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ARTICLE

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THE STORY OF THE ANTIMALARIAL DRUG ARTEMISININ: FIFTIETH ANNIVERSARY OF ITS DISCOVERY

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Malaria is an ancient disease caused by the parasite Plasmodium, *which is transmitted into the blood supply of human hosts by the bite of female anopheles mosquitoes. They require blood for the nourishment of their eggs. The use of cinchona bark for the treatment of various types of fevers was serendipitously discovered in early 17th century. Quinine was isolated from this bark in 1820, and it was the first antimalarial drug in the history of malaria. Some side effects of quinine gave an impetus for the synthesis of new antimalarial drugs such as chloroquine. However, the development of parasite strains that were resistant to new drugs became a serious challenge in malarial therapy, and warranted an urgent need for other alternatives. During Vietnam War (1955-1975), on 23 May 1967, China launched a project named as "Project 523" to discover potent antimalarial drug under the leadership of Tu Youyou, a woman scientist. Eventually, in 1972, she discovered a powerful antimalarial drug – artemisinin from a plant known as sweet wormwood (* Artemisia annua *L.). The year 2022 marks the completion of 50 years of this epoch making discovery.*

Introduction

Diseases have a dominating influence on human life. Infectious diseases spread rapidly from human, animal and environmental sources, and as a result, give rise to outbreaks, epidemics and even pandemics which cause huge damage to life all over the globe. During the past four years scientists across the world have been engaged in a battle against the sudden traumatic epidemic – Covid-19 (coronovirus disease 2019) caused by the virus Sars–Cov-2, which was discovered in December 2019 in Wuhan, China. Obviously, in this phase of agony and depression, main focus was on finding a suitable remedy for the alarming problem created by Covid–2019. These efforts also generated an increased awareness towards other global epidemics – such as malaria which is still a dire health issue in developing nations. The discovery of the wonder antimalarial drug artemisinin in 1972 was a great breakthrough in the history of malaria therapy after the discovery of quinine in 1820. Even today, despite the availability of several new antimalarial drugs and modern research activities, malaria remains a serious disease which affects approximately 40 percent of global population. Recently, in 2020, 241 million cases of malaria and 627000 deaths due to malaria were reported by World Health Organization (WHO)[1].

The name malaria is derived from medieval Italian words: "mal" meaning bad and "aria" meaning air. In his treatise, "*On Arias, Water and Places*", the renowned Greek Physician, Hippocrates (400 BC) described the disease as *marsh fevers*, *agues*, *tertian fevers*, *quartan fevers* and intermittent fevers. In 1880, the French army

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Madam Tu Youyou

Surgeon, Charles Louis Alphonse Laveran while working in Algeria, discovered the presence of single–celled protozoan parasite belonging to genus *Plasmodium* in the blood of malaria patients, and concluded that it is the pathogen causing malaria in humans[2]. For this discovery, he was awarded the Nobel Prize in Physiology or Medicine in 1907. In continuation of this work of Laveran, Sir Ronald Ross in 1897 found the presence of Plasmodium "eggs", Oocysts in the guts of female anopheles mosquitoes. His studies on birds and humans revealed the fact that female anopheles mosquitoes act as vector to transmit the malarial parasite from one individual to another[3] . He was awarded the 1902 Nobel Prize in Physiology or Medicine. Ronald Ross was a British medical doctor who was born on 13 May 1857 in Almora (Uttarakhand), India to Sir C.C.G. Ross, a General in English army, and his wife Matilda. Working in the Indian Medical Service till 1898, he was variously posted in Madras, Moulmein (in Burma/Myanmar), Baluchistan, Andaman Islands, Bangalore, Secunderabad, Kherwara in Rajputana (now Rajasthan), Assam and most importantly in Calcutta. In 1899, Ross resigned from Indian Medical Service and carried on his work on malaria at England, and other parts of the world including Africa, Greece, Mauritius and Cyprus. His work has been given in his Nobel lecture[4a] and his Memoirs[4b]. The journal Science and Culture brought a special issue on Ronald Ross and his work[4c].

A small memorial on the walls of SSKM Hospital, Calcutta commemorates Ross's discovery. The memorial was unveiled by Ross himself, in the presence of Lord Lytton, on 7 January 1927. The laboratory where Ross worked has been transferred into a malaria clinic named after him. There is also a plaque on the outer wall. Sir Ronald Ross is one of 23 names to feature on the frieze of London School of Hygiene & Tropical Medicine, pioneers chosen for their contributions to public health. Sir Ronald Ross Institute of Parasitology is the building in Begumpet where Ross made the discovery that malaria was transmitted by the female anopheles mosquito on 20 August 1897. 20 August later came to known as the World Mosquito Day. The laboratory has been transformed into a small museum exhibiting photos of Ross and his family. Various charts and diagrams explain Ross's work on malaria and its transmission.

Treatment of Malaria

Malaria is an ancient disease, and its effective treatment by quinine was known to humankind long before the discovery of its cause[5-7]. Quinine as a constituent of bark of cinchona tree (old name quina) was serendipitously discovered in 1660s. Many stories are linked with the origin of quinine[8,9]. According to a legend, an Indian residing in South America was lost in a jungle of Andes. He was miraculously cured from a high fever by unknowingly drinking water from a jungle pool. The water was bitter in taste as it was tainted with bark of surrounding quina–quina trees (the name used by natives of South America for cinchona). He shared his amazing experience with villagers, who thereafter, started the use of bark for the treatment of fever.

There is another legend which is widely accepted in Europe. According to it, the wife of Viceroy of Peru known as Countess of Chinchon recovered from malaria by taking an extract prepared from the bark of a Peruvian tree. Swedish botanist Linnaeus in 1742 gave the name cinchona to the genus of the trees from which the bark was obtained for the treatment, in order to honour the Countess of Chinchon.

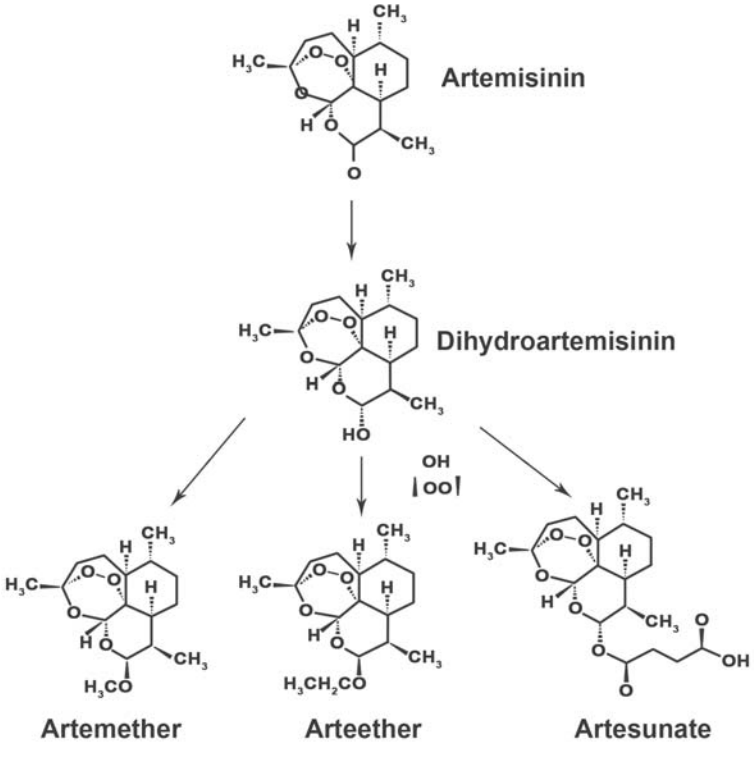
The powdered bark of cinchona tree was initially used for the treatment of malaria in South America. Subsequently, in 17th century, it was used across the world as an excellent antimalarial agent. Jesuit missionaries played a significant role in propagating the use of powdered cinchona bark. Its active principle, quinine was isolated in 1820 by French pharmacists, Pierre–Joseph Pelletier and Joseph Bienaime Caventou.

During World War I, Germany was cut off from its supply of quinine and consequently, scientists in Germany synthesised of a new antimalarial – atabrine or quinacrine which was followed by the synthesis of chloroquine. Chloroquine was ten times more effective than quinacrine at the same dosage, and it had fewer side effects. After

being used for several years, these drugs were found to be less effective due to development of strains of malarial parasite which were resistant to them. Because such resistance was not developed against quinine, this natural drug retained its importance as an antimalarial agent despite some side effects.

Discovery of the New Antimalarial Drug–Artemisinin (ATM)[10,11]

The story of how the wonder drug against malaria–artemisinin was discovered begins with a secret Chinese military Project 523 launched during the Vietnam war (1955-1975). Vietnamese soldiers fighting in mosquito infested rainforests, were dying in vast numbers from malaria. It is recorded that Ho Chi Minh, President DRV, appealed to Chairman Mao Zedong to find an urgent solution to this menace by utilising the vast scientific potential of Chinese scientists. In pursuance of this, an order was issued for a nationwide search was by hundreds of the scientists from institutions across China for the discovery of a new indigenous drug for treatment of malaria. On 23 May 1967, a joint meeting of representative of China's National Science Commission and some top army officers was convened in Beijing to launch a project named as "Project 523" (5 indicates the month, and 23 the date), to initiate a nationwide search for the malaria treatment by 60 military and civilian teams.



Structure of artemisinin and its derivatives

One branch of the project was assigned the work of visiting the various districts of China where malaria was endemic, to collect the relevant information on folklore and traditional medicines from local people. Another branch was directed to contact the drug manufactures for designing the new chemical compounds as possible antimalarial agents. In 1969, Tu Youyou who had graduated from the Department of Pharmacy, Beijing Medical University, and was working at China Academy of Traditional Chinese Medicine was asked to lead the research at the Institute of Chinese Materia Medica (ICMM) in the Project 523. She was a researcher with unique combination of expertise in modern medicines as well as traditional Chinese medicines.

Tu started an extensive search of traditional Chinese medical literature. A careful study of a book: *Zhouhou Beiji Fang* (*The Handbook of Prescriptions for Emergency Treatments*) compiled by the physician, Ge Hong in the year 340 CE revealed that a herb, *quinghao* was an effective remedy for the treatment of intermittent fevers - a symptom relevant to malaria. Tu's team extracted the herb at low temperatures using, water, ethanol, and ether as solvents. The extracts, particularly the ether extract, showed high activity against *Plasmodium falciparum* parasites in mouse models. The herb was identified as *Artemisia annua* L. which is commonly known as sweet wormwood. Although, the ether extract exhibited excellent antimalarial activity, it had some undesirable side effects. To overcome this drawback, Tu *et al*. repeated the experiment on mice and monkeys after removing the acidic impurities present in ether extract by an alkali treatment. Thus, the previously observed toxicity was greatly reduced, and the purified sample showed high efficacy. On 8 March 1972, Tu announced the result of this successful venture at a meeting of the Project 523. Conditions for pursuing further clinical trials for drug development were not conducive at that juncture due to the ongoing so-called 'Cultural Revolution' launched by ultras in China. In the prevailing circumstances, Tu and her colleagues volunteered themselves as the first human subjects for toxicity and dose finding tests. After many clinical and field trials, they found *quinghao* (*Artemisia annua* L.) extract to be safe and free from harmful side effects. Then in 1972, Tu isolated and purified the active component present in it. It was identified as a white crystalline compound, and was given the name - "quinghaosu" ("quinghao" is the Chinese name of *Artemisia annua* L., and "su" means

basic element). Complete structure elucidation of the compound as a sesquiterpene lactone was established in 1975 (***Fig.***). On the basis of the name of the source *Artemisia annua* L. The compound is internationally known as artemisinin (ATM).

Artemisinin was a new antimalarial agent with a totally different chemical structure and higher efficacy, as compared to other conventional drugs against which resistance has been acquired. Successful application of artemisinin and its semisynthetic derivatives as a remedy for malaria attracted attention worldwide during 1980s. The chemical synthesis of artemisinin is not economically viable. Therefore, on commercial scale it is mainly obtained from leaves and flowering tops of cultivated *Artemisia annua* L.

Derivatives of Artemisinin (ARTs) (Fig. *)*[11]

Artemisinin on reduction afforded dihydroartemisinin (DHA). It was found to be 10 times more active than artemisinin clinically. Three other derivatives prepared from dihydroartmisinin (DHA) are artesunate, artemether, and arteether which also exhibit antimalarial activity. Artemisenin and its derivatives (ATMs) constitute a group of significant antimalarials. They are free from any side effect or clinical resistance, although, recently few cases of tolerance have been reported. Apart from their common use in malaria therapy, they have also potent anticancer activity in nano to micromolar range in sensitive and drug or radiation resistant cell – lines.

Role of Artemisinin in Some Recent Approaches to Antimalarial Drug Development

In recent years a plethora of effective and safe drugs has been discovered to combat the menace of malaria. But it is distressing that emergence of resistance to available drugs continues to grow and diminish their efficacy. However, it is reassuring that some new approaches to antimalarial drug development have been designed on the basis of various crucial parameters such as efficacy, toxic side effects, pharmacokinetic compatibility and potential to develop resistance. A brief introduction of these approaches is being given below.

1. Artemesinin – Based Combination Therapy (ACT)[12]**:** In malaria therapy treatment by artemisinin and its combination with other drugs provides good results with decreased chances of resistance. This protocol based on involvement of two drugs in a curative procedure, is known as combination therapy. The drugs that are selected as partner, should ideally be structurally different, more slowly eliminated *in vivo* , and should target those parasites which have not yet developed resistance. Currently, large number of drug combinatios, *e.g., artmether - lunefartricne, artemesunate – mefloquine, DHA - piperaquine, artemesunate - pyaronaridine,* are reported to possess a magnificent efficacy against malaria.

2. Artemisinin Hybrids[13]**:** In an another approach, pharmacological parts from two or more drug molecules are combined in a single entity which is known as hybrid molecule, and acts as a single molecule. The process of formation of a hybrid molecule in known as molecular hybridization. A hybrid has double action following two distinct mechanisms. Sometimes it may follow an entirely new third mechanism also as these compounds are new pharmaceutical entities. The hybrid drugs possess properties of higher safety, higher efficacy and greater reduction in resistance than the original drugs used in their formation. Artemisinin and its derivatives have been employed in the production of many new hybrid antimalarial drugs using quinine, quinacrine, *etc*. as their hybridization counterparts.

3. Dimeric, Trimeric and Tetrameric Artemisinin Drugs[14,15]**:** Antimalarial property of artemisinin and its derivatives has been attributed to presence of endoperoxide group in their sesquiterpene lactone structure. Therefore, it was anticipated that by increasing the number of these units in a drug would enhance its therapeutic potency. The concept gave an impetus for the synthesis of dimers, trimers and tetramers of artemisinin with various length, stereochemistry and flexibility. Efficacy of these possible antimalanials is under investigation. In some mice-models encouraging results have been reported.

Nobel Prize for Artemisinin

For her outstanding contribution in the field of malaria therapy by discovering artemisinin and its derivatives (ARTs), Tu Youyou was awarded Nobel Prize in Physiology or Medicine in the year 2015. She was born on 30 December 1930 in the Port City Nigbo of Zhejiang province of China. Her name "Tu Youyou" is based on a verse mentioned in the *"Book of Songs"* which is a collection of Chinese ancient poetry believed to be compiled by reknowned Chinese philosopher, Confucius. After graduation from department of pharmacy, Bejing Medical University (Previously, known as Peking University) she started working at Chinese Academy of Traditional Chinese Medicine as a pharmacologist, where later she had the honour of being elevated to the coveted positions of Director and Life-long Professor. She was a research worker *par excellence* having extensive knowledge of both modern and traditional Chinese medicines. She was the

first Chinese citizen to receive the Nobel Prize. The Nobel prize was also shared by Willium Campbell and Satoshi Omura for their discovery concerning novel therapy against infections caused by round worm parasites.

In her autobiography to Nobel Foundation, Tu mentions the various difficulties encountered by her team during the discovery of artemisinin. Lack of funding and inadequate laboratory facilities were the great handicaps they faced. Poor ventilation in the laboratory created health related problems for team members. No manufacturing support was available to them as most pharmaceutical workshops ware closed due to the political turbulence going on in China then under the socalled 'Cultural Revolution'. Team members had to extract the herb in wooden household vats. The team worked very hard for a very long time each day without any weekend off. As a mother, she had the responsibility of looking after two young daughters - 2-year old Li Min and 4- year old Li Zun. But in the interest of the nation and the project of national importance, she remained away from her family for long period. This was the time when her husband Li Tingzhao was also interned in a 're-education camp for intelligentsia' in accordance with a protocol of the so-called 'Cultural Revolution'. It is worthwhile to quote these motivating words of her which would inspire students, teachers and scientists all over the world: "Every Scientist dreams of doing something that can help the world. I do not want fame. When you are entrusted with an assignment do your best".

Concluding Remarks

Artemisinin and some of its derivative (ATMs) constitute a group of novel antimalarial drugs providing an effective cure to patients across the globe. Due to their outstanding potency, safety, and accessibility, these compounds provide a powerful tool to combat the malaria scourge which still haunts humankind. In view of some characteristic properties, currently, artemisinin is also being investigated for the treatment of some other diseases such as cancer. The imminent possibility of anticancer activity in artemisinin has paved the way for challenging researches in the realm of cancer therapy. It is expected that the present knowledge about the arteminsinin will provide clues for overcoming the problem of resistance and making it a multifaceted drug of future. Amazingly, to date only drugs which have constantly retained their efficacy are quinine and artemisinin. Both are natural product isolated from plants. ❒

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