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Artemisinin: From Chinese Herbal Medicine to Modern Chemotherapy

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Artemisinin: From Chinese Herbal Medicine to Modern Chemotherapy

Anthony Butler

Malaria is a disease that has blighted humankind since early times. The first antimalarial treatment available to Europeans was the dried bark of the cinchona tree from Peru. The main problem in its use was adulteration by other material. The 'active principle' was first extracted in 1820 and named quinine. It was found to be a more powerful and reliable drug than cinchona bark. Once its chemical structure had been determined, it was possible to synthesize substances chemically related to quinine that were equally powerful but could be manufactured industrially. Mepacrine (atabrine) was amongst the most successful, but had adverse side effects. To avoid these side effects, further chemical modification gave chloroquine, a highly successful drug. This sequence is a common way of converting an herbal remedy into a modern-style chemical drug. It parallels, to some extent, the process of potentiation common in traditional herbal medicine. By the 1970s, drug resistance had developed

with chloroquine. To find and develop a new antimalarial drug that worked on an entirely different pharmacological principle, Chinese scientists turned to their herbal compendia (*ben cao*) and found that *Artemisia annua* (*qing hao*) was frequently mentioned as a treatment for intermittent fever. Whether, in view of the distinctive doctrines of Chinese medicine, it should be possible to extract an active principle as described above is discussed. After a very careful reading of the procedure given for the use of *qing hao*, an active substance, artemisinin, was extracted. Artemisinin has a truly remarkable chemical structure, and chemical modification produced artesunate, the drug of choice. To prevent the development of resistance, artesunate is used in combination with other antimalarial drugs. Modern pharmacology has largely ignored that other substances in artemisia and the cinchona bark may contribute to their therapeutic effect. This matter is also discussed.

Keywords: malaria, quinine, chloroquine, artemisinin, drug discovery.

Introduction

Malaria is a disease that has been with humankind since the dawn of civilization. It has been suggested that more humans have died of malaria than any other disease in the history of the world (Packard 2007). Malaria is caused by the presence of the parasite *Plasmodium* in the bloodstream. There are five species of *Plasmodium* that give rise to malaria, of which *P. falciparum* is the most serious as it can cause blood clots to form in the brain. This condition is known as cerebral malaria and can be the cause of death. One of the most characteristic symptoms of all types of malaria is an intermittent fever, and the interval between bouts corresponds to the reproductive cycle of the particular species of *Plasmodium* present in the patient's blood.

The vector that carries the parasite from an infected person to a new person is the female *Anopheles* mosquito, as she requires human blood for the nourishment of her eggs. Thus, any attempt to counter malaria in both the individual and the community must include a drug with directed toxicity towards *Plasmodium* and a means of controlling the mosquito. Here we are concerned with only the former. Malaria is a serious health problem in mosquito-inhabited parts of the world and is thought to cause the death of around a million children a year in Africa since their immune system is not fully developed (Maitland 2016). Those living permanently in malarious areas do acquire some immunity as they mature.

Early Treatment for Malaria

Before the seventeenth century, Europeans tried a number of herbal remedies, but none were effective. The first success came with the Spanish colonization of South America. Jesuit missionaries in Peru brought back to Europe the bark of the fever tree (*Cinchona* spp.) (Rocco 2003). They likely learned of its healing properties from Inca herbalists. It proved to be an effective remedy for malaria; since the disease occurred all over central and southern Europe, the effect of its arrival was dramatic and meant that all who could afford the bark stood a chance of recovering from malaria. It also allowed people to explore and colonize malarious regions of Africa that previously had been left alone. Demand for cinchona bark (sometimes known as 'Jesuits' powder') soon outstripped supply. One reason for this was that removing the bark often killed the cinchona tree, and the search for more bark took hunters to more and more remote parts of Peru until, eventually, the supply dried up. The British government managed to obtain seeds of the cinchona tree around 1850, raised seedlings at Kew Botanic Gardens in London and established

plantations in India. The trees did not flourish. The Dutch authorities obtained some of the seeds and were much more successful with plantations in Java, and this eventually became the chief source of cinchona bark (Jercho 1993).

Extraction of Quinine

One of the main drawbacks with bark as a medicine is the possibility of adulteration. Unscrupulous traders substituted bark from other trees, with no curative properties, for cinchona bark. By the beginning of the nineteenth century, organic chemistry had developed a number of experimental procedures that allowed two French chemists to extract the active principle—that is, the substance or substances amongst the dozens in the bark responsible for cure of malaria—from the Peruvian bark (Pelletier and Caventou 1820). The active principle in cinchona bark is composed of two substances, which are both alkaloids: quinine and cinchonine. The former is easier to isolate and became the world's first antimalarial drug. Thus quinine (Figure 1) was born and rapidly became the drug of choice, rather than the crude bark, for the treatment of malaria. This is an early example of the transformation of an herbal remedy into a modern-style chemical drug.

The curative properties of Peruvian bark were always uncertain, even if the bark was authentic, because the amount of quinine it contained varied according to the season of harvesting. Extraction of the active principle led not only to a more powerful but also a more reliable drug as it was possible, by means of an assay, to assess its purity. Quinine is still used today for the treatment of malaria. The quinine story, of extraction and purification from an herbal source, is a frequent sequence of events in the development of a new drug from a medicinal herb. The process may also be seen as parallel to that used in biomedicine for the potentiation of an herbal remedy. A further example is the use of powdered foxglove leaves in the treatment of dropsy. They were the recommended remedy for centuries, and it was not until the 1920s that the glycoside responsible for its effect was extracted, purified, and identified (Smith 1930). Digoxin is now used in preference to the dried leaves.

Synthetic Antimalarial Drugs

The German effort during World War I was severely compromised by poor access to quinine since fighting took place in malarious parts of Europe, such as Italy and the Balkans. During the 1920s, German chemists studied compounds that retained some aspects of the chemical structure of quinine but were much simpler and could be

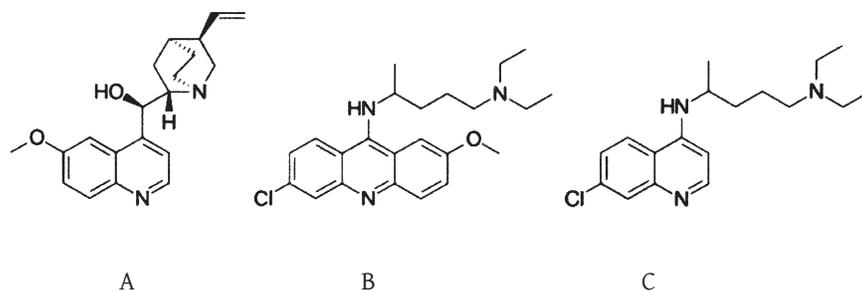


Figure 1. Chemical structure of quinine (A), mepacrine (B), and chloroquine (C). (Butler, 2019)

prepared in the laboratory and then in a chemical factory. Many of them had quinine-like curative properties. A particularly successful one was mepacrine, or atabrine (Figure 1B). It was used extensively by United States (US) troops during the war in the Pacific, and was found to be superior to quinine as an antimalarial drug (Sneider 1996). By 1945, the Americans had produced an even better, chemically related, antimalarial drug: chloroquine (Surrey and Hammer 1946; see Figure 1C). It was inexpensive to make and showed few adverse side effects. For a number of years, it was the drug of choice in the treatment of most forms of malaria.

The sequence of events described above (synthesizing compounds chemically related to the active principle as extracted from the herb, thus leading to a more powerful and effective drug) is a common part of modern drug development. The lead comes not from the wisdom of modern pharmacologists but rather from a humble herbal cure. Chloroquine can be seen as the climax of a series of chemical modifications of the quinine molecule, all yielding a better drug than that supplied by nature.

Project 523

The triumph of chloroquine did not last for long. By the late 1960s, its efficacy as an antimalarial drug showed a significant decline; the malarial parasite had mutated in some way as to resist the toxicity of chloroquine. This is the parasite showing a characteristic of all living things, namely the wish to live. Resistance caused grave concern in the West and removed any chance of success in attempts to eradicate malaria worldwide. It was also causing concern in a part of the world of which, at that time, we knew very little: China.

As China went through a period of great tumult and cruelty during the Cultural Revolution (1966-1976), Chinese soldiers were fighting a war in the jungles of Vietnam against the South Vietnamese. It was a highly malarious region and soldiers, normally free of malaria because they took chloroquine as a prophylactic, started to develop symptoms of the disease. Without effective

malarial chemotherapy, success in jungle warfare is almost impossible. As a result, the Chinese government, led by Mao Zedong at the prompting of Zhou Enlai, set up an extensive research program (known as Project 523) to find an alternative to chloroquine (Li 2007: 5-20). By 1967, over five hundred scientists from sixty institutions had been recruited, and the group included chemists, pharmacologists, entomologists, and doctors.

Although Mao's aim was to modernize China, he insisted that traditional Chinese medicine was a 'great treasure house,' a phrase made famous by its inclusion in the 'The Little Red Book.' He insisted that it should be taken seriously in spite of the views of some Chinese scientists that it should be relegated to the waste bin. Accordingly, part of the work of Project 523 was to see if there was anything in traditional Chinese herbal medicine that would give a lead to a new antimalarial drug in the way that Peruvian bark had led to quinine. Herbs were harvested in the traditional way and subjected to extraction and analysis. The extract was then tested against murine malaria. To see which herbs should be tested, it was necessary to know how malaria was named in the old herbals. This matter has been examined authoritatively by Hsu (2006a, 2009). The term 'intermittent fever' (a hallmark symptom of malaria) occurs in several texts and, although not all sufferers from malaria display this symptom, it is so characteristic of the disease that we may say that many people experiencing intermittent fever had what we now call malaria. Any herb said to treat intermittent fever was felt worthy of consideration, and this is what the scientists on Project 523 set out to do (Hsu 2014).

The Doctrines of Chinese Medicine

We now come to a more complex problem peculiar to the Chinese situation. In Chinese medicine, herbs were prescribed according to a highly organized system, seeing the functioning of the body in a holistic manner. Bad health and disease were seen as the body working in a non-harmonious way. *Yin* and *yang* were not in balance, *qi* was not flowing freely, and the five elements (*wu xing*)

were not in accord. An herb, or more likely a mixture of herbs, would restore harmony and balance, but this might work only in a human system and not *in vitro* or in a mouse model. The malarial parasite is difficult to culture *in vitro*. How closely was herbal prescribing in China inextricably bound to its distinctive medical system? Modern western phytotherapy has long since abandoned Galen's theory of the four humors, but the parallel process in Chinese medicine has not occurred. A recent edition of the official Chinese pharmacopoeia (Chinese Pharmacopoeia Commission 2015) uses the vocabulary of both Western pharmacology and traditional Chinese medicine. To believe that Chinese medicine is truly a 'treasure house,' do we have to accept what Sivin has called the 'doctrines' of Chinese medicine (Needham et al. 2000), or can we ignore them and just note what herbs were used, as done in Western herbalism?

Ackerknecht (1982) has argued that medical doctrines are a reflection of the society in which they were conceived. This is certainly true of Chinese medicine where, in the early centuries of the first millennium, there were many different medical doctrines. As the country became more united, efforts were made by scholars over the centuries to unify the doctrines. For example, *The Yellow Emperor's Classic of Internal Medicine (Huang Di nei jing su wen)* was probably first written in the second century BCE and revised by different scholars until Wang Bing completed the work in the eighth century CE. To this day, it is still consulted by practitioners of Chinese medicine, which indicates the continuing importance of the doctrines. The *Emperor's Classic* describes in elaborate detail the workings of *yin/yang*, the flow of *qi*, and balance of the *wu xing*.

Alongside medical theory existed the work of artisan physicians, who prescribed cures for the ills that beset humankind using mainly the herbs that grow so abundantly in China, but also the distinctive therapies of acupuncture and moxibustion. Over the centuries, details of therapeutic herbs were collected and published in 'herbal compendia' called *ben cao*. The earliest of the *ben cao*, *The Divine Husbandman's Classic of Materia Medica (Shen Nong ben cao jing)* was completed in the first century BCE, and many others were produced over subsequent centuries, reaching a climax in the posthumous publication of the *Ben cao gang mu (Materia Medica Arranged according to Drug Description and Technical Aspects)* by Li Shizhen in 1596 CE. It lists over 1,800 medicinal herbs. To what extent are these remedies linked to the doctrines of Chinese medicine?

Needham, the great historian of all things scientific and medical in medieval China, was in no doubt about the link. He held that Chinese medicine was a body of knowledge derived directly from empirical findings. Chinese

scholars may have been deficient in relevant information because they lacked the tools for studying the human body, but what they asserted may contain 'heralds' of what modern science now understands about the human body. He saw Chinese medicine as a river flowing into an ocean that is 'modern science.' Other rivers include Greek and Ayurvedic medicine, but modern science is the unifying destination of them all. This view is fully expounded throughout Needham's writings, as well as by Ho and Lisowski (1993). In opposition to this view, Unschuld sees little connection between the doctrines of Chinese medicine and the empirical prescribing to be found in the *ben cao*. In his discussion of the *Huang Di nei jing su wen*, he suggests that Section 74 is really the birth of prescription pharmacy. This section is a substantial one and the subject matter diverse (for a full discussion of Unschuld's commentary on the *Huang Di nei jing su wen*, consult Unschuld 2003: 301-313). Interestingly, Section 74 points out that it is not only the qualities of each herb in the remedy that makes the cure effective but also the combination and the location of the disease. It suggests there is a specific prescription for each diseased condition. Significantly, he remarks that "neither the yin-yang nor the five-agents doctrine are taken into account here" (Unschuld 2003: 312).

According to Unschuld, the doctrines of Chinese medicine were the speculations of scholars, detached and intellectually curious, and they changed in step with cultural changes, but the cures were the province of artisans interested in earning a living by offering hope to suffering humankind. The cures remained remarkably constant. The compilers of the *ben cao* may have been scholars but they merely assembled material that had been unearthed by others. Unschuld sums up the dilemma for those trying to assess the value of Chinese medicine for the current time:

Are these foundations [the doctrines] required to understand Chinese medicine and practice it successfully, or can the substances and techniques used in Chinese medicine be effectively separated from their traditional background and explained in terms of Western science without becoming useless? (Unschuld 2003: 323)

His answer is an unequivocal yes, and one with which I concur. When the separation is made, one of the barriers to the use of the *ben cao* in drug discovery is removed and the valuable observations contained therein may be utilized in the modern treatment of disease by the process of extraction and biological testing. In a limited but valuable way, this has already been done. *Ma huang*, from *Ephedra sinica*, is mentioned in the comprehensive



Figure 2. *Artemisia annua*.

(Butler, 2015)

Ben cao gang mu as treatment for impaired circulation and coughing. Its medicinal properties were rediscovered in the West by a Japanese chemist when ephedrine was extracted from the plant and used, initially, as a mydriate and later for the treatment of asthma and chronic pulmonary disease (Amatsu and Kubota 1913). An account of the use of saltpeter (potassium nitrate, *xiao shi*) for the relief of the pain of angina reveals a perceptive piece of empirical prescribing that can be rationalized by recent discoveries in cardiac physiology (Butler and Moffett 2009). In both these cases, no reference is made to the doctrines of Chinese medicine, but valuable insight has been gained from information in a *ben cao*. What follows is an account of an even more spectacular example.

Treatment of Malaria from the *Ben Cao*

Plants of the *Artemisia* genus are recommended in the *ben cao* for the treatment of intermittent fever. The two varieties mentioned are *qing hao* and *huang hua hao*. Hsu has shown that, strictly, *Artemisia annua* (from which a new antimalarial drug was eventually extracted in Project 523) is *huang hua hao* and not, as commonly supposed, *qing hao* (*A. apiacea*) (Hsu 2006a). The researchers of Project 523 used *A. annua* (Figure 2), but called it *qing hao* (sweet wormwood). Initial experiments in extracting from the plant some pharmacologically active material were unsuccessful for an interesting reason. Instructions for the use of the herb in the treatment of intermittent fever were given by the fourth century alchemist and physician Ge Hong. He writes:

Another recipe: *qinghao*, one bunch, take two *sheng* [0.4 litres] of water for soaking, wring it out, take the juice. Ingest it in its entirety. (Ge Hong, fourth century: 3.16)

As part of Project 523, a modern version of this was tried in which the leaves were immersed in hot water, the solid material filtered off, and the filtrate tested on a malarial murine model. No effect was observed. However, when a nonpolar solvent (petroleum ether) was used instead of hot water, material was extracted that proved to be highly

toxic towards the malaria parasite in a murine model. The extract was named *qing hao su* (extract of *qing hao*) and later given the Westernized name of artemisinin. Further tests confirmed its effectiveness. It was purified and its chemical structure determined. The reason why the traditional route of administration, as described by Ge Hong, yielded a negative result was possibly the consequence of the now standard process of filtering off any solid material before testing the juice. Artemisinin forms in trichomes of the plant (Xiao et al. 2016) and soaking will release it into the water but it will not dissolve and therefore will be present in suspension. Hsu (2006b) has pointed out that Ge Hong instructs us to drink the juice without further refinement. Once in the body, it can be solubilized by formation of a glucuronide—a frequently employed strategy in human physiology—to give artemisinin human metabolite, which is water-soluble, and this enters the bloodstream. Artemisinin does not appear to be solubilized by any of the other substances derived from the plant (Butler and Renton 2000).

Chemical Structure of Artemisinin

Elemental analysis and nuclear magnetic resonance spectroscopy indicated that artemisinin is a sesquiterpene lactone with many oxygens present. The full structure (Figure 3) was revealed by an investigation using X-ray crystallography to show three fused alicyclic rings, one of which is 7-membered and, most surprisingly, one ring is spanned by a peroxide bridge. Peroxides are normally very unstable, but in artemisinin the peroxide group is quite stable, and artemisinin can be heated to 150 °C without decomposition. Although the mode of action of artemisinin is uncertain, it is probably the peroxide group that is responsible for its antimalarial activity. In the presence of a metal ion, such as the iron of hemoglobin, the oxygen-oxygen bond breaks giving rise, after a series of transformations, to carbon-centered radicals that destroy the malarial parasite (Butler et al. 1998; Meshnick 2002). All the three chemical features mentioned (fused alicyclic rings, a 7-membered ring and the peroxide bridge) are unusual in a plant natural product, and to find all three in the same material is astonishing. When news of artemisinin reached the West, there was considerable skepticism, particularly over the chemical structure, but the Chinese work was fully confirmed by other researchers.

Artemisinin is not an ideal drug as its low water solubility limits its bioavailability. Therefore, it has been chemically modified to give an even better drug. The most successful modification is to convert it into the half ester of succinic acid to give artesunate (Figure 4) (Rosenthal 2008). This is generally the form in which artemisinin is

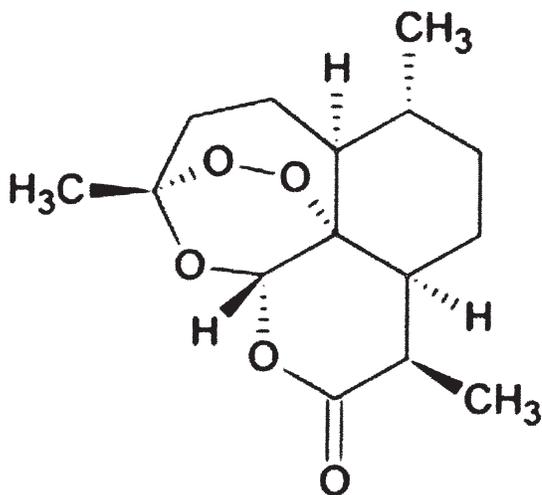


Figure 3. Chemical structure of artemisinin.

(Butler, 2019)

used therapeutically, although there are other chemical modifications in use. Artesunate is water-soluble and can be used orally, rectally, intramuscularly, or intravenously. As is the case with quinine, parts of the molecule may not be necessary for its antimalarial action, and simpler molecules with a trioxolane structure have been synthesized. One, arterolane, looked promising in *in vitro* testing but performed less well in clinical trials and has not challenged artesunate's position (Posner et al. 1999). For the large-scale production of artemisinin, *A. annua* is cultivated by small farmers in Africa and China, the leaves harvested and sent to factories where artemisinin is extracted and purified. High-yield plants have been developed by a process of selective breeding at the Centre for Novel Agricultural Products at the University of York. One of the difficulties with this system for the production of a product where the demand is about the same each year is that farmers are not willing to grow *A. annua* when the prices of other farm products are high. Production of the drug in a factory through biosynthesis involving genetically engineered yeast is under development. This has recently become quite successful and may provide a more reliable source. However, farm-produced artemisinin will probably remain an important source of the drug.

The Nobel Prize

In 2015, half the Nobel Prize in Physiology or Medicine was awarded for the discovery of the antimalarial properties of artemisinin. The other half of the Prize went to William C. Campbell and Satoshi Ōmura for work on parasitic worms. The Nobel Prize has to be awarded to a person, and one of the problems was that all the early papers on artemisinin were ascribed to groups rather than people. Thus, studies of its clinical potential, although published in the *Chinese Medical Journal*, were credited to the 'Collaborative research

group on *qinghaosu*' (Collaborative Research Group 1979: 811-816), and its crystal structure was reported in *Scientia Sinica* and credited to 'Qinghaosu Research Group' (Qinghaosu Research Group 1980). However, investigation revealed Tu Youyou as the person largely responsible for the herbal work, and she went to Stockholm to collect the Prize.

Artemisinin Combination Therapy

Not long after artemisinin (which includes the original drug and all its chemical modifications used therapeutically) was first used as a treatment for malaria, it became clear that resistance to artemisinin could develop quite readily. In some parts of Southeast Asia, it was sold over the counter, and there was no attempt at ensuring compliance. Now that artemisinin is the frontline drug in the treatment of cerebral and vivax malaria, preventing resistance is a matter of great importance. To lose the drug because of resistance, as was the case with chloroquine, would be a major tragedy as no new antimalarial drug is waiting in the wings to take its place.

The World Health Organisation (WHO) strongly recommends that, in the treatment of uncomplicated cerebral malaria, artemisinin should always be given in combination with another antimalarial drug, as Artemisinin Combination Therapy (ACT) (Rehwagen 2006). An ACT is a combination of fast-acting, highly potent artemisinin with a slow-acting, less potent drug such as mefloquine, piper-quine, and even chloroquine. ACT is normally given over three days. Artemisinin kills the vast majority of the parasites by one mechanism, and the partner drug eliminates any remaining parasites over a much longer time period by another mechanism. It is thought that the two drugs protect one another from the development of resistance. However, combination therapy is expensive. Many poorer

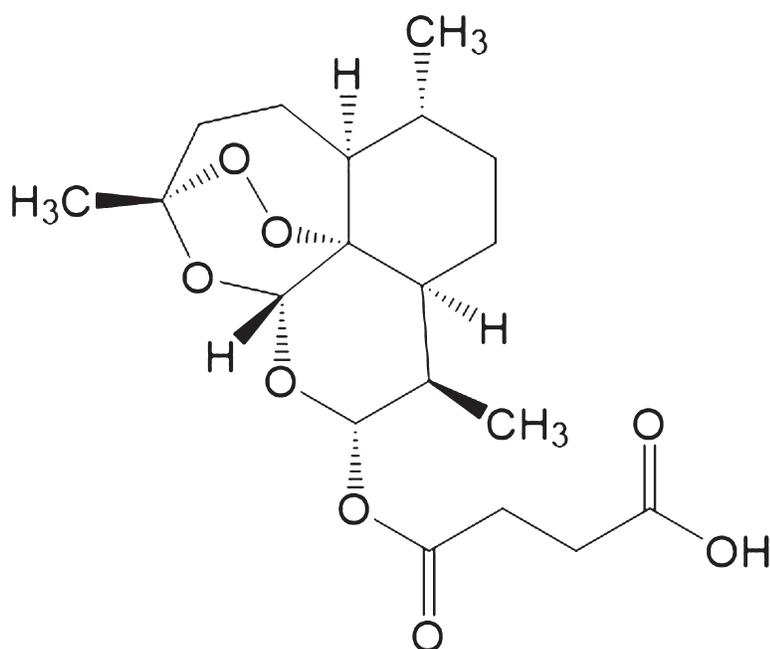


Figure 4. Chemical structure of artesunate.

(Butler, 2019)

countries have tried to use a monotherapy to control malaria, but this is dangerous not only for that country but also its neighbors, as the artemisinin-resistant parasite does not recognize national boundaries. To avoid the use of monotherapies, the WHO has urged manufacturers to package the drugs in such a way that two components are given together.

Much is known at a molecular level about the cause of drug resistance, and its development can be predicted by blood tests. In Western Cambodia, where resistance even to an ACT has developed, frequent tests would allow the ACT used in surrounding provinces to be changed before resistance has taken hold (Noedl et al. 2008). The success of combination therapy in the treatment of malaria suggests that it may be the way forward in the treatment of other diseased states, particularly those treated with antibiotics, but it is bound to be more expensive.

The Future of Drug Discovery

The era of small drugs—that is, molecules of below 400 daltons—is coming to a close (Le Fanu 1999). Drugs like penicillin, aspirin, and the sulphonamides have made enormous improvements to human life, but most bioactive substances (which includes therapeutic drugs) are much larger molecules. Synthesizing large molecules with the hope that they will display drug action when tested is too demanding a program to undertake, as up to 1,000 compounds may be needed to find the one that is active enough to submit for full clinical trials. However, natural products (i.e., substances that can be extracted from living

sources such as plants, animals, and microorganisms) are a ready source of such compounds. We therefore look to living things, principally herbs, for possible therapeutic drugs, as they do the task of synthesis effortlessly, having been provided with enzymes to do the job.

The constituents of the herbal extract are identified and tested for biological activity by a technique known as High Throughput Screening. This approach to drug discovery has proved successful in the past. For example, taxol or paclitaxel was found in an extract from the Californian yew tree during a massive screening of many thousands of natural products found in US plants and trees. This survey was financed by the US Government. Evidence of anti-cancer activity with the extract led to a more detailed study. From this, the first successful drug for the treatment of ovarian cancer emerged. The effort involved in making this discovery was enormous, and government finance was required. Initially, the cost of taxol was costly, which does very little for the general health of humankind. Fortunately, some very clever chemistry involving chemical modification of a more abundant natural product reduced the cost substantially, and taxol is now generally available (see also Tidwell and Nettles 2019).

We are in a promising era for this type of drug discovery, as a number of sophisticated techniques for the separation of the complex mixtures obtained during extraction, and the chemical identification of the components are available. They mostly involve some form of chromatography linked to mass spectrometry. Moreover, in recent years it has been discovered that life can flourish under extreme

conditions, such as in hot springs or at very high pressure at the bottom of the sea. Living things found in such places must have unique physiologies, possibly involving substances not found elsewhere and, possibly, new to chemistry. These are exciting possibilities to develop new drugs for conditions untouched by current therapies.

If herbal medicine is used to select the plants studied, there is a sense in which some of the screening has been done already by countless herbalists over hundreds of years. The chances of success are higher but, disappointingly, rarely is a new drug born in this way. Herbal medicine generally yields a weak drug or one no better than that already available. The discovery of artemisinin is a case when it did work, and worked spectacularly well. The herbs of a country with an unusual or little studied flora are of particular interest, especially if the medicinal values of the herbs have been recorded. However, for many herbalists, by extracting the active principle from the herb we are missing the point of herbal medicine (Butler and Keating 2011). They insist that it is the whole plant, rather than its components, that give it medicinal value. This proposition poses a considerable challenge when it comes to be tested experimentally as herbal extracts often vary in composition. It would be better if the constituents were identified and the pure compounds identified were paired, say, and the biological activity of each pair tested. There might be up to fifty biologically significant compounds in an herbal extract. Consequently, there would be many pairs, and the work would be both tedious and expensive but not impossible. If a pair showed enhanced therapeutic activity, this would suggest that there was some sort of synergy between the constituents of the pair.

The success of ACT in both preventing resistance and enhancing the power of the drug, as described previously, does suggest that mixtures are better than single substances, and sometimes it is a case of '2+2 = 5.' The effect of the combination is greater than the sum of its parts (see also Schwabl and van der Valk 2019). This is known to be true also for the treatment of tuberculosis and leprosy; malaria is in no way special. More experimental work is required if this approach to chemotherapy is to be of general value. It is interesting to note that, in cinchona bark, there are two antimalarial alkaloids, as described previously. Possibly, they act synergistically to give the bark a curative power, which is greater than the small amount of quinine present in cinchona bark might have suggested. There is evidence of synergistic effects in the herbal remedies used for the treatment of malaria (Rasoanaivo et al. 2011).

Conclusion

The isolation of artemisinin from *Artemisia annua* during the most testing of times, was an example of the triumph of perseverance and good scientific skills. Many people were involved in its success that it would have been fairer had others shared the Nobel Prize with Tu Youyou, which was not possible according to the rules. The story of the birth of artemisinin, when told in outline, is a simple one: a common herb, used for centuries by Chinese physicians for the treatment of fever, is now being used worldwide for the treatment of malaria, but that hides much of the good science for which the Nobel Prize was awarded. First, there was the problem of identifying malaria in the *ben cao* and choosing the correct species of *Artemisia* for study. Second, finding the correct procedure for extraction of the drug was a challenge. Drug action is enhanced by extraction. Since extraction concentrates the drug (and thus makes it more powerful), it might be seen as a process that parallels, in modern chemotherapy, the potentiation gained by drug-drug interaction in biomedicine (Jia et al. 2009). Further potentiation, using the term in its more expansive sense, was possible once the chemical structure (mainly from nuclear magnetic resonance spectroscopic and X-ray crystallographic studies) had been elucidated. This allowed chemists to see how the molecule could be modified to increase its bioactivity by making it more water-soluble. It turned out that the most successful way of achieving that was to convert artemisinin into the half ester of succinic acid, to give artesunate. The final step in potentiation was setting up the regimens for artemisinin combination therapy. The drug is potentiated so that resistance will not diminish its power. The attempt at further potentiation by making simpler molecules that contain just the essential part of the artemisinin molecule has been unsuccessful so far. It is perhaps stretching the meaning of the term potentiation somewhat, but promising work on the industrial synthesis of artemisinin, which should reduce its cost, could be considered part of that process. Designing new and costly drugs for diseases that are endemic in poor parts of the world is valueless. Instead, basing a drug on an existing herbal remedy that has been potentiated is much more likely to come up with an affordable drug. Many thousands throughout the world who owe their lives to the development of ACT should be grateful to Tu Youyou and Project 523.

There is one remaining matter for consideration. For the last century or so, one of the aims of pharmacology has been to extract from herbs the active principle and, as new herbs are examined, this is still important. However, it is just as important to examine other substances present in

the herb in order to understand better how potentiation may be achieved by drug-drug interactions and synergy. The presence of substances in the herb, other than the lead compound, may help in avoiding the build up of resistance. Nature may have many more secrets, yet to be revealed.

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References

- Ackerknecht, Erwin Heinz. 1982. *A Short History of Medicine*. Baltimore: The Johns Hopkins University Press.
- Amatsu, H. and S. Kubota. 1913. Über die pharmakologische Wirkung des Ephedrins und Mydriatics. *Kyoto Igaka Zassi* 10: 301-309.
- Butler Anthony R. and John Moffett. 2009. Saltpetre in Early and Medieval Chinese Medicine. *Asian Medicine: Tradition and Modernity* 5(1): 173-185.
- Butler, Anthony R. and Louise Renton. Unpublished observations.
- Butler, Anthony R., Bruce C. Gilbert, Philippa Hulme, Lee R. Irvine, Louise Renton, and Adrian C. Whitwood 1998. EPR Evidence for the Involvement of Free Radicals in the Iron-Catalysed Decomposition of Qinghaosu (Artemisinin) and Some Derivatives: Antimalarial Action of Some Polycyclic Endoperoxides. *Free Radical Research* 28(5): 471-476.
- Butler, Anthony R. and Ruth Keating. 2011. Old Herbal Remedies and Modern Combination Therapies. *Scottish Medical Journal* 56(3): 170-173.
- Collaborative Research Group on Qinghaosu. 1979. Antimalarial Studies on Qinghaosu. *Chinese Medical Journal* 92(12): 811-816.
- Ge Hong (Fourth century CE). 1983. Emergency Prescriptions Kept Up One's Sleeve (Zhou hou bei ji fang) Chapter 3.16. In *Si ku quan shu (Collection of the Works from the Four Storehouses)*. Taipei: Shangwu yinshuguan.
- Ho, Peng Yoke and E. Peter Lisowski. 1993. *Concepts of Chinese Science and Traditional Healing Arts: A Historical Review*. Singapore: World Scientific.

- Hsu, Elisabeth. 2006a. The History of *qing hao* in the Chinese *Materia Medica*. *Transactions of the School of Tropical Medicine and Hygiene* 100(6): 505-508.
- . 2006b. Reflections on the ‘Discovery’ of the Antimalarial *Qinghao*. *British Journal of Clinical Pharmacology* 61(6): 666-670.
- . 2009. Diverse Biologies and Experiential Continuities: Did the Ancient Chinese know that *Qinghao* had Anti-Malarial Properties? *Canadian Bulletin of Medical History* 26(1): 203-213.
- . 2014. How Techniques of Herbal Drug Preparation Affect the Therapeutic Outcome: Reflections on *Qinghao* 青蒿 (*Herba Artemisiae annuae*) in the History of the Chinese *Materia Medica*. In *Artemisia annua: Pharmacology and Biotechnology*, edited by Tariq Aftab *et al.*, 1-7. Berlin: Springer-Verlag.
- Jercho, Saul. 1993. *Quinine’s Predecessor: Francesco Torti and the Early History of Cinchona*. Baltimore: The Johns Hopkins University Press.
- Jia, Jia, Feng Zhu, Xiahua Ma, Zhiwei W. Cao, Yixue X. Li and Yu Zong Chen. 2009. Mechanisms of Drug Combinations: Interactions and Network Perspectives. *Nature Reviews: Drug Discovery* 8(2): 111-128.
- Le Fanu, James. 1999. *The Rise and Fall of Modern Medicine*. London: Little, Brown and Company.
- Li, Ying. 2007. *Discovery and Development of a New Antimalarial Drug (artemisinin)*. Shanghai: Scientific and Technical Publishers.
- Maitland, Kathryn. 2016. Severe Malaria in African Children—The Need for Continuing Investment. *New England Journal of Medicine* 375(25): 2416-2417.
- Meshnick, Stephen R. 2002. Artemisinin: Mechanism of Action, Resistance and Toxicity. *International Journal of Parasitology* 32(13): 1655-1660.
- Needham, Joseph, Lu Gwei-Djen, and Nathan Sivin. 2000. *Science and Civilisation in China*. Vol. 6 Biology and Biological Technology. Part VI: Medicine. Cambridge: Cambridge University Press.
- Noedl, Harald, Youry So, Kurt Schaecher, Bryan L. Smith, Duong Socheat, and Mark M. Fukuda 2008. Evidence of Artemisinin-resistant Malaria in Western Cambodia. *New England Journal of Medicine* 359(24): 2619-2620.
- Packard, Randall M. 2007. *The Making of a Tropical Disease: A Short History of Malaria*. Baltimore: The Johns Hopkins University Press.
- Pelletier, Pierre Joseph, and Joseph Bienaimé Caventou. 1820. Recherches Chimiques sur les Quinquinas. *Annales de Chimie et de Physique* 15: 89-294.
- Posner, Gary H., Michael H. Parker, John Northrop, Jeffrey S. Elias, Poonsakdi Ploypradith, Suji Xie, and Theresa A. Shapiro. 1999. Orally Active, Hydrolytically Stable, Semisynthetic Antimalarial Trioxanes in the Artemisinin Family. *Journal of Medicinal Chemistry* 42(2): 300-304.
- Qinghaosu Research Group. 1980. Crystal Structure and Absolute Configuration of Qinghaosu, *Scientia Sinica* 23: 380-384.
- Rasoanaivo, Philippe, Colin W. Wright, Merlin L. Wilcox, and Ben Gilbert. 2011. Whole Plant Extracts versus Single Compounds for the Treatment of Malaria: Synergy and Positive Interactions. *Malaria Journal* 10(Suppl. 1): 54-66.
- Rehwagen, Christiane. 2006. WHO Ultimatum on Artemisinin Monotherapy is Showing Results. *British Medical Journal* 332(7551): 1176.
- Rocco, Flametta. 2003. *The Miraculous Fever Tree: Malaria and the Cure that changed the World*. London: Harper Collins.
- Rosenthal, Philip J. 2008. Artesunate for the Treatment of Severe Falciparum Malaria. *New England Journal of Medicine* 358(17): 1829-1836.
- Schwabl, Herbert and Jan M. A. van der Valk. 2019. Challenging the Biomedical Notion of ‘Active Substance’: The Botanical Plasticity of Tibetan Medical Formulas. *HIMALAYA* 39(1).
- Smith, Sydney. 1930. Digoxin, a new Digoxin Glucoside. *Journal of the Chemical Society*, 508-510.
- Sneader, Walter. 1996. *Drug Prototypes and their Exploitation*. Chichester: Wiley.
- Surrey, Alexander R. and Henry F. Hammer. 1946. Some 7-Substituted 4-Aminoquinoline Derivatives. *Journal of the American Chemical Society* 68(1): 113-116.
- Tidwell, Tawni and James H. Nettles. 2019. Conceptions of Potency, Purity, and Synergy-by-Design: Toward Developing a Sowa Rigpa Medical Theory-based Approach to Pharmaceutical Research. *HIMALAYA* 39(1).
- Unschuld, Paul U. 2003. *Huang Di nei jing su wen*. Berkeley: University of California Press.
- Xiao, Ling, Hexin Tan, and Lei Zhang. 2016. *Artemisia annua* Glandular Secretory Trichomes: The Biofactory of the Antimalarial Agent Artemisinin. *Science Direct* 61(1): 26-36.