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## From plant to medicine: How an ancient plant-based remedy became a modern malaria medicine (11 min read)

Access to Healthcare

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The plant's Latin name is *Artemisia annua*, but it is also known as “Sweet Annie,” “Sweet Wormwood” and also “Qing Hao,” arising from its origins in traditional Chinese medicine. Today artemisinin, a powerful ingredient extracted from *Artemisia annua*, is used to create modern antimalarial drugs.

Turning this readily available plant into a highly effective medicine requires a huge effort and significant coordination. That is why organizations and partnerships that are dedicated to broadening access to medicines worldwide step in and help, by providing antimalarial drugs without profit to the places where they are needed most. Through programs such as the Novartis Malaria Initiative this vital medication can reach millions of people in malaria-affected, low-income regions.

Education and the use of insect-repellant nets have generated huge gains in preventing the disease. Malaria-control programs have made major advances in diagnosing malaria, and patient care has greatly improved. Availability of essential medication supports patient recovery. Since the early 2000s, according to the World Health Organization's “World Malaria Report 2016,” some 6.3 million deaths have been prevented, most of them in Africa.

### Lost in history, found in war

For more than 2,000 years *Artemisia annua* had been used in China to alleviate fevers, without knowing what those fevers were caused by, often in combination with other herbs. The modern part of *Artemisia annua*'s story begins in 1967, as the Vietnam War was escalating. For Viet Cong troops operating in the humid, warm jungle, malaria was a serious problem.

The disease is caused by parasites that are transmitted through mosquito bites. A standard medicine that had previously prevented malaria, chloroquine, was no longer effective because malaria parasites had built up resistance. As a result, the Vietnamese troops became ill at an unprecedented rate, and thousands of them died – more than were killed in combat.<sup>1</sup> Desperate to find medical assistance, the Viet Cong's leader, Ho Chi Minh, turned to his Chinese neighbors for help.

China was already a producer of antimalarial medicine, and was intensifying its efforts to fight the disease.<sup>2</sup> Chinese leader Chairman Mao Zedong agreed to support medical research on a new antimalarial drug. The program was called Project 523, named for the program's starting date of May 23, 1967. More than 800 Chinese scientists from more than 60 institutes participated. A team from the China Academy of Chinese Medical Sciences identified the active ingredient artemisinin in the *Artemisia annua* plant in 1972.<sup>3</sup> This led to the development of artemisinin-based combination therapies (ACTs), which revolutionized the treatment of malaria. The team's principle investigator, Dr. Youyou Tu was awarded the Nobel Prize in Medicine or Physiology in 2015 for finding a way to extract artemisinin from the plant.

Sweet Annie, or *Artemisia annua* grows well in hot, moist climates, particularly in Asia and parts of Africa

Image not found or type unknown

Sweet Annie, or *Artemisia annua* grows well in hot, moist climates, particularly in Asia and parts of Africa. It can yield two harvests per year in Africa.  
Credit: mauritius images / Markus Shimizu

Traditionally used in Chinese medicine for treating fever, the dried leaves and stem are of *Artemisia annua* are most

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Traditionally used in Chinese medicine for treating fever, the dried leaves and stem are of *Artemisia annua* are most commonly brewed as tea. However, treating malaria with teas could contribute to development of resistance in the parasites.

Credit: picture alliance/Arco Images/O. Dietz

This active ingredient is effective against malaria, but is not easy to extract

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Leaves may not be stored at high temperatures, or they lose much of their artemisinin content. This active ingredient is effective against malaria, but is not easy to extract. Modern-day pharmaceuticals offer it in tablet form, not dried leaves.

Credit: ddp images/ Xinhua

In laboratories, the plant's active ingredient, artemisinin, is extracted from the plant and chemically modified into art

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In laboratories, the plant's active ingredient, artemisinin, is extracted from the plant and chemically modified into arthemether. It is combined with other antimalarials, such as lumefantrine, to create a powerful artemisinin-combination therapy or ACT.

Credit: laif/Keystone Schweiz/Gaetan Bally

Education, early treatment as well as medication have helped to avoid millions of malaria deaths in the past decade

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Education, early treatment as well as medication have helped to avoid millions of malaria deaths in the past decade.

Credit: Novartis Brand Lab

Another effective tool to help fight the disease is early diagnosis

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Another effective tool to help fight the disease is early diagnosis.  
Credit: Novartis Brand Lab

Testing and early treatment improves chance of cure

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Testing and early treatment improves chance of cure. About 70 percent malaria deaths are children, most of them under age five, so Novartis has developed a child-friendly antimalarial formulation.

Credit: Novartis Brand Lab

## **Paving the way for anti-malarial research**

Today, artemisinin is the base for the standard antimalarial treatment worldwide recommended by the World Health Organization. But for decades, knowledge of this important treatment remained within China, where research continued on the plant and its powerful ingredient. By 1981, Chinese scientists developed the first tablet formulation,<sup>4</sup> but in the meantime, worldwide malaria mortality had increased year after year, particularly in Africa.

## **A devastating illness**

On the African continent, malaria infection and mortality rates remain the highest in the world, with nine of ten global malaria victims. In the 1980s and 1990s, an already alarming number of malaria deaths on the



continent increased sharply, from estimated 493,000 to about 800,000 per year.<sup>5</sup> Something had to be done. Again, *Artemisia annua* played the leading role. The development of the first fixed-dose artemisinin-based combination therapy began in the 1990s, when Novartis joined forces with Chinese researchers to transform the traditional herbal remedy into a modern antimalarial medicine.

Novartis and its Chinese partners signed a license agreement to develop and produce artemisinin-based medication for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria, responsible for most deaths from malaria in 1994. “In the earliest days, it was a small research project in partnership with Chinese scientists. Out of that project came one of the best drugs ever developed to combat malaria,” says Dr. Professor William Rodriguez, Chief Medical Officer, Foundation for Innovative New Diagnostics (FIND).

Five years later, the first fixed-dose artemisinin-based combination therapy to treat malaria was in production. Artemisinin, combined with a partner drug lumefantrine, was also shown to achieve cure rates of more than 95 percent.<sup>6</sup> This effectiveness led the World Health Organization to change its treatment guidelines to recommend the use of ACTs for *Plasmodium falciparum* malaria. Today, this drug is part of the [Novartis Malaria Initiative](#). [1] Begun in 2001, the program provides the antimalarial therapy without profit to public health systems in developing countries, and it has contributed strongly to a global decrease in malaria prevalence.

800 million

The number of antimalarial treatments provided without profit since 2001 through the Novartis Malaria Initiative.

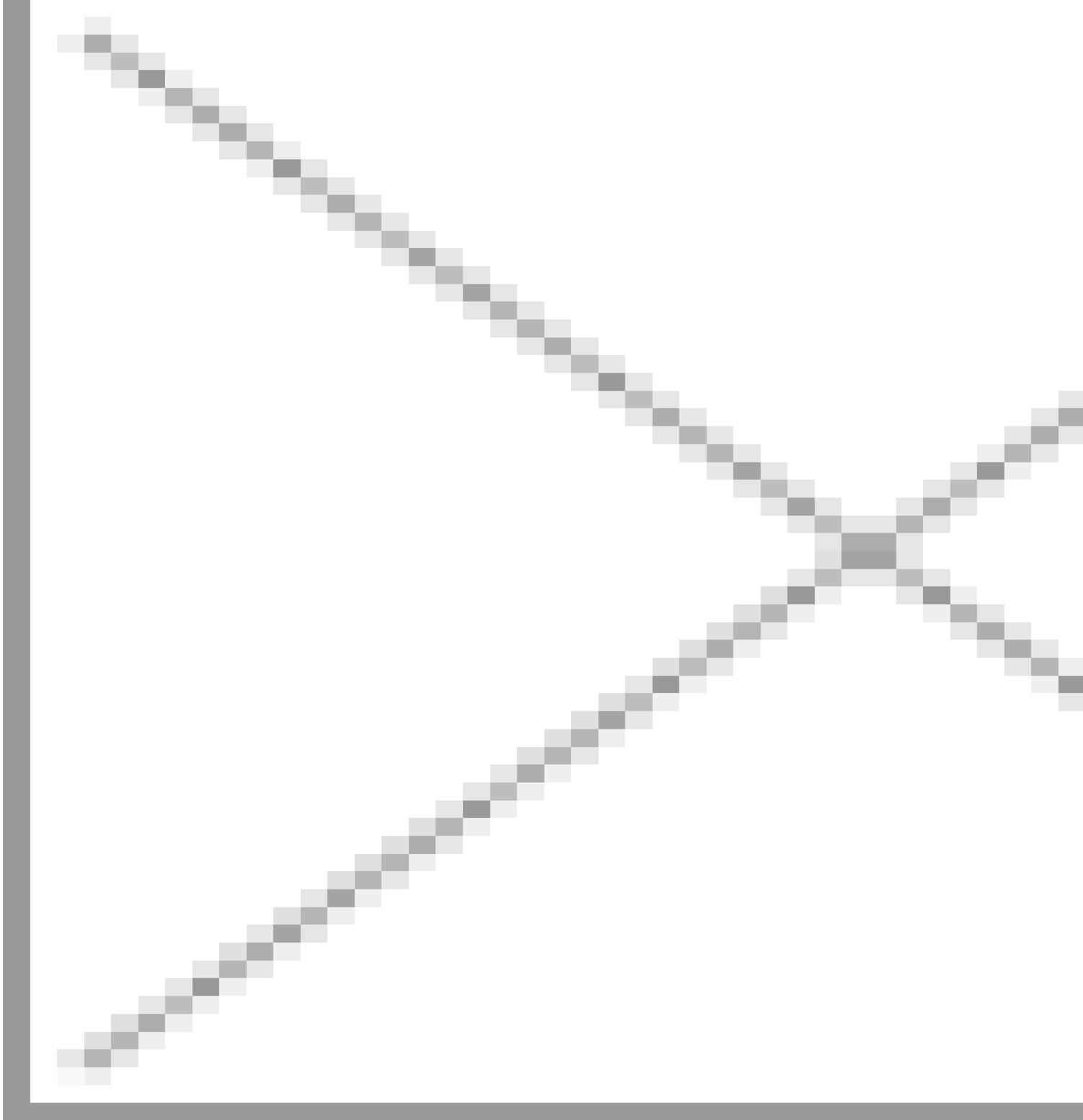
## Dangerous resistance

Monotherapies can be the cause of dangerous resistance, explains Dr. Pascal Ringwald, who coordinates the unit drug efficacy and response at the WHO. Over the years, in many parts of the world, the malaria parasite has become resistant not only to conventional treatments, notably chloroquine, but also to any substance, including other antimalarials when they are used on their own. “A drug like lumefantrine could effectively fight malaria on its own, but relying on a single active ingredient would accelerate the development of resistance,” says Ringwald. Because lumefantrine has not been used as a monotherapy to treat malaria, the risk of resistance to this combination may be lower than with other ACTs. “Used in combination, artemisinin is delaying the resistance to the partner drug.”

You would have to drink five or six liters of tea daily for seven days.

**Dr. Pascal Ringwald**, Drug Efficacy and Response Unit at the World Health Organization

Another method of using the antimalarial agent artemisinin in Sweet Annie is to dry the plant and make tea out of it. This treatment is encouraged by some NGOs, but Dr. Ringwald is unconvinced. “This approach could cure malaria, but you would have to drink five or six liters of tea daily for seven days,” he says. “This isn’t possible, especially when you’re sick.” Ringwald adds that if the medication is under-dosed, it could also contribute to resistance. This is because parasites that are exposed to a dose of a substance that is too low to kill them build immunity to the substance, which they pass on to the next generation. “That’s why we must avoid monotherapies.”



Percentage decrease in deaths from malaria (2000- 2015).

Education, the use of insect-repellent nets, faster and more accurate diagnosis, as well as the introduction of antimalarials have helped to greatly lower malaria mortality. Health organizations, governments and pharmaceutical companies are working together to reduce malaria. Source:

[http://www.who.int/gho/malaria/epidemic/malaria\\_007.jpg](http://www.who.int/gho/malaria/epidemic/malaria_007.jpg) [2]

## The fight against malaria continues

Parasites build up an immune response and resistance to substances as part of the normal reproduction cycle. Early signs of resistance to artemisinins and ACTs have appeared in five countries of South-East Asia. To

stay ahead of the selective pressure, the drugs that exist need to be used properly, along with research and development for the next generation therapy. “We have emerging resistance to artemisinin and its partners,” says Ringwald. “We need to move to different combinations in the future,” he adds. Currently Novartis is leading two programs to develop new antimalarials not belonging to the artemisinin class.

However, even the best medicine can’t help if it’s not broadly available in affected regions. “As a public-health community, we have made significant progress in providing malaria patients with much-needed medicines and reducing malaria mortality,” says Dr. Harald Nusser. He serves as Head of Novartis Social Business, a unit that includes the Novartis Malaria Initiative. Statistics published in the World Health Organization’s *World Malaria Report 2016* support his statement. Millions of lives have been saved in recent years. According to the report, the incidence rate of malaria has decreased 41 percent globally between 2000 and 2015, and mortality rates have declined 62 percent.<sup>7</sup>

## Children need special attention

But Nusser is not yet ready to relax. “Despite the great progress made against malaria, we should not lean back,” he says. “We need to stay vested, we need to stay concerned and even increase efforts in order to eradicate this terrible disease, country by country.”

Every two minutes, a child still dies of malaria – this is unacceptable!

**Dr. Harald Nusser**, Head of Novartis Social Business

Up to 70 percent of those dying from malaria in Africa are children under the age of five.<sup>8</sup> “Every two minutes, a child still dies of malaria – this is unacceptable!” Nusser says. Because infants and children are the most vulnerable to the disease, Novartis and Medicines for Malaria Venture partnered to develop a sweet-tasting dispersible ACT version for children. In tablet form, ACTs are bitter. So, parents or doctors usually needed to crush and mix the medicine with liquid to get children to take it. This made it difficult to administer. However, when children accept the taste of the medicine, it becomes easier to ensure that they are getting the right dose. “With so many children victims of malaria, there was a need to develop medicines tailored to children’s specific needs,” Nusser explains.

Like the tablet formulation, this medicine is sold by Novartis to the public sector without profit. While the right dosage and formula of a medicine is crucial to fight malaria, prevention and treatment also require the right mixture of action, strategy and policy, and close collaboration by pharmaceutical companies, governments, and local organizations. Anti-malaria initiatives help to train local medics to recognize symptoms. They may be equipped with rapid diagnostic tests, so diagnosis and treatment can follow more quickly. People in the community are taught how to reduce the risk of mosquito bites, and they are given insect-repellent nets, and houses are sprayed. Parents are advised to take their children to the doctor at the first sign of malaria’s flu-like symptoms, such as fever. Children learn about malaria prevention and treatment through educational cartoon stories. Ultimately, these measures are stepping-stones on the journey to eliminating the disease completely.

## The Novartis Malaria Initiative

Novartis launched its Malaria Initiative in 2001. In the past 15 years, the initiative has provided more than 800 million malaria treatments without profit. The program’s four pillars are treatment, access, capacity building, and research and development. Operated by Sandoz, the Novartis generics and biosimilars division, the Malaria Initiative is one of the pharmaceutical industry’s largest access-to-medicine programs<sup>9</sup>.

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