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HONOR THE PAST WHILE CELEBRATING THE PRESENT: TU YOUYOU AND THE 2015 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

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If a man keeps cherishing his old knowledge,
so as continually to be acquiring new,
he may be a teacher of others

Confucius

This article aims to highlight the major milestones in the life of a medical scientist, pharmaceutical chemist, and educator Tu Youyou who, without a doctoral degree, a top position at a research institution and background of studying or researching abroad, made a breakthrough in world medicine. Turning to the treasury of Chinese wisdom – traditional Chinese medicine, she, together with her group, created an antimalarial drug that saved the lives of millions of people.

K e y w o r d s: Tu Youyou, 2015 Nobel Prize in Physiology or Medicine, malaria, Artemisia annua, Ge Hong, artemisinin, dihydroartemisinin.

Modern medicine, following in the footsteps of science, often leaves behind the centuries-old achievements of humankind and, by doing so, it can overlook traditional methods of treating diseases that can be more effective in some cases [1]. Although conventional (allopathic, western) medicine often treats traditional medicine at best as an outdated and poorly educated distant relative, “various systems of traditional medicine being used around the world include acupuncture, herbal medicines, indigenous traditional medicine, homeopathy, traditional Chinese medicine, naturopathy, chiropractic, osteopathy, ayurvedic and Unani medicine” [2]. According to the WHO Global Report on Traditional and Complementary Medicine 2019, the number of Member States with national policies on T&CM (traditional and complementary medicine) increased from 25 in 1999 to 98 in 2018, with national or state level laws or regulations – from 45 in 1999 to 109 in 2018, with a national program for T&CM – from 23 in 1999 to 79 in 2018, with a national office for T&CM – from 49 in 1999 to 107 in 2018, with a national expert committee on T&CM – from 32 in 1999 to 93 in 2018, with a national research institute for T&CM – from 19 in 1999 to 75 in 2018 [3].

Nowadays, traditional, complementary and alternative medicine play a big role in health care around the world providing a holistic approach to a human [4]. A 2012 US survey found that more than 30 percent of adults and about 12 percent of children used health care approaches beyond conventional medicine/Western practices [5]. As of 2021, 24 percent of adults in the United States reported using herbal medicine, supplements or teas, 18 percent – essential oils, 15 percent – chiropractic medicine, 14 percent – yoga or meditation, 11 percent – aromatherapy, 10 percent – non-prescribed drugs, 9 percent – acupuncture, 6 percent – homeopathy, 4

percent – crystal healing, 4 percent – Reiki, 2 percent – other [6]. Lee at al. noted that in 2022, the reported prevalence of use of traditional, complementary and alternative medicine over the previous 12 months was 24 – 71.3% [7].

Albeit biomedicine and traditional and complementary medicine have pros and cons, integration of these approaches seems to be beneficial for humanity ensuring a holistic approach to an individual and developing novel therapies [8]. One of the striking instances of "the marriage" of biomedicine and traditional medicine is the discovery of antimalarial properties of artemisinin by Tu Youyou who won the Nobel Prize in Physiology or Medicine in 2015 [9].

Tu Youyou [10]

A Chinese medical scientist, pharmaceutical chemist, and educator Tu Youyou was born on December 30, 1930, in Ningbo, Zhejiang province, China, where her family lived for many generations [11]. Her father worked in a bank, and her mother looked after the daughter and four sons [12]. An interesting coincidence is that the girl's father named her Youyou "based on a famous poem which means a deer is eating the artemisia in outside while calling its friends to come together" [13]. And the plant Artemisia mentioned in the poem became inextricably linked with Tu's career.

As Tu Youyou mentioned, her family had a "*long history of highly valuing children's education*" [11], which contributed to her own educational background. She attended private schools – Ningbo Chongde Primary School (1936–1941), Ningbo Maoxi Primary School (1941–1943), Ningbo Qizheng Middle School (1943–1945) and Ningbo Yongjiang Girls' School (1945–1946) [11].

Tu Youyou with Prof. Lou Zhicen in the 1950s [10]

Unfortunately, the girl's successful education was suddenly interrupted: at the age of 16 she had contacted tuberculosis. She had to take a two-year break before resuming her study at the private Ningbo Xiaoshi High School (1948–1950) and Ningbo High School (1950–1951). The sad experience of illness determined Tu's future career – she decided to devote herself to medicine. She passed the entrance exam allowing her to enroll at Peking University Medical School's Department of Pharmacology. As a student, she learned to classify medicinal plants, extract bioactive chemicals, and determine their chemical structures that later became the basis for her professional success. In her biography published by People's Literature Publishing House, Tu Youyou stated that "s*he felt lucky about having a chance to further her education after high school as a girl in that unenlightened period*" [14].

After graduating with a degree in Pharmacology in 1955, she joined the Institute of Materia Medica at the Academy of Traditional Chinese Medicine (later the China Academy of Chinese Medical Sciences), where she would remain for her entire career [15]. Being exposed there to new areas of research, Tu Youyou started her research projects on Lobelia chinensis (the herb traditionally used to treat schistosomiasis) and Radix Stellariae (the root used to treat fevers) [11].

From 1959 to 1962, she participated in a training program on Chinese medical theory and practice

geared toward professionals with a Western medical background [16]. Tu Youyou learned traditional Chinese medical theory and attended the program on the processing of Chinese Materia Medica, about which she said: "*This processing skill is a unique and exclusive pharmaceutical technology and has been widely used for the preparation of Chinese materia medica. The traditional way of processing was developed and summarized from thousands of years of experience in the traditional Chinese medical practices, with a belief that processing could alter the properties and functions of remedies, increase medical potency and reduce toxicity and side effects. In fact, differences in chemical compositions have been detected between herbs treated with different processes. Knowledge of such processing, in combination with the scientific explanation, benefited my work enormously*" [11]. This experience has largely become the foundation for the application of ancient Chinese knowledge to the creation of modern drugs.

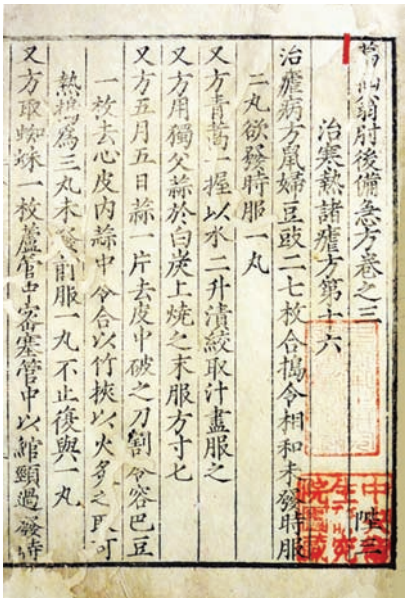
In 1963, Tu Youyou married Li Tingzhao, a former school classmate and factory engineer with whom she would have two daughters, and settled down in Beijing serving as the Chief Scientist at the Academy of Traditional Chinese Medicine [12, 17].

Tu Youyou lived in times of turmoil. During his last decade in power (1966–1976), Mao Zedong tried to renew the spirit of the Chinese Revolution [18]. During this period, intellectuals were declared to be the "Stinking Old Ninth" and were seen as "offenders" such as landlords, right-wingers, and people who wanted to take China on a capitalist road. Schools and universities did not escape the sad fate and came under pressure or were shut down [12]. Many research programs were stopped, and many intellectuals were executed or imprisoned in re-education camps [19]. The consequences of the war and the Cultural Revolution led to inadequate scientific funding, unfair treatment and a shortage of research-oriented scientists [13]. In a climate of constant fear, Tu Youyou kept her head down. One can only imagine what she felt when she was recruited for Project 523.

Project 523 is a code name for a 1967 secret military project of the PRC to find antimalarial medications. It was set up by Chairman Mao Zedong in order to help Communist troops fighting in the jungles of Vietnam, where they were losing more soldiers to malaria than bullets [10]. The increasing number of chloroquine-resistant malaria cases in the civilian population further heightened North Vietnamese concern. Initially the project was directed by the Chinese military medical research authorities, however it became so extensive that civilian scientists were involved (over 60 institutions and more than 500 scientists and other personnel). The plan aims at integrating Chinese and Western medicines, taking Chinese drugs as its priority, emphasizing innovation, unifying plans, dividing labor to work together [20].

In 1969, Tu Youyou was appointed head of Project 523. She began researching the effects of malaria *in situ* by traveling to Hainan Island in Southern China, which was currently experiencing its own malaria outbreak. Recalling this, she said: "*The task I took was to search for a new drug from the traditional Chinese herbal medicine to fight against malaria. We needed a totally new structured antimalarial to deal with the drug resistance*" [21]. This responsible task left its mark on Tu's entire life including her family. Her husband was a detainee in a labor camp, her elder daughter was sent to a full-time nursery where she had to live with her teacher's family, and her younger daughter stayed with Tu's parents in Ningbo. Tu Youyou regretfully noted that her younger daughter could not recognize her when she visited her parents three years later, and her elder daughter hid behind her teacher when Tu Youyou picked her up upon returning to Beijing [11]. However, seeing many children died of malaria in Hainan, the researcher realized that work was the first priority and that it was necessary to sacrifice her personal life for it [22].

Her search for antimalarial drugs began with collection of relevant information and recipes from traditional Chinese medicine: "*To start with, I began to search the ancient medical books, compendium of Materia Medica, folk formulary and so on. I visited and interviewed many old doctors, including doctors in Southern China*" [21]. Within three months after the start of the project, Tu Youyou and her team screened over 2,000 herbal, animal and mineral prescriptions and made 380 herbal extracts, which were tested on mice [16]. Later on, she summarized 640 prescriptions in a brochure "Antimalarial Collections of Recipes and Prescriptions" [11] for further evaluation. Researchers searched for the names of the most frequently repeated plants, and one of them was *Artemisia annua* (also known as sweet wormwood, sweet annie, sweet sagewort, annual mugwort or annual wormwood). In ancient TCM sources, *Artemisia annua* is more commonly referred to as qinghao.



Ge Hong. A Handbook of Prescriptions for Emergencies [22]

Professor Tu's team tested extracts from more than 100 plants on the rodent malaria parasite *Plasmodium berghei*. An extract from *Artemisia annua* "had ~68% inhibition rate initially, but the activity was not stable, varying from 12–40% inhibition in subsequent repeats. The variation in antimalarial activity could be due to many factors, including (as reported by Prof Tu in 1972 presentation to the scientists in the project) geographic origins of the plant, seasonal variation, different parts of the plant (leaves or stem) and the methods used in extraction" [24]. Tu Youyou, as a true researcher, was constantly looking for an answer in ancient texts, in which the use of qinghao was recorded as relieving malaria symptoms.

A key insight into an antimalarial was provided by Ge Hong (III–IV century AD) – a philosopher, alchemist, Taoist practitioner, physician of the Eastern Jin Dynasty, and the author of the treatise "Zhou Hou Jiu Zu Fang" (A Handbook of Prescriptions for Emergencies) [26]. Like many Taoist masters, Ge Hong pursued the idea of creating a medicine that would turn people immortal. For Taoists, life is the highest value. According to some researchers [27, 28], Taoism has contributed to the development of science and medicine in China. Taiwanese say: "Confucianism is a food store, Buddhism is a department store, and Taoism is a drug store" [29]. Ge Hong discovered numerous herbal remedies to treat diseases. Reading his treatise, Tu Youyou found a

Artemisia annua [23]

suggestion to use one quantity of qinghao plus two quantities of water to squeeze the juice out of the substance. Drinking this juice would treat the symptoms of malaria [21].

Tu Youyou realized that high temperature could be the cause of instability in antimalarial activity they experienced. As she put it: "*This unique way of using Qinghao gave me the idea that heating during extraction might have destroyed the active components and the high temperature might need to be avoided in order to preserve the herb's activity*" [11]. The second hint that also determined the successful creation of the drug was that the plant leaf was likely the part having the most activity, because the juice could be obtained from the leaves much easier than other parts of the plant [24].

After realizing that the application of high temperature during the extraction process may cause damage to the active ingredients of *Artemisia annua*, Tu Youyou decided to use ether instead of ethanol for extraction (ether has a lower boiling point). On Octo-

Ge Hong [25]

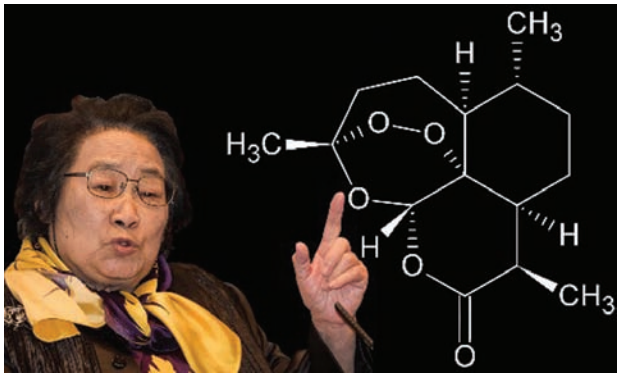
ber 4, 1971, her team observed that sample number 191 of *Artemisia annua* ethyl ether extract showed 100% effectiveness in inhibiting malaria parasites in rodent malaria [11, 30].

On March 8, 1972, Tu Youyou presented her work at a meeting held in Nanjing. The obtained results were exciting, and the leadership of 523 Project decided that she should conduct a clinical trial. To do this, it was necessary to produce large quantities of *Artemisia annua* extract. However, most pharmaceutical workshops were shut down during the Cultural Revolution, and researchers had to do it themselves using household vats and working long hours. The facility where the ether tanks were located had no ventilation system or protective measures from toxic chemicals and gases. Working under these conditions was dangerous: Tu Youyou was ultimately diagnosed with toxic hepatitis. The harsh working conditions had a negative impact on her health. As she noted: "*I lost all my teeth after the research. We had no chemical protection at that time*" [31]. Other research members also suffered, one of them lost her life during this work [14].

To expedite the safety evaluation as soon as possible, Tu Youyou volunteered to be the first human subject. "*As the head of this research group, I had the responsibility*", she said [17]. She and two other team members took the extracts under close monitoring in the hospital. Then, another five members volunteered in the dose escalation study.

In August 1972, Tu Youyou tested her extracts on 21 patients in Hainan. The trial was successful, all patients recovered from the fevers and no malaria parasites were detected after treatment. Nine other patients were also successfully treated in Beijing.

On November 17, 1972, the exciting results from the first clinical trial in Hainan and Beijing were reported at the National Project 523 meeting that led to a large-scale effort to extract large quantities of the pure ingredient – *artemisinin crystal* (Qinghaosu in Chinese). Tu Youyou pointed out that her team "*started to determine the chemical structure of artemisinin in December 1972. The first thing we verified was that the compound did not contain nitrogen. This gave us a hint that the compound we found could be a new chemical different from quinolines. The team later confirmed that the compound was a new sesquiterpene lactone containing a peroxy group with a formula of* $C_{15}H_{22}O_5$ *and a molecular weight of 282… We started collaboration with the Shanghai Institute of Organic Chemistry and the Institute of Biophysics of the Chinese Academy of Sciences on artemisinin chemical structure analysis in 1974. The stereo structure was finally determined using X-ray crystallography at the Institute of Biophysics. This was one of the first applications reported in China in determining an absolute molecular configuration utilizing the scattering effects of oxygen atoms by X-ray diffraction technique*" [11].



The structure of artemisinin [12]

Artemisinin is poorly soluble in water and decomposes in other protic solvents [32], and in 1973, Tu Youyou synthesized dihydroartemisinin, which, unlike artemisinin, is water soluble. Artemisinin and dihydroartemisinin have proven to be highly effective in antimalarial preparations and have become part of the standard treatment for malaria. Other derivatives of artemisinin were also synthesized in other parts of the country, such as Shanghai and Guangzhou. Pharmaceutical companies in Kunming and Guiling were among the first to bring artemether and artesunate onto the market [33].

The discovery of artemisinin and dihydroartemisinin proved to be the turning point in the battle against life-threatening malaria. Nowadays, artemisinin compounds are the backbone of malaria treatment and are used in combination therapy to reduce the risk of the development of resistance (though there is always a risk of resistance problems) [10]. Artemisinin mainly targets the malaria parasite during the blood stage, disrupting the parasite's ability to replicate within red blood cells and helps reduce the parasites. It is usually combined with another drug, which eliminates the remaining parasites over a longer period [34]. Transforming the way humanity fights malaria, artemisinin compounds ultimately saved millions of lives [35-37].

Despite Tu's enormous contribution to world medicine, recognition came late in her life. In China, under Mao Zedong, she and her team were not

allowed to publish their results, because they were participants in the secret military project. After Mao's death, in 1979, the "Qinghaosu Antimalaria Coordinating Research Group" published an article in English in the "Chinese Medical Journal", but the authors' names were not used. According to a chief researcher of the China Academy of Chinese Medical Sciences L.D. Li, the reason that Tu's research results were recognized so late is excessive government intervention, privilege and hierarchy in the scientific research system [38]. The first international paper was published in "The Lancet" in 1982, and Tu Youyou was not mentioned. However, she had been chosen to present the findings to a visiting study group from the World Health Organization in 1981 [39].

It took two decades, but finally, the WHO recommended artemisinin combination therapy as the first line of defense against malaria, signing an agreement with Novartis, the manufacturer of Coartem® (one of these drug combinations) [40]. The Lasker Foundation, which awarded Tu Youyou its Lasker~DeBakey Clinical Medical Research Award in 2011, called the discovery of artemisinin "arguably the most important pharmaceutical intervention in the last half-century" [22].

In 2015, Tu Youyou received the highest award in science, becoming the first mainland Chinese scientist to receive a Nobel prize for scientific research performed in China and the first Chinese woman – Nobel laureate [22, 41].

The Nobel Prize in Physiology or Medicine 2015 was divided, one half jointly to William C. Campbell and Satoshi Ōmura "for their discoveries concerning a novel therapy against infections caused by roundworm parasites" and the other half to Tu Youyou "*for her discoveries concerning a novel therapy against Malaria*" [42].

In her Nobel Lecture, Tu Youyou quoted a poem "On the stork tower" by Wang Zhihuan (the Tang Dynasty) "*The sun along the mountain bows; The Yellow River seawards flows; You will enjoy a grander sight; By climbing to a greater height*" *and encouraged the world to "reach to a greater height to appreciate Chinese culture and find the beauty and treasure in the territory of traditional Chinese medicine!"* [44].

Tu Youyou has received numerous national and international awards for her outstanding contributions to antimalarial research, including the Lasker~DeBakey Clinical Medical Research Award,

Tu Youyou at the Nobel Prize Award Ceremony [43]

the Prince Mahidol Award and the Medal of the Republic, P.R. China – China highest scientific honor [45-47].

In 2016, MDPI, a publisher of open-accessed scientific journals, established the Tu Youyou Award to honor scientists in the field of natural products chemistry and medicine chemistry and grant CHF 100,000 for their research [48, 49].

Regardless of her achievements and worldwide fame, Tu Youyou remains a very modest person, stating that "*nothing can be more rewarding than the fact that artemisinin, since its discovery, has saved many malaria patients' lives*" [11]. In her own words, "*every scientist dreams of doing something that can help the world. I do not want fame. When you are entrusted with an assignment, you do your best*" [50].

Referred to as the "Three-Without Scientist" (she won the Nobel prize without a doctoral degree, without holding a top position at a research institution, without background of studying or researching abroad, Tu Youyou was promoted to Researcher (the highest researcher rank in mainland China) in 1980. In 2001, she was promoted to academic advisor for doctoral candidates. As of 2023, she is the Chief Scientist of the China Academy of Chinese Medical Sciences [51].

Despite worldwide recognition, Tu Youyou remains a controversial figure in the Chinese scientific community, since some feel that her recognition has come at the expense of other participants in Project 523 [10]. This attitude is closely related to the collective identity of Chinese scientists, which is in opposition to the Western emphasis on individualism and the pursuit of personal values [38]. However, Tu Youyou has always acknowledged that the discovery of a new drug was the fruit of lots of collective work.

She expressed deep gratitude to her colleagues from Project 523 and various research institutes across China for their vital contributions, coordination efforts and dedication to the research [44].

Tu Youyou and her team's discovery gradually brought the world's attention to traditional and complementary medicine, which had been considered in opposition to Western (allopathic) medicine. It turns out that they are not mutually exclusive but are parts of one and the same puzzle that humanity has yet to assemble.

Unfortunately, nothing lasts forever under the moon. Lately, artemisinin is losing its effectiveness, and its magic has not been working as well. Therefore, attempts were made to create combination drugs, and malaria vaccines have become available [52, 53]. It is quite possible that ancient Eastern wisdom can help us address this pressing problem, and the "marriage" of Western and Eastern medicines will make humans' lives safe and healthy. Tu Youyou is convinced that "*Chinese medicine will help us conquer life-threatening diseases worldwide, and that people across the globe will enjoy its benefits for health promotion*" [22].

ШАНУЙТЕ МИНУЛЕ, ОСПІВУЮЧИ СЬОГОДЕННЯ: ТУ ЮЮ І НОБЕЛІВСЬКА ПРЕМІЯ В ГАЛУЗІ ФІЗІОЛОГІЇ АБО МЕДИЦИНИ 2015 РОКУ

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Стаття спрямована на висвітлення головних віх у житті вченого-медика, хіміка-фармацевта та педагога Ту Юю, яка, не маючи докторського ступеня, керівної посади в науково-дослідній установі та досвіду навчання або досліджень за кордоном, зробила прорив у світовій медицині. Звернувшись до скарбниці китайської мудрості – традиційної китайської медицини, вона разом зі своєю групою створила протималярійний препарат, який врятував життя мільйонам людей.

Ключові слова: Ту Юю, Нобелівська премія 2015 року з фізіології або медицини, малярія, *Artemisia annua*, Ге Хун, артемізинін.

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