Life Research

doi: 10.12032/life2021-0121-601

COMMENT

Science in Chinese medicine

C.P. Ong[1]

[1]11420 Beall Mountain RdPotomac, MD 20854, USA.

*Corresponding to: C.P. Ong. Independent Researcher, 11420 Beall Mountain RdPotomac, MD 20854, USA. Email: cpTaiji@gmail.com.

This paper reviews the discovery of artemisinin, an antimalarial compound from an herbal plant that was awarded the Nobel Prize. The recognition has brought traditional Chinese medicine and science closer but traditional Chinese medicine therapeutics are still poorly understood. The deployment of traditional Chinese medicine drugs with the support of medical science has contained the COVID-19 pandemic in China. But the success has not resulted in a global effort to study the Chinese therapies as the pandemic continues to rage across the Western world. The paper aims to draw more science into "Qi" and traditional Chinese medicine, and promote the scientific investigation of the functional efficacy of Chinese medicine and its treasure trove of materia medica. All these point to the imperative to update and consolidate traditional Chinese medicine diagnostics and therapeutics with medical science and technology to unlock traditional Chinese medicine's potential.

Key words: Chinese medicine, TCM, Qi, Artemisinin, COVID-19, Youyou Tu

***Abbreviations*:**

TCM, traditional Chinese medicine; WRAIR, The Walter Reed Army Institute of Research; WHO, the World Health Organization; ACTs, artemisinin-based combination therapies; QFPD, the experienced prescription Qingfei Paidu decoction.

***Competing interests*:**

The author declares that he has no conflict of interest.

***Citation*:**

C.P. Ong. Science in Chinese medicine. *Life Res*. 2021;4(1):5. doi: 10.12032/life2021-0121-601.

***Executive Editor*:** Yu-Ping Shi.

***Submitted*:** 06 December 2020, ***Accepted*:** 20 January 2021, ***Online*:** 24 January 2021

Background

"Qi" is central in traditional Chinese medicine (TCM) theory. It is viewed as a vital life-force energy coursing through the meridian network and the system of organs. TCM physiology and pathology are based on the dynamics of this energy which takes on multiple functional forms. Despite "Qi's" permeating presence in TCM it eludes Western medical science. "Qi" escapes being measured as a physical quantity. TCM's prognosis of health is based on a person's "Qi", which is composed of "Qi" energies of physiological activities. Health wellbeing means a store of robust "Qi" in flux and which dynamics is in accord with the principles of "Yin" and "Yang". Diseases are consequences of the disharmonies of "Qi" activities that stretch beyond healthy limits, affecting the normal functions of the organs, which can be caused by internal or external pathogenic factors. The TCM treatment principle is to restore a relative balance to the "Qi" disharmony. The diagnosis of diseases is an art of reading the patient's "Qi" for "patterns of disharmony" and signs of "functional disturbance" at pulse-points, the color of the tongue, the face complexion, the quality of breathing, and others. The deciphering of the changes in "Qi" is a cultivated art of "Qi", guided by TCM theory and supported by a rich compilation of Chinese medical knowledge and case studies. Treating a disease necessarily includes manipulation of "Qi" to restore it to normalcy by physical therapeutics such as acupuncture or herbal intervention.

Western medical science relies on a battery of tests to measure quantitatively the vital signs, such as body temperature, heart rate, blood pressure, levels of sugar levels, cholesterols, hormones, etc. to ascertain the state of health based on variations from statistical norms. Nevertheless, in the final analysis the diagnosis of a syndrome calls on the physician's expertise and experience, which includes a subjective element. In TCM, the diagnosis is nuanced by the pathogenic factors of "wind, cold, heat, dampness, dryness and fire" that affect the "Qi" state. These factors could introduce differences in the diagnosis, based on the individual, climate, region or season. This may result in 2 persons with the same disease receiving different therapies, and people with different diseases receiving the same therapy. The variability in prescription remedies for the same disease does not lend well to the protocol standards of control in clinical trials. This, in conjunction with the esoteric concepts, couched in metaphysics, which arose 2,000 years before science, renders the task of reconciling TCM with medical science an intractable challenge [1].

We take a pragmatic approach by reviewing the science in TCM let the reconciliation emerge. Section 1 reviews the discovery of artemisinin, a potent antimalarial compound from the extract of the *Artemisiae annuae herba* used in the TCM herbal treatment for malaria symptoms. The discovery received Nobel recognition in 2015, opening TCM to more collaboration with science. At the time of the award, TCM was still being viewed with skepticism and dismissed as a pseudoscience in the medical science establishment [2]. In Section 2 we see the science of TCM less directly, by the efficacy of TCM treatment program in containing the COVID-19 pandemic in China.

TCM's gift to science

Youyou Tu was awarded the Nobel Prize for Medicine, jointly with William C. Campbell and Satoshi Omura, in 2015. She was also the first and only Chinese national to receive the Prize for Medicine and also the only Chinese woman to be a Noble Laureate. She was honored for the discovery of artemisinin, an extract from *Artemisiae annuae herba*, a TCM herbal plant, which proved to be a game-changer in killing quinine resistant malaria parasites. Youyou Tu's discovery was an integration of training in TCM and Western medicine. It shows what Science can do for TCM and what TCM can contribute to Science. In 1955, Tu graduated from Beijing Medical College in pharmacology. She then underwent TCM training designed for professionals with a Western science background from 1959 to 1962. Youyou Tu is distinctive as a homegrown scientist with no academic title.

In the 1960s, malaria emerged again as an epidemic disease of global concern. A new strain of parasite, *Plasmodium falciparum*, had made it resistant to the known antimalarial drugs of chloroquine and quinolines. In the jungle war theatre of the Vietnam War, malaria infection was claiming more casualties among soldiers than in actual combat on both the U.S. and the Vietnamese sides. As many as 1% of the US combat troops were succumbing to malaria a day, making it deadlier than the enemy. Fighting malaria was thus a top military priority. The Walter Reed Army Institute of Research (WRAIR), the US Military's research arm on medical science, embarked on the largest program then to find antimalarial drugs.

The malaria toll was worse for the North Vietnamese soldiers in the jungles, with their military strength reduced by as much as half at one stage. Ho Chi Minh sought help from China. In response, Mao Zedong launched an antimalarial drug research program (named Project 523) in 1967. The project could not have been undertaken at a worse time as the country was in turmoil, engulfed by the Cultural Revolution (1966–1976). Intellectuals were publicly denigrated. Among them were scientists, whose morale could not have been lower. Research facilities, if any, were limited and old, and basic resources were scarce in China. On the other

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doi: 10.12032/life2021-0121-601

hand, the US had enormous resources and the most advanced and state-of-the art technology in medical research. Therefore, there was no question that the US would sprint out way ahead in the race to find new antimalarial drugs. It appears that the vast TCM materia medica of drugs tipped the scale of the overwhelming odds.

In the 15-year period from 1963, the US WRAIR discovery program screened over 250,000 potential compounds and found 2 which were developed as Lariam and Halfan. These drugs were approved by the US Food and Drug Administration on a fast-track with the randomized tolerability study waived, Lariam in 1989 and Halfan in 1992, and marketed. Soon after, severe adverse side effects were reported. Later studies confirmed that Lariam caused erratic psychiatric behaviors due to its neurotoxicity. And Halfan was found to cause irregular heartbeats (ventricular dysrhythmias) that could be fatal. That put an end to the antimalarial promise of the drugs [3].

On the other side, the Chinese scientists managed to screen only tens of thousands of potential compounds between 1967 and 1969, and not surprisingly, turned up no effective antimalarial substance. In 1969, Youyou Tu, who was researching at the Institute of Chinese Materia Medica of the Academy of Traditional Chinese Medicine, was put in charge to head the Institute's search for novel antimalarial drugs from Chinese medicines. She was then 39. She immediately proceeded to comb through the extensive TCM literature, which turned out to have a comprehensive record of treatment for malaria symptoms. Besides reviewing the records, Tu also went on field trips to interview TCM practitioners for any malaria treatments, including folk recipes. In three months she was able to gather over 2,000 herbal, animal and mineral prescriptions, which she winnowed down to 640. Unfortunately, extracts from the hundreds of herbs failed to produce any promising results tested on rodent malaria. Beginning in June 1971, she began to focus on the common *Artemisiae annuae herba* that was most frequently used for malaria symptoms. It was first prescribed for "intermittent fevers" in a 4th-century text, *A Handbook of Prescriptions for Emergencies*, by Ge Hong. But the multiple tests of its extract still failed to produce any promising antimalarial results. On rereading Ge Hong's herbal recipe, Tu was struck by its singular preparation method of soaking the fresh herbal plant in water and then "to wring out its juice". It immediately dawned on her that the standard method of decoction by boiling was damaging the extracted compound. She modified the extraction process using ethyl ether, which reduced the decoction temperature. The extract sample No. 191 in October 1971 proved 100% effective on rodent malaria resistant to chloroquine. (The *Artemisiae annuae herba* extract was specifically that of the *Artemisia annua L.* species; there were 5 other *Artemisiae annuae herba* plants which did not produce meaningful active extracts). The same positive results were obtained when tested on malaria-infected monkeys, between December 1971 to January 1972. This represented the breakthrough in the discovery of artemisinin or Artemisinin, its Chinese name. On working with its chemical structure, Tu accidentally synthesized dihydroartemisinin in October 1973, which turned out to be even more potent (and more soluble in water) than the parent compound in antimalarial activities. After testing its safety on themselves, Tu and her colleagues conducted the clinical trial of *Artemisiae annuae herba* ethyl ether extract for the first time on human subjects, 21 malaria patients in Hainan and 9 in Beijing, between August and October 1972. All the patients recovered with full clearance of chloroquine-resistant malaria parasites. Extended clinical trials were then carried out in collaboration with other institutes between 1973 and 1978 [4].

In the subsequent years, other institutes synthesized and developed a number of derivatives of dihydroartemisinin into new drugs, such as, artemeter, artesunate and arteether. The research works were not hidden from the world. The seminal work of Tu's clinical trials was first published in 1977, albeit in a Chinese journal. With an eye to the West, a more comprehensive and up-to-date report of the groundbreaking research of artemisinin's antimalarial activities was published in English in the *Chinese Medical Journal* in 1979. The world took notice. In 1981, the World Health Organization (WHO), the World Bank and United Nations Development Programme held the 4th Joint Malaria Chemotherapy Science Working Group meeting in Beijing, which highlighted the development of artemisinin research. Subsequently, WHO issued a comprehensive report on the development of artemisinin and its derivatives in October 1986, which also announced the adoption of arteether (rather than artemether favored by the Chinese in their research) as the derivative compound to focus on [5]. Although Project 523 was officially shut down in 1981, the malarial research work continued. In 1985 Zhuo Yiqing at the Institute of Microbiology and Epidemiology of the Chinese Academy of Military Medical Sciences, took the new artemether drug one step further, combining it with another antimalarial lumefantrine, which multiplied the antimalarial potency. His team found a cure rate of over 95% in severe malaria cases with the combination drug in clinical trials. This combination drug became the first of the many artemisinin-based combination therapies (ACTs) that would follow.

Even as evidence in more studies of the effectiveness of ACTs was mounting and the clamor for the drugs getting louder, it would not be until 2006 that WHO threw its weight fully behind the Chinese ACTs,

endorsing them as the first-line of antimalarial drugs in its treatment guidelines [6]. No doubt, the WHO action was also pushed by the Bush administration's unveiling of the *President's Malaria Initiative* in 2005. Now, thanks to the Global Fund and other international agencies, over a hundred million doses of antimalarial ACTs are made available each year to poor countries [7]. From *Artemisiae annuae herba* tea, TCM's age-old prescription for malaria symptoms, to the tablet form of artemisinin-based combination therapies, as the world's most potent antimalarial drugs, a lot of science has gone into the development. The Nobel Laureate, Youyou Tu, touted this as TCM's gift to science. The artemisinin extract has dragged TCM out into modern science but, in its ancient garbs, TCM remains opaque to science. With the Nobel light shining on, its treasure trove of herbs and remedies may yield yet some more medical gems in the future.

TCM's role in COVID-19

By March 10, 2020, Wuhan, the first ground zero epicenter of the COVID-19 pandemic, had been brought under control by a national program that combined TCM and medical science. New confirmed cases were down to a trickle from 2,000 a day at the height of the crisis. China's confidence in the coronavirus containment was in full display when President Xi Jinping visited Wuhan on that day to inspect the work of the pandemic and to express the country's gratitude to the frontline medical workers as well the many military and community staff, grassroots party officials, and volunteers. The turnaround came about a month and a half after the city of 11 million, was put under lockdown on January 23, which soon after was extended to the rest of the country. The lockdown could not have come at a worse time, as China was in the midst of a weeklong celebration of the most important and festive occasion of the year, the Lunar New Year of the Rat which fell on January 25. This disrupted an estimated 3 billion trips of annual Chinese workforce migration returning home for a family reunion across the country. By late March, the number of infections in China had stabilized at around 83,000, with 80% in the Province of Hubei where Wuhan is. While the Province was reporting no new cases in five consecutive days, outside in the world, the numbers were soaring in Italy, Spain, France, UK, and the USA. As the lockdown was lifted on April 8 in Wuhan and the last COVID-19 patient discharged on April 27, a day after, the number of cases in the US surpassed a milestone million mark. China's success in containing the outbreak came at an incalculable cost of a frozen economy and an unquantifiable social and personal pain. The price was well paid as the early containment lowered the base of the spread of the coronavirus from China, which must be a country's foremost duty and responsibility in a pandemic.

Just before the lockdown, China's National Health Commission had formed a National Task Force consisting of 14 experts from both TCM and Western science, headed by a renowned pulmonologist and respiratory scientist Zhong Nanshan, to battle the outbreak. By the time they descended on ground zero, the novel coronavirus had had at least a month's head start. In December, a SARS-like coronavirus was known to be the cause of a cluster of pneumonia cases. Early on some research scientists in the international community were made aware of the concerns of the novel coronavirus. Four days into 2020, the medical scientists in Wuhan officially contacted their US counterparts and WHO and apprised them of the situation. There was no let-down in the assault on the research front to unravel the virus. On January 7, a consortium of international scientists led by Professor Zhang Yongzhen of Fudan University, Shanghai, succeeded in deciphering the genome of the novel coronavirus. Three days later, the genomic sequence was posted and made publicly available on an open-access site, virological.org, and was also deposited in GenBank [8]. That the research works in vaccines and therapeutics are advancing as rapidly as they have been, are due to the warp speed effort of genomic sequencing by the Chinese scientists.

The *Science* publication picked up the ground-breaking news on January 11. To put a marker on the timeline, on the same morning, the first death from the new disease was reported by the Wuhan health authorities. The patient was a 61-year-old man who also suffered from abdominal tumors and chronic liver disease. As the task force experts were formulating actions, the cases were exploding exponentially and overwhelming the city's hospitals. They were immediately pushed into a race against time. Early treatment was critical to stop the virus from ravaging through the patient quickly. In response to the urgency and the surging logistical demands, a 1,000-bed hospital was built and put into operation with staff and medical equipment, in a record 10 days, and then another was built. On the treatment end, with no cure or vaccine in sight, the default line of defense against the novel coronavirus pneumonia fell on TCM which had been deployed with efficacy during the SARS outbreak in 2003, and the H1N1 flu epidemic in 2009. Science gives us the specific strain of the coronavirus complete with a picture and a genomic print. We can see the progression of the virus's action as captured graphically in the COVID-19 video [9]. Once the virus finds its way inside the lungs, its spikes latch onto an ACE-2 receptor-key to enter a host cell to replicate and spread, causing pneumonia and other illnesses. But medical science could offer no treatments as yet. TCM pointed to a "dampness toxin" ("Shidu") as the pathogenic agent of the pestilent "Qi" causing communicable pneumonia

disease. Although unscientific, TCM could turn immediately to therapies that would invigorate the Spleen "Qi" to remove dampness.

Dr. Zhang Boli, an Academician of China's Academy of Engineers (Division of Medicine and Health) and one of the 14-member National Task Force, was in charge of the TCM treatment effort, with a team of 209 TCM doctors and nurses. At one of the make-shift hospitals in Wuhan that was designated primarily for TCM care, Zhang and his team decided to implement a comprehensive treatment plan for the 564 coronavirus patients in the hospital with mild symptoms (heavy coughing, loss of appetite, nausea, vomiting, diarrhea, shortness of breath and tiredness) to stop them from getting severe. They applied a prescription, primarily, using the experienced prescription Qingfei Paidu decoction (QFPD) [10], the experienced prescription Xuanfeibaidu and other formulas, complemented with Taiji exercise, Baduanjin (a "Qi"-energetic exercise) and acupuncture therapy. With the treatment program, none of the patients developed into severe cases, a remarkable achievement, given that 6% to 10% of mild COVID-19 cases would become severe, according to WHO statistics. Also, Zhang noted that the blood biochemical indices taken in the treated patients showed an increase in the number of leukocytes, neutrophils, lymphocytes, and platelets, indicating deployment of defensive-"Qi" (immune agents). The success pushed the adoption of the TCM treatment to complement Western medicine across 90% of the Wuhan hospitals and inclusion in the National Health Commission's guidelines for fighting the epidemic. Six hundred thousand sets of the TCM drugs were distributed in Wuhan alone. The treatment served crucially to bring control to the epidemic as it was peaking in mid-February, as well as to bring down the fatality rate. Zhang attributed the success to the integrated treatments, "Western medicine offers important life-supporting measures such as respiratory and circulatory assistance, while TCM focuses on improving the patients' physical conditions and immune function. They complement each other [11]."

The use of TCM was not without controversy and the claims of its efficacy were not without challenge [12]. Indeed, the publicity and promotion of its use were criticized as China's push for selling TCM, as splashed in South China Post headlines (March 23), "Beijing pushes traditional Chinese medicine as coronavirus treatment despite questions over benefits." And there was the usual chorus of critique that TCM is not science-based. The QFPD drug consists of 21 herbs and thus is multi-dimensional in its target in a network of pathways. The drug's multi-components clear away heat, detoxify, dry dampness, and boost immunity and fight the virus as it progresses in the host body but the science is not established. Nevertheless, the positive therapeutic effects of QFPD are being confirmed based on the relatively new discipline of network-pharmacology [13]. An up-to-date list of publications on the use of TCM to treat COVID-19 is available at the website of the UCLA Center for East-West Medicine [14]. Five months after the COVID-19 outbreak was brought under control in late March in China, the global number of infections exploded past 25 million. The United States, with 4% of the world's population, leads the world with 25% of the COVID-19 cases, passing another milestone of 6 million (183,068 deaths) as of August 31, 2020. (December 5 Update: Global cases 66,065,479, global deaths 1,521,598; US cases 14,385,385, US deaths 279,008) [15]. It is hard to quantify the role of TCM but the program has successfully contained COVID-19 in China. Science may not be there yet, but science will follow and catch up with functional efficacy.

Conclusion

TCM and medical science may have established a handshake but they remain far apart. TCM diagnostics and therapeutics are drawn from TCM theory and in practice rely on the physician's cultivated cognition of "Qi" and clinical expertise, thus subjective. They do not communicate well with medical science as they are not based on scientific data. Nevertheless, they have the test of efficacy to fall on supported by a vast store of case studies. In large enough numbers the anecdotal cases prove to be a reliable guide as to the effectiveness of the remedies. TCM theory is driven by functional efficacy and science follows efficacy. Science caught up with the *Artemisiae annuae herba* plant and unlocked its antimalarial potency to the benefit of medical science. Science is always behind in the event of epidemic disease and it takes time to develop vaccines and cures. TCM has an advantage in that TCM drugs are not tied to specific diseases. Using the basic treatment principle, TCM could tap into its vast medical materia to find QFPD and other drugs that worked to ameliorate the symptoms of COVID-19 and boost the immune system, which functioned well to help contain the pandemic in China. Despite the advances in medical science and technology, some diseases, like advanced metastatic cancer, elude dependable cure. The clinical conditions of diseases are not framed in the same logical format as that of the physical sciences. The cause-and-effect of diagnoses and treatments cannot be analyzed with the same level of precision except in cases of identifiable pathogenic agents. This helps to explain why the results are very mixed in treatments for a large number of common chronic complaints or disease syndromes. Treatment regimes are further challenged by the placebo effect, the positive outcome of a sham treatment given to a control group in a clinical trial. The placebo effect represents a significant number, between 20% to 40%, with some registering over 50%. This means that an

inert treatment administered in an illness could get a significant therapeutic outcome. This is very unlike the experimental studies in the physical sciences where the margin of error in experiments is relatively small and directly attributable to measurements. To further compound the issues, several published reviews have now questioned the placebo effect as unreliable. Notably, a report in the Cochrane collaboration has found that "in general, placebo treatments produced no major health benefits, although on average they had a modest effect on outcomes reported by patients, such as pain [16]." A more recent review concludes that the placebo effect is "in part a muddle and part a phantasm [17]." Western medicine has the clear advantage of medical technology in diagnostics—blood tests, blood pressure readings, ultrasound imaging, EKG, EEG, X-rays, CT scan, PET scan, etc., but ultimately, treatment boils down to the clinical analysis of the disease. Whether with TCM or Western medicine, this calls on the clinical expertise of the physician, part science and part art (the art in healing). In this regard, TCM may hold an advantage as its treatment rationale is almost purely healing as an art.

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