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Review

Discovery and Development of Artemisinin and Related Compounds

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ABSTRACT

Artemisinin is isolated from the plant *Artemisia annua*, sweet wormwood, an herb employed in traditional Chinese medicine. Prof. You-you Tu discovered artemisinin in the 1960s, so she was awarded the 2015 Nobel Prize in Physiology or Medicine. Artemisinin and its semi-synthetic derivatives are a group of drugs that possess the most rapid action of all current drugs against *Plasmodium falciparum* malaria. In this review, the author investigated history on discovery of artemisinin, ethnopharmacology of *Artemisia* plants, chemistry and pharmacological activities of the relative compounds, and introduced Tu and other Chinese and world scientists' contribution, development of artemisinin and the related compounds and registered and marketed artemisinin drugs in China, UK, and USA. The author also recalled the studies on the mechanism of action of artemisinins and artemisinin combination therapies and summed up the resistance issues. In *Current Recommendations and the Global Plan for Insecticide Resistance Management in Malaria Vectors (GPIRM)*, that the WHO prevents the development and manages the spread of insecticide resistance is summarized in the technical basis for coordinated action against insecticide resistance: preserving the effectiveness of modern malaria vector control. Prof. Tu re-emphasized the artemisinin resistant on five principles to the WHO. She called on the world's scientists to pay attention to the study of drug resistance, and hopes scientists to contribute to break resistance of artemisinins.

Key words

Artemisia; antimalarial drugs; antimalarial resistance; artemisinin; the 2015 nobel prize

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1. Introduction

According to the World Malaria Report 2015, released today, more than half of the 106 countries with malaria in 2000 had achieved reductions in new malaria cases of least 75% by 2015. In that same time frame, 18 countries reduced their malaria cases by 50%–75% (WHO, 2015). The decreases in case incidence and mortality rates were the

slowest in countries that had the largest numbers of malaria cases and deaths in 2000. Reductions in incidence need to be greatly accelerated in these countries if global progress is to improve. Historically, the emergence of chloroquine resistance in the 1970s and 1980s in Africa was associated with increased hospital admissions and mortality at the community level. Antimalarial resistance has also been associated with increased risk of anaemia and low birth weight, and with

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malaria epidemics and increased transmission. The development and spread of resistance to antimalarial medicines have significantly increased the global cost of controlling malaria over time, and given that new drugs must be continually developed to replace medicines that have become ineffective (WHO, 2015).

Artemisinin is isolated from the plant *Artemisia annua* Linn., sweet wormwood, an herb employed in traditional Chinese medicine (TCM). Prof. You-you Tu discovered artemisinin in the 1960s and was awarded the 2015 Nobel Prize in Physiology or Medicine. Artemisinin and its semi-synthetic derivatives are a group of drugs that possess the most rapid action of all current drugs against *Plasmodium falciparum* malaria. Tu's discovery of a cutting-edge drug developed from an ancient Chinese folk remedy was hardly known beyond China (Tu, 2011). She is best known for discovering artemisinin and dihydroartemisinin which are used to treat malaria. Treatments containing an artemisinin derivative (artemisinin-combination therapies, ACTs) are now the standard treatment worldwide for *P. falciparum* malaria. However, slow parasite clearance in patients treated with ACTs causes more parasites to be exposed to the partner medicine alone, increasing the risk of developing resistance to the partner medicine. If resistance develops to the partner drug, treatment failures with ACTs are likely to increase, as have already been observed in some areas. Malaria control programs in 2015 are deploying tools such as ACT that was not available in 2000. According to the World Malaria Report 2015, it suggested that similar innovation and wide-scale deployment of new tools would be required in the next 15 years, for malaria programs are to advance further and overcome the challenges the current face (WHO, 2015).

2. Ethnopharmacology and chemistry of *Artemisia* plants

2.1 Ethnopharmacology

Artemisia plants were used by Chinese herbalists for thousands of years as a remedy for many illnesses (Figure 1). The earliest record, written on a piece of silk unearthed from the Mawangdui Han Dynasty tombs (168 BC), described the *Artemisia* plants as a treatment for hemorrhoids. Later, in *the Handbook of Prescriptions for Emergency Treatments* by Hong Ge during the Jin Dynasty (Figure 2). In *Compendium of Materia Medica* by Shi-zhen Li (1518–1593) during the Ming Dynasty, sweet wormwood (qinghao) was specifically described as a remedy for fever (Figure 3). Artemisinin (qinghaosu, Figure 4) is the antimalarial principle isolated by Chinese scientists in 1972 from the aerial part of *A. annua*, a plant used in TCM for over 2000 years (Tu, 2011).

2.2 Chemistry studies

In 1971, Chinese scientists demonstrated that the plant extracts had antimalarial activity in primate models. In 1972, the active ingredient, artemisinin (Figure 4), was isolated and

its chemical structure was described. Artemisinin is found in the glandular trichomes of the leaves, stems, and inflorescences, and it is concentrated in the upper portions of plants within new growth. Prof. You-you Tu and other researchers firstly isolated artemisinin within the Chinese Project 523.



Figure 1 Plants in genus *Artemisia* Linn. *Sensu stricto*, excl. Sect. *Seriphidium* Bess.

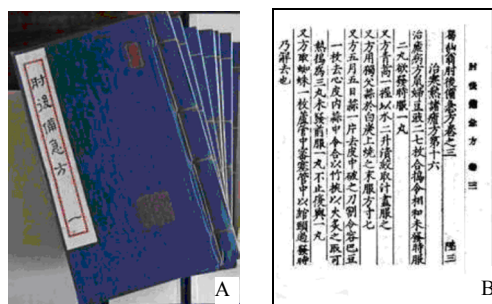


Figure 2 *A Handbook of Prescriptions for Emergencies* by Hong Ge (284–346 CE)

A: Ming dynasty version (1574 CE) of the handbook B: “A handful of qinghao immersed with two liters of water, wring out the juice and drink it all” is printed in the fifth line from the right (From volume 3).

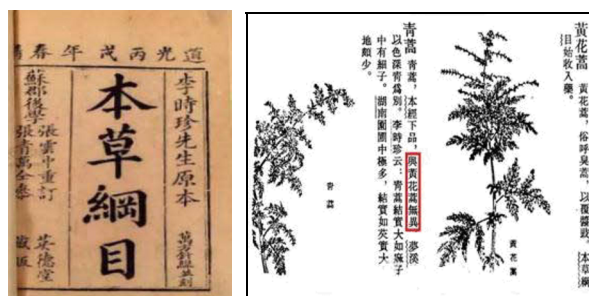


Figure 3 *Compendium of Materia Medica* by Shi-zhen Li, which records *A. annua* and *A. carvifolia*

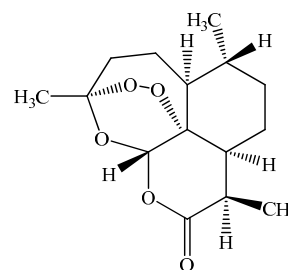


Figure 4 Chemical structure of artemisinin

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