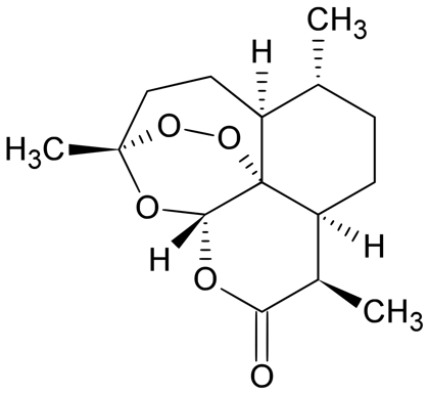
Tu Youyou: “a gift from traditional Chinese medicine to the world”

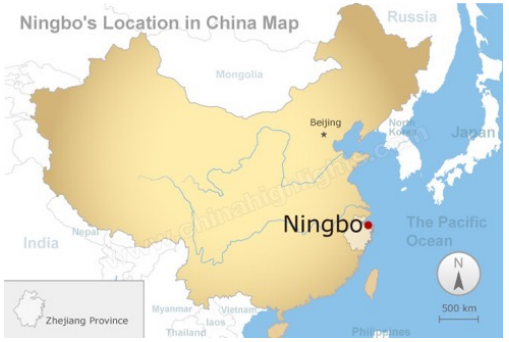
2015 Nobel Laureate



Early Life and Influences

My [first] name, Youyou, was given by my father, who adapted it from the sentence ‘呦呦鹿鸣, 食野之蒿' translated as 'Deer bleat "youyou" while they are eating the wild Hao’ in the Chinese *Book of Odes*. How this links my whole life with qinghao will probably remain an interesting coincidence forever.

- Born December 30, 1930 in Ningbo, China
- Father worked in bank, mother raised her and 4 brothers
- Family lived in Ningbo for many generations
- Highly valued education
  - They did everything possible for her to attend the best public and private schools in the region
  - Era when few girls went to school



Influence of Medicine

- Grew up watching people get cured by traditional Chinese herbal medicine
- Contracted tuberculosis at age 16
  - Stayed home for 2 years to recover before returning to high school
- Wanted to study medicine upon return to school
- Wanted to be able have medical skills
  - find treatments for other people
  - keep herself healthy

Education

- In 1951 admitted to the Department of Pharmacy at the Medical School of Peking University
- Studied both Western and traditional Chinese medicine
  - Studied the extraction of active ingredients from herbs
  - Studied the chemical basis of the medical properties of plants
- After graduation worked as a researcher at the Academy of Traditional Chinese Medicine
- Tu Youyou is known as the “Three No’s Professor”
  - No postgraduate study (did not exist in China at the time)
  - No research abroad
  - No membership of academy of sciences

Major Mentor: Lou Zhicen

- Lou Zhicen (楼之岑), mentor and teacher
- Pharmacognosist, studied at China's National Military Academy and University of London
  - Expert in medicinal plants
- Taught Tu Youyou how to identify plants from botanical descriptions, how to extract active substances from plants
- Tu Youyou researched Lobelia chinensis (半边莲) with Lou Zhicen for her first publication
  - An herb for treatment of *Schistosomiasis,* disease caused by parasitic flatworms

Lou Zhicen and Tu Youyou

Cultural Revolution

- From the 1960s-70s
- Academics and intellectuals as a group were considered the “stinking old ninth” and widely persecuted
  - Beaten and killed
  - Imprisoned
  - Sent to labor camps
- Tu Youyou’s husband Li Tingzhao, a metal engineer, was sent away during this time
- In 1967 Tu Youyou was recruited by the government to work on Project 523

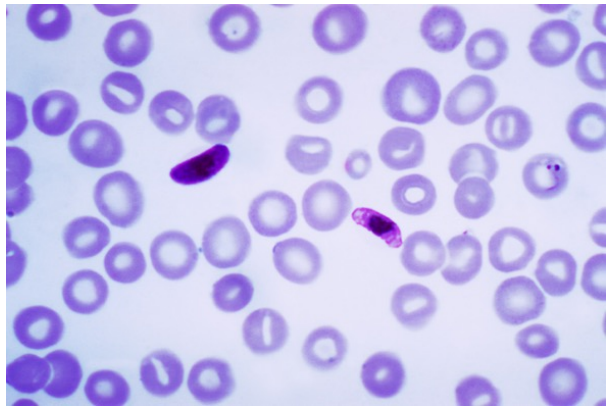
Above is not an academic. But the picture demonstrates the public humiliation and abuse suffered

Project 523

- Launched on May 23 1967 (hence the name)
- Secret Chinese military project initiated by Mao Zedong to find a cure for malaria
  - At request of Ho Chi Minh during the Vietnam war
  - Malaria was becoming resistant to treatment by Chloroquine
- More than 500 Chinese scientists were recruited
  - Tu Youyou was recruited to head the traditional Chinese medicine arm of the project
- Immense responsibility and sacrifice for young Tu Youyou
- Two daughters
  - Sent 4 year old to nursery, sent 1 year old to parents

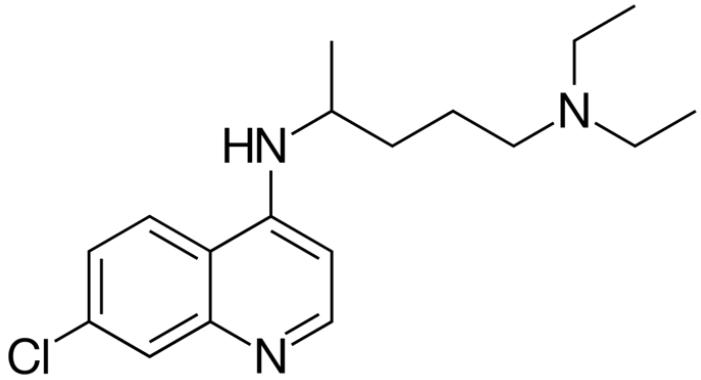
Preceding Science: Malaria

- Global epidemic disease for thousands of years
- Plasmodium bacteria attack red blood cells
  - Transferred by mosquitoes
  - Grow in liver, release eggs into blood stream
  - Juveniles hide in red blood cells from immune system, continue to grow and reproduce
- Periodic fevers associated with malaria
  - In plasmodium reproductive cycle when released
- Death from anemia or infected blood cells may blocking small vessels in brain



Preceding Science: Chloroquine

- Chloroquine concentrates in the food vacuole of Plasmodium, preventing production of hemazoin
  - A nontoxic heme metabolite
- Plasmodium dies due to build up of toxic byproducts of hemoglobin metabolism
- Malaria was becoming resistant to treatment by Chloroquine in Vietnam
  - Project 523 sought to find a new cure.
  - Malaria was disastrous for Vietnam in the war



Winning Science

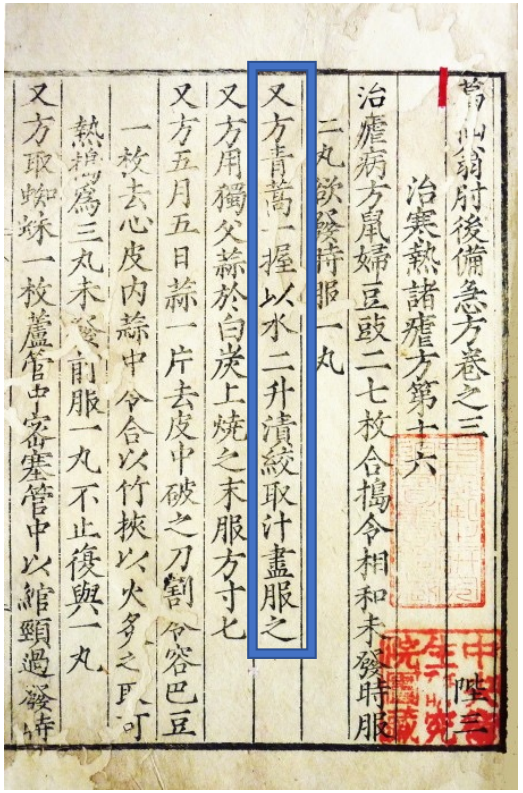
- Tu Youyou discovered artemisinin, a previously unknown chemical which could treat malaria
  - From ancient Chinese medicinal texts
- Extracted, tested, and identified the chemical structure of artemisinin

Winning Science: Screening

- Scientists worldwide had screened over 240,000 compounds to treat malaria without success
- Tu Youyou's lab group focused on traditional Chinese herbs
- Group effort from labs across the country
  - Institutes of Chinese Materia Medica
  - Academy of Traditional Chinese Medicine
- Collected over 2000 herbal animal and medicinal prescriptions for malaria
- Interview traditional Chinese medicine experts
- Testing hundreds of herbs on mice with Malaria

Winning Science: Isolation of qinghao

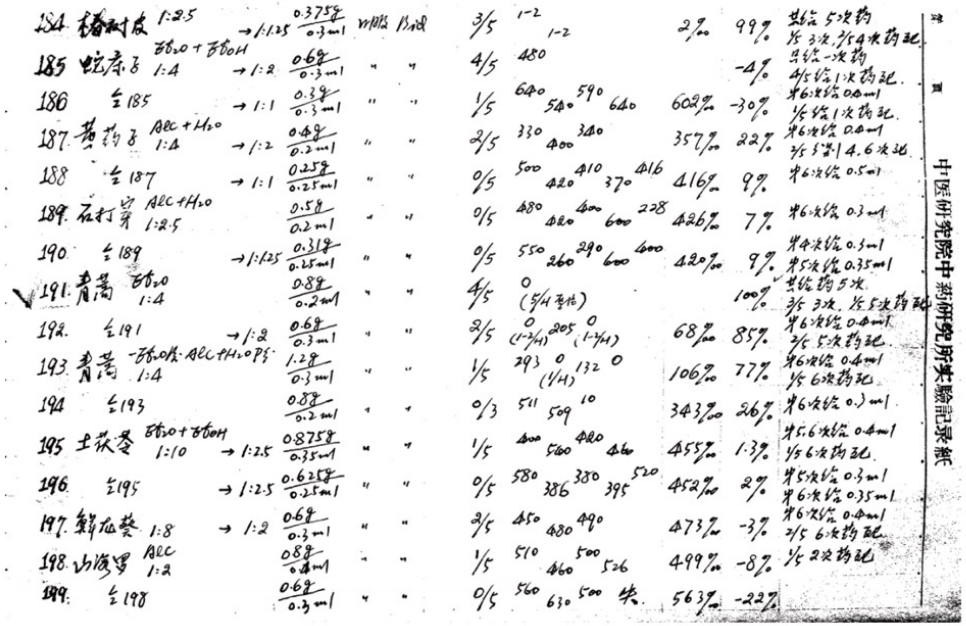
- An ancient Chinese herb used to treat "intermittent fevers,"
  - 青蒿一握 以水二升渍 绞取汁 尽服之
- “A handful of qinghao, place in two liters of water, squeeze it dry, then consume it all”
- *The Handbook of Prescriptions for Emergencies,* by Ge Hong, 4th century CE;
- Qinghao is an herb named “sweet wormwood” in English
- Herbal chemicals typically extracted using boiling water
- The ancient description not mentioning boiling suggested to Tu Youyou that heat may damage the active chemical in qinghao
- Distilled using ethyl ether, with a boiling point of 34.6°C instead



The text is boxed here

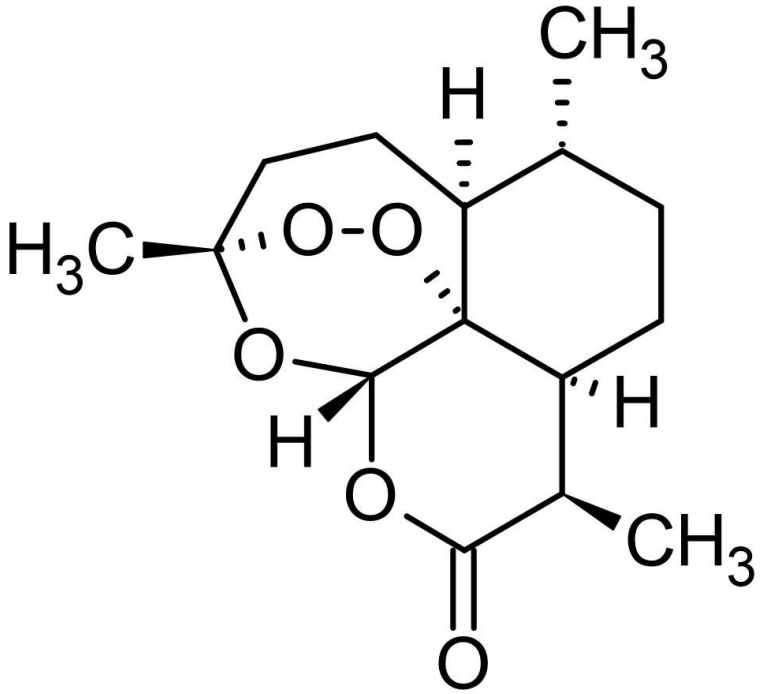
Winning Science: Testing Qinghao Extract

- Sample 191 in October 4 1971: neutral portion of 青蒿 ether extract
  - 100% effective on malaria mice
  - 100% effective on malaria monkeys
- Poor research conditions 1970s
  - Without industrial facilities, researchers used massive water pots to carry out mass extraction themselves
- To expedite the drug approval process, Tu Youyou volunteered to test the extract on herself (with official approval)



Winning Science: Isolating Artemisinin

- Silica gel thin-layer chromatography isolated the antimalarial compound from the extract
- Elemental analysis, spectrophotometry, mass spectrometry, polarimetric analysis
- Formula of $C_{15}H_{22}O_5$
- stereo-structure
- X-ray crystallography, one of first uses in China
- new sesquiterpene lactone containing a peroxy group



Pay attention: the peroxyl bridge O-O in the top left is the novel characteristic of Artemisinin

Drug Trials

- To expedite the drug approval process, Tu Youyou volunteered self as first patient along with other scientists
- 1977 she published her findings on artemisinin anonymously
- 1986 artemisinin received a China Ministry of Health New Drug Certificate
- 青蒿素高效缩小低度
  - Artemisinin is effective, fast, and has low toxicity


新药证书

编号：（86）卫药证字X-01号

中国中医研究院中药研究所

你单位研制的新药 青蒿素 ，

根据《中华人民共和国药品管理法》，经审查，符合我部颁发的《新药审批办法》的规定，特发此证。

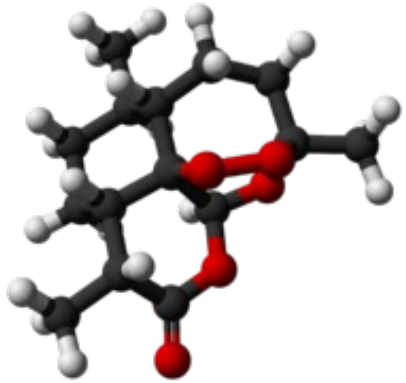
中华人民共和国卫生部

一九八六年十月三日

Still used today!

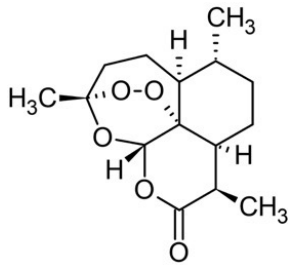
Winning Science: Structure of Artemisinin

- It is important to verify that Artemisinin as chemically different from chloroquine
  - Plasmodium had chloroquine resistance
- Stereo-structure of artemisnin was identified with X-ray crystallography
  - one of the first uses of the technology in China
- Artemisinin was a previously unknown sesquiterpene lactone containing a peroxy group

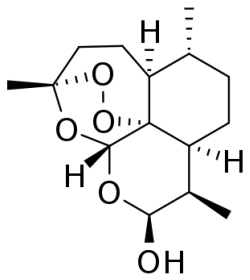


Winning Science: Derivatives of Artemisinin

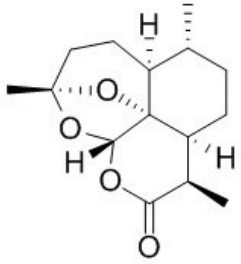
- Tu Youyou set out to study the functional groups of artemisnin
  - peroxyl bridge
  - carboxyl groups
- Modified to
  - Dihydroartemisinin
    - Reduced carboxyl group to hydroxyl group using sodium borohydride
  - Deoxyartemisinin
    - Reduced peroxyl group to an epoxy group using palladium and calcium carbonate methanol solution
- Dihydroartemisinin 10x as effective
- Deoxyartemisinin had no effect on malaria
- Conclude that the peroxyl bridge is essential to drug function



artemisinin



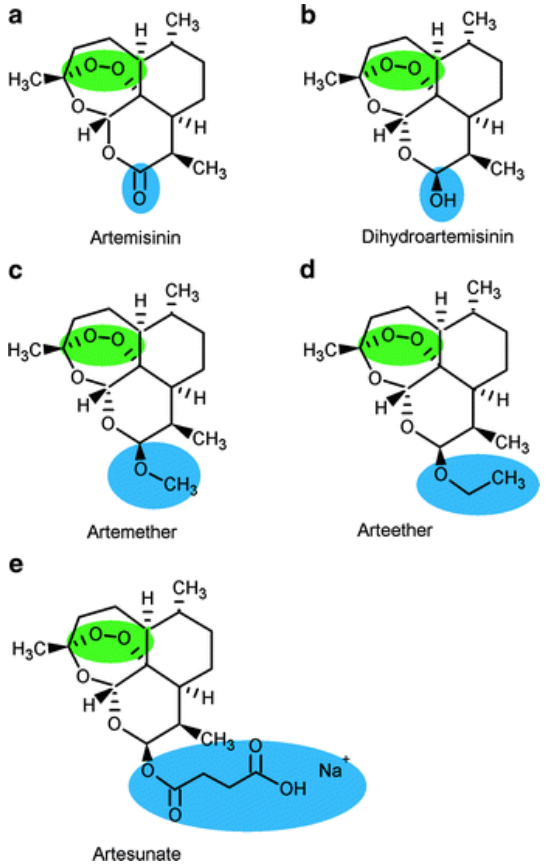
dihydroartemisinin



deoxyartemisnin
- Note the single O in the top left

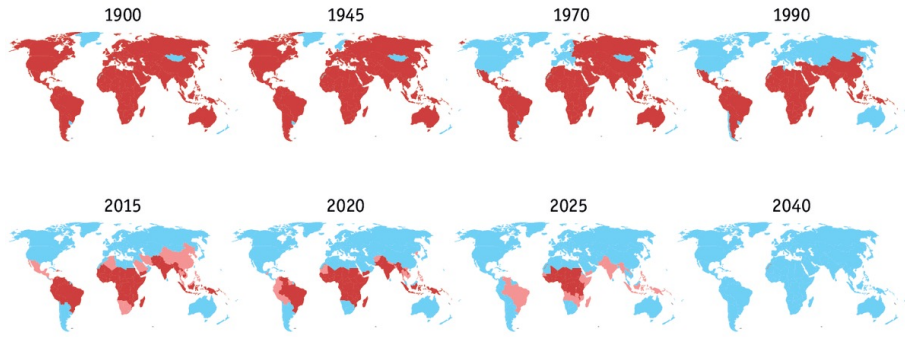
Winning Science: Further Reductions of Artemisinin

- Dihydorartemisinin then derived to
  - Arteether
  - Artesunate
  - Artemether
- All of which contain the peroxide bridge
- All are effective for malaria
- Used in therapies today



Impact on field and medicine

- First Chinese woman to win a Nobel prize
- Credence to the modern study of traditional Chinese medicine from chemistry to find new medical treatments
- Treated millions of patients
- Saves 100,000 lives in Africa alone every year
- 2017, malaria eradicated from China

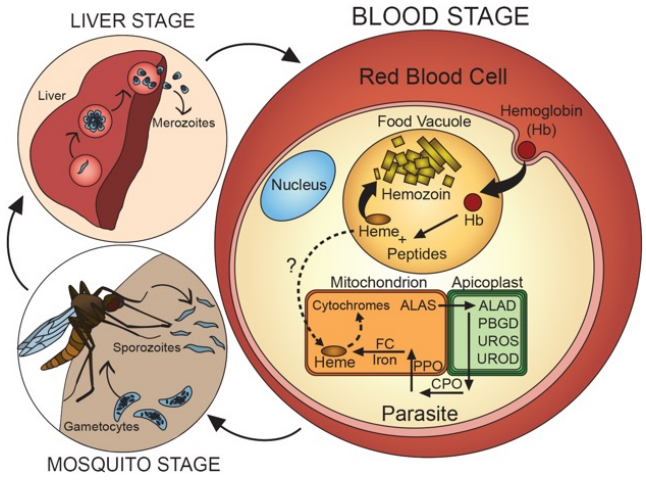


After Artemisinin

- Eventually reunited with daughters and husband
- “I only won the second prize for China’s National Science and Technology Invention Awards in 1981. It provided a 5,000 Yuan (about $500 at that time) scholarship,” she said, “but all of a sudden, five other research institutions came to split the money. I never worked with some of them. As the chief researcher, all I got was 200 Yuan (approximately $20).” Tu said that the final attribution list contained 40 institutions.

Post-Prize Science: function of artemisnin

- Plasmodium consumes hemoglobin when inside red blood cells
  - We find lots of heme inside the body of the plasmodium
- It is believed that the heme interacts with the peroxyl bridge, cleaving it apart and activating artemisinin
- Artemisinin is believed to bind indiscriminately to essential proteins in plasmodium
- In this way, artemisinin capable of completely disrupt cell function, but only when switched on inside a heme consuming parasite



Post-prize science: Artemisnin Resistance

- Artemisinin treatments used in combination with other partner drugs to combat resistance
- In recent years resistance found in Mekong region and in Africa
  - Used to be 3 days to eradicate all Plasmodium, now takes 7 days
- Tu You You currently worked on this, paper in 2019
- Found that plasmodium is now able to lay dormant, surviving artemisinin attacks for longer before
- Conclude that this resistance is mostly because of resistance to the partner drug
- Research suggests artemisinin attacks proteins indiscriminately, making resistance unlikely
- Drug resistance can be resolved by switching partner drug

Final Remarks from Tu Youyou

- “On the stork tower,” written during the Tang Dynasty by Wang Zhihuan (688–742 AD).

白日依山尽
黄河入海流
欲穷千里目
更上一层楼

“The sun along the mountain bows;
The Yellow River seawards flows;
You will enjoy a grander sight;
By climbing to a greater height.”

- "Let us reach to a greater height to appreciate Chinese culture and find the beauty and treasure in the territory of traditional Chinese medicine!”

Questions

- 1) What is the significance of the peroxide bridge of artemisinin?
- 2) Why do we use artemisnin over chloroquine?
- 3) How did Tu Youyou integrate traditional Chinese medicine with Western medicine with?

Sources

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