 a.m., midday, 4 p.m. and 8 p.m. The blood smears began to turn negative and the fever gradually subsided. In fact, the changshan cases recovered as well as another group of patients who were dosed with quinine. A mere herb, crudely concocted according to an ancient recipe, seemed to be as effective as the established quinine treatment [2].

Since then, such research has been cast in an intensely nationalist light. ‘China’s medicine and pharmacology is a great treasure house and should be diligently explored and improved upon’, wrote Chairman Mao Zedong in 1958 [3]. Today, exactly 50 years on, the Chinese government continues to exploit traditional Chinese medicine for its nationalist propaganda value, claiming that the integration of traditional and Western medicine is a uniquely Chinese policy born of Mao’s vision.

In the 1950s, Mao hijacked nationalist rhetoric, a rhetoric that dated at least to the early twentieth century, to promote Chinese medicine [4]. Mao’s views still dominate Chinese health policy in the national network of traditional medicine hospitals and research institutes and, for example, in article 138 of Hong Kong’s Basic Law enacted after the British handover that calls on the Hong Kong government to ‘...formulate policies to develop Western and traditional Chinese medicine’ [5].

Mao’s medical policies are also credited with the discovery of the blockbuster antimalarial drug qinghaosu, or artemisinin, isolated from a Chinese herbal medicine in the 1970s [6]. ‘This breakthrough in malaria research is one of the results of China’s integration of medical and pharmacological heritage with Western Medicine’, wrote a Chinese journalist in the propaganda magazine China Reconstructs in 1979 [7]. While certainly not the only Chinese view today [8], it is not uncommon to hear ancient Chinese heritage explicitly associated with modern drugs like qinghaosu. In 2003, for example, prominent scientists Ying Li and Yu-Lin Wu wrote of the ‘over four millennium story behind qinghaosu’ [9].

Such claims brush aside the complex nature of such discoveries and the contributions of individual scientists. To get a more nuanced picture of the interplay between traditional and Western medicine, it is worth taking a closer look at the intellectual origins of Zhang Changshao’s anti-malarial discovery.

Active principles

In 1820, two Parisian pharmacists, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou, extracted the active principle quinine from the bark of the Cinchona tree that had been the standard cure for malaria in Europe since the seventeenth century. It was not the first active principle to be isolated, but because of Pelletier and Caventou’s determined efforts to promote its use in patients, it became the prototype for an entire scientific discipline, what is now known as ethnopharmacology. Western science reinvented old herbal cures for profit by extracting their active principles to use as drugs [10].

Zhang’s work was born out of this tradition. The first Western description of changshan and its properties appeared in Flora Cochinchinensis, a book published in 1790 by the Portuguese Jesuit João de Loureiro (1717–
He gave it the Linnean name *Dichroa febrifuga* (Figure 1) and recorded both its febrifugal and emetic properties: ‘it ... cures quotidian, tertian, and quartan fevers; if taken in the crude state it usually causes vomiting, but if slowly stewed in wine until the latter has evaporated, it purges the bowels and removes obstructions of the viscera’ [12].

In a monograph on *D. febrifuga*, published in 1862 [13], a French army doctor, Monsieur Weber, gave a more detailed account of the herb. ‘The indigenous people of Cochinchina [Southern Vietnam], who don’t yet know about quinine sulphate, use many different remedies to cure intermittent fevers [malaria]’, he wrote. ‘[B]ut the plant to which they attribute the most marked febrifugal properties and that they use most often is a shrub cultivated in their gardens that they call *thuong son* [the Vietnamese pronunciation of *changshan*].’

There was, however, little interest in the plant because, as Weber pointed out, ‘the Annamite [Vietnamese] febrifuge had a marked efficacy in several cases, but it was inferior to quinine sulphate ... [and] in a country where quinine is easy to obtain and where fevers are often dangerous, it is not sensible to experiment without enormous care’. The plant could not compete with the dependable quinine, particularly after the 1870s when the Dutch began to harvest *Cinchona* bark on an industrial scale from trees grown in Java [14].

**Early analysis**

In 1890, the British pharmaceutical chemist and evangelical Christian preacher David Hooper (1858–1947) [15] published the first detailed chemical analysis of *D. febrifuga* or *basak* as it was known in British India. Working at the *Cinchona* plantations in Madras, he identified a type of

![Figure 1. *Dichroa febrifuga*. Reproduced from Bouillat (op. cit. p. 20).](http://www.sciencedirect.com)
wax and a crystalline glucoside he named *dichroin* [16]. But Hooper could find no quinine-like alkaloids that might account for *changshan*’s anti-malarial properties.

It was then several decades before anyone returned to study *changshan*. The catalyst for this renewed interest was World War I, when the warring armies’ demand for quinine to protect their troops from malaria drove up the quinine price. The Dutch, who now produced virtually all the world’s quinine, could control the amount of the anti-malarial available on the market and thus increase the price even more, much to the consternation of other nations (Figure 2).

In a report published in July 1926, Emile Perrot (1867–1951) [17], a professor at the Faculty of Pharmacy in Paris and senior advisor to the French government on the economic value of medicinal plants, lamented his country’s failure to grow *Cinchona* in its colonies and its reliance on the costly Dutch product [18]. Mindful of France’s *mission civilisatrice*, Perrot also briefly raised the issue of France’s responsibilities for the health of her colonial subjects who lived in tropical countries where malaria ran rife: ‘it is necessary to look for the solution, if it exists, to the problem of supplying the poor nations with a medicine to fight malaria’, he wrote. If quinine was too expensive for mass treatment, might *D. febrifuga* not be the solution?

With French Indochina a ready source of exotic herbs, the Agronomic Research Institute in Saigon sent a consignment of *D. febrifuga* to Perrot’s laboratory in Paris. The task of analysing it fell to Perrot’s graduate student Maurice Bouillat [19] (Figure 3). He made ether extracts, as did the drug house Boulanger-Dausse on his behalf, and found that ‘the stem and leaves of *Dichroa febrifuga* contain, in a very minimal quantity, a substance giving the general reactions of alkaloids’.

Here was the first sign that the herb really worked against malaria and in a similar manner to *Cinchona* bark. Bouillat set about testing the hypothesis that his *D. febrifuga* extract had its effect in a way not dissimilar to aspirin, calming the patient’s immune system and bringing down their temperature in the process. He used an injection of brewer’s yeast to induce a fever in rabbits and followed it with a dose of his extract. But this had no effect on his animal subjects.

Perhaps there was a problem with the dried samples of the plant he had worked with. ‘It is reasonable to think that freshly harvested plants could have a febrifugal action’, he suggested. But there was a more obvious reason why his herbal extract had no effect: a fever induced by a yeast injection is not the same as fever caused by malaria.
This might have led Bouillat to realise that the active principle in *D. febrifuga* worked not on the fever but on the parasite itself. It was a possibility he certainly entertained: ‘We also cannot reject *a priori* the hypothesis of specific drug action in certain ailments due to the presence of parasites in the blood typically accompanying febrile attacks’. But for reasons that remain unclear, it is not one he explored, concluding only that ‘nothing allowed us to confirm the febrifugal action attributed by the indigenous people to the root and the leaves of *Dichroa febrifuga*’.

Instead, Bouillat devoted the rest of his thesis to physiological experiments with the extract in dogs and rabbits that demonstrated its well-known emetic side effects and showed how it lowered the blood pressure and stopped the heart in high doses (Figure 4).

**Quinine shortage in WWII**

The onset of World War II exacerbated the quinine shortage and when the Japanese seized the Dutch *Cinchona* plantations in Java, matters only worsened, particularly in China. Faced with Japanese attacks in the east, the Chinese Nationalist government under Chiang Kai-chek retreated west to Chongqing, an area rife with malaria. Half-hearted attempts to control the parasite-carrying mosquitoes failed and the army, government officials and the refugees fleeing the Japanese succumbed to the disease [20]. Consequently, the Chinese government launched a research project to uncover *changshan*’s essence and turn it into a drug that could be given to troops and civilians *en masse* [21].

In 1940, Zhang completed his PhD on adrenergic nerve transmission at the College of the Pharmaceutical Society in London, under the physiologist Sir John Gaddum. He briefly took a job at Harvard, before returning to China in 1941 and joining the *changshan* project. After conducting the clinical trial at the cotton mill in the summer, Zhang, who in one photo wears rimless glasses and an ironic smile, moved to a makeshift laboratory in the hills above Chongqing and set to work extracting *changshan*’s active principle [22] (Figure 5).

Chongqing was under siege and short of everything. Scientific materials and reagents had to be flown in over the Himalayas by China’s American and British allies, brought hundreds of kilometres across the desert from...
the Soviet Union, or smuggled through Japanese lines, and few, if any, reached Zhang. It was only in 1945 that he got hold of the experimental *Plasmodium gallinaceum* model of malaria that he could use to test his extracts [23].

China was not the only country to show an interest in *changshan* [24]. Joseph Needham, the biochemist and head of the wartime Sino-British Science Co-operation Bureau in Chongqing, sent a *changshan* sample to the National Institute for Medical Research (NIMR) in London. Tests there in chickens confirmed Zhang’s early results and were published in *Nature* in November 1945 [25]. A few months later, on 11 January 1946, Zhang reported in *Science* that he had isolated *changshan’s* active principle. As predicted, it was an alkaloid and he named it dichroine B.

For David Hooper, in retirement in Weston-super-Mare on the west coast of England and in the last year of his life, the NIMR paper in *Nature* brought back memories of his work on *D. febrifuga* and he wrote to *Nature*, perhaps to remind the world of his contribution. ‘When in India more than fifty years ago, a native physician sent to me some stems of the plant as a fever remedy and suggested that it might contain an alkaloid similar to quinine’ [26].

In human trials conducted in the USA, this alkaloid was found to be 100 times more effective at curing malaria than quinine. But like the original herb, it remained strongly emetic. Purification had simply worsened the side effects and the pure compound was less useful than the herbal extract. Soon after, the drug – which is now known as febrifugine – was declared useless and abandoned as an antimalarial [27].

Qinghaosu

Although *changshan* never resulted in a safe alternative to quinine, the story of the discovery of its active principle is telling in the way it illuminates the discovery of another, much more effective antimalarial drug, *qinghaosu*.

After Chairman Mao seized power in 1949, the Chinese Communist Party pulled the names of ancient physicians, such as the Ming Dynasty herbalist Li Shizhen, from the historical record and cast them both as proto-Marxists and as empiricists in the best scientific tradition. ‘In the past 10 years, the people’s government of China has begun paying particular attention to the centuries-old Chinese art of healing, and has called upon the medical profession to study and develop the art. In this development, Li Shihchen’s [Li Shizhen’s] work has special significance’, [28].

Li Shizhen’s medical book, published in 1597, mentions *changshan* to treat fever but it also cites another herb, *qinghao* [29]. In May 1967, the Chinese government launched a project to investigate *qinghao* as a malaria cure, this time because the parasite had become resistant to the existing synthetic anti-malarial drug, chloroquine [30].

But China had no use for the older generation of scientists in this new investigation. Zhang Changshao was accused of being a spy and a counter-revolutionary and, in December 1967, he committed suicide during the reign of terror intended to purge China of its intellectuals [31].

The breakthrough in the *qinghao* research came in the 1970s, possibly as early as 1971, when the pharmacologist Tu Youyou extracted the herb’s active principle (later named *qinghaosu*) [32]. Tu had graduated from university at the height of Mao’s success in the 1950s and thought herself part of his grand revolutionary project. Writing much later in 2004, she echoed Mao’s own words: ‘it was my firm belief that traditional Chinese medicine was a great treasure house, and efforts should be made to explore its essence’ [33].

Tu’s recollection apparently links *qinghaosu* to Mao’s policies. But viewing the discovery solely from her perspective seems to suggest that it was uniquely Chinese and could not have happened elsewhere. This recapitulates the fallacy of the ‘mysterious East’, a place that now owes as much to Chinese government misinformation as it does to Western misconceptions.

China was not unique in its efforts to extract active principles from herbal medicines. Tu was a scientist like

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any other and she did not apply the tenets of Mao, or those of Li Shizhen, to make her discovery. Rather, she used ether in her extraction, just as Pelletier and Caventou had done with quinine in 1820 and, therefore, she worked in the Western tradition of extracting active principles from herbs that was invented in early nineteenth-century France.

It is ironic that research connected with the staunch anti-colonialist Mao actually has more in common with European colonial projects to extract active principles from indigenous herbal medicines. But recognizing the European scientific tradition, with all its nuance and complexity, also allows us to credit the efforts of scientists like Zhang Changshao who helped establish ethnopharmacology in China in the first half of the Twentieth Century, long before Mao's policies took hold.

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