Ann Ibd. Pg. Med 2015. Vol.13, No.2

ARTEMISININ: THE JOURNEY FROM NATURAL PRODUCT TO NOBEL PRIZE

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SUMMARY

The 2014 Nobel Prize for Physiology and Medicine was announced on 5th October. One-half was awarded jointly to William C. Campbell and Satoshi Ômura "for their discoveries concerning a novel therapy against infections caused by roundworm parasites" and the other half to Youyou Tu "*for her discoveries concerning a novel therapy against Malaria.*" The novel therapy that was given this huge recognition was artemisinin, a drug (isolated from the plant *Artemisia annua)* that has saved millions of lives and rekindled the dream of a world where malaria has been eradicated. This is a brief review of this important landmark in the chemotherapy of malaria; a victory for purified and refined herbal medicines.

There is no doubt that the plant Quinhao or Artemisia annua L., commonly known in English as sweet wormwood, contains the most rapidly effective antimalarial compound yet discovered.
Nicholas J. White
Foreword: Artemisinin; *Transactions of the Royal Society of Tropical Medicine and Hygiene*, volume 88, supplement 1, June 1994

INTRODUCTION

In a rural area about 10 km from the city of Ibadan, a three-year-old girl developed high-grade fever with repeated vomiting. The parents, who have now become very familiar with the symptoms, were not too bothered. In their home, they kept a bottle of a herbal medicine which they rubbed on the girl and forced some into her mouth. But her condition rapidly deteriorated. She became unconscious after an episode of convulsion. Neighbours urged the parents to take the child to the primary health center closest to them. On arrival, the health workers seeing the child unconscious put some money together and sent the family off to the main teaching hospital, the University College Hospital, Ibadan. The child was brought to the emergency children ward, popularly referred to as OTCHEW (Otunba Tunwase Children Emergency Ward). Doctors on call recognized the clinical features of cerebral malaria and knowing they had very little time to act to save the child, intravenous quinine was commenced immediately. This particular child was fortunate; she recovered fully without sequelae, and was discharged eighteen days after admission. This scenario is repeated every day and not many children are as fortunate as the child described here. Held down by myths, too far away from proper healthcare services, many parents lose their children to complications of malaria. About 3.2 billion people remain at risk of malaria.[1] In 2014 alone, there were an estimated 214 million new cases of malaria and 438 000 deaths.[1]

For a considerable length of time, chloroquine was the drug of choice for treatment of malaria. Prior to and during the era of decline in the efficacy of chloroquine, plant products have produced effective antimalarial medicines. In 1820, quinine was isolated from cinchona bark and has remained an effective option for the treatment of malaria especially severe and complicated malaria.[2] For Peruvian Indians, the cinchona branch was a chewing stick. The Europeans discovered its usefulness as an antimalarial and from it, quinine was isolated. In those days, Europeans were skeptical about the use of herbal medicines. The isolation of quinine and the impact it had on fevers of malaria origin rapidly changed the general opinion on the chewing stick called the Peruvian bark. Before quinine was purified out of the bark, some European doctors and 'quack doctors' had the courage to use it in the treatment of malaria, with good results but the scientific community in those days paid little attention.[2] The initial scientific results from the use of crude extracts of cinchona were not consistent, but once quinine was purified, the results became consistent. Today all that is history. Quinine has saved countless lives and offered hope for effective control of all species of malaria in humans.

However, by the early 1990s, the malaria parasite *Plasmodium falciparum* had developed resistance to all antimalarial drugs, including quinine. Although quinine retains its effectiveness on a large population, its use has decreased due to associated side effects. The world was in need of another antimalarial and it came from an unexpected source; a drug that today has become the most famous antimalarial emerged. From the plant kingdom, from far away China, artemisinin was identified and isolated. Today, a relatively short period from purification and deployment, artemisinin has surpassed chloroquine and quinine and has become a drug that has given malariologists the courage to foresee the possibility of a world where malaria no longer exists- a world free of malaria.

The Discovery

The Chinese sweet wormwood or quinghaosu has been in use in China for over 2000 years. Local Chinese herbal medicine doctors prescribed it as treatment for fevers. In 1967, the government of the Republic of China set up a program to screen for medicines from plants. The goal was to refine traditional medicines to conventional products that will have market value. The sweet wormwood was tested and in 1972, artemisinin (qinghaosu) was purified from it. Tests on it showed that the extract had very potent antimalarial properties, against all forms of the parasites in humans. From artemisinin many derivatives with very potent antimalarial properties were isolated. These include artesunate, artemether, arteether, and dihydroartemisinin. Pharmacologically, artemisinin is a sesquiterpene lactone endoperoxide whose parasiticidal action resides in the endoperoxide moiety. As a class, the artemisinins are the most rapidly acting antimalarial agents ever in use. The discovery was made possible under a clandestine project called Project 523 led by a woman who until now was relatively unknown to many.

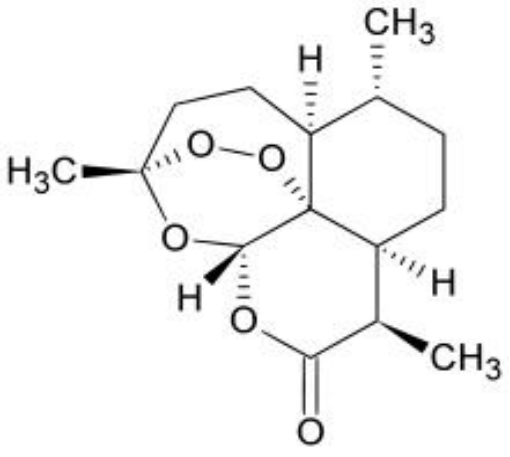

Fig 1. Chemical structure of artemisinin (https://en.wikipedia.org/wiki/Artemisinin)

Youyou Tu and Project 523

Youyou Tu was born in 1930 at Ningbo, a city on the east coast of China.[3] She received four years of training at the School of Pharmacy, Beijing Medical College, between 1951 and 1955. After her education, she was sent by the Chinese government to work at the Institute of Materia Medica, Academy of Traditional Chinese Medicine, where she has remained for over 55 years. After joining the Institute of Materia Medica, Tu attended a 2.5-year full-time training course on the use of traditional Chinese medicines. At the Institute, the primary goals were to search for medications to treat various diseases, in particular those that remained uncured by Western medicines. The Institute had a multi-disciplinary composition, where scientist worked side-by-side with historians and traditional medicine practitioners.

The search for antimalarials in plant extracts by the Chinese was partly stimulated by war. Malaria infection caused many casualties during the Vietnam War (1955–1975). The Japanese requested assistance from the Chinese government. The Chinese set up a clandestine project called project 523 (on May 23, 1967) and appointed Youyou Tu to lead a team of carefully selected scientists, all sworn to secrecy. The team led by Tu searched ancient texts and folk remedies for potential malaria remedies and within three years, they collected 2,000 recipes from 640 herbs. From this collection, after extreme hard work and a commitment to succeed, Quinhaosu was isolated as the most promising substance. Trials in animal models followed and these revealed the remarkable antimalarial effects of the purified extracts. However, clinical trials required the identification and isolation with purification of the active components in the extract. Laboriously, by applying methods in chemistry and novel approaches to isolation of different components of the extract, artemisinin and derivatives were purified. In 1975, the molecular structures were determined as sesquiterpene lactone. With the identification and purification of the active components, clinical trials followed.

The Landmark Studies

Evidence from clinical trials began to be published, initially from China, later from Southeast Asia and eventually from every region of the World. Initial trials were published in Chinese but, for those not familiar with Chinese, they were difficult to access or read. One of the first reports was by Jiang *et al* in 1982 where he reported that "in a chloroquine-resistant *Plasmodium falciparum* endemic area of Hainan Island, China, 1·0 g oral mefloquine produced a radical cure in 47 of 48 semi-immune patients. A comparison between patients treated with mefloquine and with oral qinghaosu showed a more rapid clearance of

Fig 2: Youyou Tu and husband at the Nobel Awards ceremony 2015 (Source: www.nobelprize.org)

parasitaemia with qinghaosu (68·2±21·4 h vs 103·1±18·0 h) and a greater inhibition of in-vivo trophozoite development. An advantage of mefloquine is the effectiveness of a single oral dose, whereas the advantages of qinghaosu are the speed of onset of action and inhibitory effect on parasite maturation".[4] In 1984, Li and colleagues reported a randomized trial of 80 participants given different combinations of antimalarials and where they found that mefloquine plus fansidar produced a radical cure with slight side-effects but the addition of qinghaosu greatly increased the rate of parasite clearance with no additional side-effects.[5]

As it became clear that the malaria parasite, especially *Plasmodium falciparum* was rapidly becoming resistant to all available antimalarials, more interest was developed in the new drug artemisinin. Studies by Hien and colleagues produced more evidence for rapid efficacy and good safety profile of artemisinin mono- and combination therapies against chloroquine-sensitive and chloroquine-resistant malaria.[6-13] By mid 1990s, it was clear that chloroquine needed replacement; the combination of mefloquine and artesunate was already the standard for management of uncomplicated malaria in Southeast Asia where chloroquine resistance had become very prevalent. It became clear that combining failing antimalarials with artemisinin derivatives halted their declining efficacies and also reduced the incidence and prevalence of malaria.[14] White, one of the most prolific malariologist in the world, and other workers conducted studies and provided strong evidence for adoption of artemisinin-based combination therapies rather than artemisinin monotherapy for the treatment of uncomplicated and chloroquine-resistant malaria.[14-18] Combination therapy reduced the rate of treatment failure with artemisinin monotherapy and prolonged the efficacies of the antimalarials in the combination. In 1994, Salako and colleagues reported the efficacy of intramuscular artemether in Nigerian children with moderate to severe falciparum malaria.[19] In 2001 the World Health Organization (WHO) recommended the use of artemisinin-based therapies as first-line treatment for uncomplicated falciparum malaria and in 2004 it became the malaria policy in Nigeria.[20,21] Today, artemisinin has become the cornerstone of treatment of all forms of malaria in the World.

The Nobel Award

In the foreword to the World Malaria Report of 2013, Dr Margaret Chan (WHO Director-General) wrote, "Each year we have a better understanding of global malaria trends and the burden of disease, as measured against the situation in 2000. According to the latest estimates, malaria mortality rates were reduced by about 42% globally and by 49% in the WHO African Region between 2000 and 2012. During the same period, malaria incidence rates declined by 25% around the world, and by 31% in the African Region. These substantial reductions occurred as a result of a major scale-up of vector control interventions, diagnostic testing, and treatment with artemisinin-based combination therapies, or ACTs[22]." The benefits of use of artemisinin-based combination therapies were undisputable; millions of lives have been saved globally.

This year's Nobel Prize for Physiology or Medicine, announced on October 5 and was awarded in recognition of chemotherapeutic advances in tropical

medicine. One-half was awarded jointly to William C. Campbell and Satoshi Ômura "for their discoveries concerning a novel therapy against infections caused by roundworm parasites" and the other half to Youyou Tu "for her discoveries concerning a novel therapy against Malaria." A fine recognition for a long and very successful journey of a branch from a plant from far away China. Artemisinin has since continued to render immense benefits to the entire World.

The Dream of a World Free of Malaria

As the cost of drug development continues to escalate, big drug companies have reduced interest in the discovery and development of antimalarials. Not much profit exists in the sale of antimalarials as the disease affects the poorest parts of the world. In addition, resistance to artemisinin has arisen with a threat of spreading globally.[23-25] Malaria is hyper-endemic in Nigeria and we must play key roles in finding a permanent solution to the scourge. Resistance to artemisinin threatens every gain made against falciparum malaria in recent years. This is a significant threat. Malaria endemic countries need to intensify efforts at averting a looming disaster.

Research leadership is required and great institutions like the University of Ibadan and her Teaching Hospital, the University College Hospital (UCH) will have to bear the burden of expectation from citizens of this country. A clear path has to be charted for the defeat of the malaria. The approach must be multi-disciplinary, multi-institutional and extensively innovative. The Nobel Prize comes with huge recognition, enough to establish a culture of international research excellence. The prize is awarded for discoveries/contributions with the greatest benefits to humanity. The eradication of malaria is one of such beneficial expectations.

With the united focus and teams of excellence that have been reborn, it is a matter of time; Ibadan, Nigeria, will bring home a Nobel Prize in malaria and other tropical diseases, just as Youyou Tu took it to China this year. This is a worthy dream; more importantly, the defeat of malaria will add significantly to economic gains. This dream is more than Institutional or national pride. It is a duty we owe to every child that has died from malaria and other tropical diseases; and it is a challenge to all biomedical research scientists in sub-Saharan Africa. Malaria is our cross and we must bear it, conquer it. The world is already offering all the assistance that is required. The dream of a world free of malaria is achievable; new thinking, innovative approaches, and commitment from our leaders are required. Added to this, sub-Saharan Africa needs a science-related Nobel Prize that will be a source of motivation for coming generations.

Fig 3: Nobel medal

ACKNOWLEDGEMENTS

Historical aspects of this brief review were from documents from the Nobel Foundation website (www.nobelprize.org) and Wikipedia. I acknowledge USA National Library of Medicine for free access to the public database, PUBMED, an all-important source of biomedical information; a most noteworthy service to humanity. I thank AIPM for the opportunity to maintain the Chronicles of Medical History. I acknowledge my beloved wife Afieharo, Consultant, Plastic and Reconstructive Surgery, University College Hospital, Ibadan; a scholar and close companion whom I respect and admire a lot, for continued encouragement and all-encompassing support. Grace for this work continues to be from God, to whom I owe it all.

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