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Plant-Derived Drugs in Malaria Treatment

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Introduction

Every year 880,000 people are killed by malaria, most of them children in impoverished regions of the world lacking adequate medical care. While many preventative measures, such as mosquito nets have decreased the incidence of malaria, once the disease is contracted, it must be treated. Many plasmodial species have developed a frightening resistance to antimalarial agents, making the search for new, effective antimalarial agents an urgent priority of global importance.

Even now the World Health Organization estimates that 80% of the population in Africa and Asia relies on plants and plant-derived products, rather than conventional medical therapies, to treat many different types of diseases.

Malaria, in particular, has a long history of plant-derived anti-malarial therapy. Of the over 1200 plant species reported to possess anti-malarial properties, the development of plant-based antimalarial agents has focused primarily on two sources: Artemisia annua and Cinchona ledgerania, both of which are discussed in this paper [1].

In light of the rising appearance of drug-resistant strains of Plasmodium falciparum, the World Health Organization has issued a recommendation for the treatment of Plasmodium falciparum malarial infections showing resistance to monotherapies. In all regions in which such resistance is common, combination therapies – preferably containing an artemisinin derivative - should be the first line of treatment [2].

The First Recorded Use of the Term Malaiere

In the 5th century, during the demise of the Western Roman Empire, the mainland in northern Italy remained unsafe. At that time Torcello was one of the first islands to be successfully settled in the Venetian Lagoon. Until the 10th century Torcello remained the greatest commercial centre in the lagoon. As silt from rivers on the mainland filled up the shallow waters around Torcello, trade became more difficult and the foul-smelling waters of reduce salinity became perfect breeding places for mosquitoes, turning the northern lagoon into dead water (“laguna morta”). From the 12th century Torcello rapidly deteriorated and the inhabitants gradually made their way to nearby Venice. Buildings in Torcello were dismantled and Venetians recycled useful building materials.

The fate of Torcello may still have been well remembered when in 1440 Venice itself was hit by a fever outbreak, as documented by Marco Cornaro [3].

...Et cusi scorse le cose senza alcuna provision per fina al 1440, del qual anno el fu molte fievre in Venesia in modo chel se diceva che le aque dolce conduseva questo mal aiere...

... That’s how this went on without any protective measures until 1440, a year in which there were many cases of fever in Venice and the people meant that fresh water was responsible for the mal aiere...(Translation Paolo Arese, Turin)

The essay of Cornaro is written in old Venetian dialect.
“Mal aiere” is spelled in Toscanic dialect as “mala aria” by Acciajuoli in 1476 [4].

The term gained popularity in Britain in the 1800s, replacing words like “ague” (from Latin: febris acuta), “marsh fever” or “intermittent fever” [4].

**Artemisinin compounds**

*Artemisia annua* is a two-meter high plant with aromatic leaves and tiny yellow flowers. A common weed in southern China, *Artemisia* is also a native plant in temperate regions across the globe, including Europe and North America. In Africa, where the need for antimalarial drugs is increasing, many current initiatives are in place to foster growth and production of this plant.

**Chinese origins**

*A. annua* is so named because it is the only member of the genus which has an annual growth cycle [5]. The Chinese name for *A. annua* is *qinghao*: Qing (Chinese for green) refers to the dark green uppermost leaves of the plant, which contain the highest concentration of drug when the plant is in flower, Hao refers to the tall stature of the plant.

*A. annua* was used by Chinese herbalists in ancient times to treat fever and other diseases. The earliest known Chinese medicinal recipe book, entitled “The Prescription for fifty-two kinds of diseases” was unearthed in 1979 from a Han Tomb (Han dynasty 206 BC – 220 AD) at Mawangdui in the Hunan Province [6]. In this book, *qinghao* (*A. annua*) was prescribed as a treatment for hemorrhoids.

**Ge Hong**

Ge Hong (283–343 AD) was a prolific writer of alchemical, medical and religious (Daoist) texts. He was frequently offered positions by authorities but denied them all, believing that high and honourable positions were bothersome and fleeting.

In 331 Ge Hong retired to Mount Luofu where he wrote the book “Emergency Prescriptions Kept in One’s Sleeve”, also known as “Handbook for Emergency Prescriptions.” In his book Ge Hong is the first in medical history to prescribe the use of *qinghao* for the treatment of what he terms “intermittent fevers”. His ingenious method consisted of soaking the fresh plant in water, wringing out the whole plant, and ingesting its juice in its entirety [7] (Figure 1).

In 343 Ge Hong died on Mt. Luofu at the age of sixty. His treatment was later popularized by the legendary Chinese pharmacist Li Shizhen (1518–1593) in his book entitled “Ben Cao Gang Mu” (“Compendium of Materia Medica”), published posthumously in 1596. In his book Li Shizhen describes in detail over 1,800 drugs. The book also describes the type, form, flavour, nature and therapeutic application of 1,094 herbs and plants, among them, *qinghao*, which is mentioned as a cure for intermittent fevers. Several new editions and numerous translations of the Compendium have been made throughout the centuries. In modern times the herb *qinghao* has been used as an antimalarial in the countryside of Southeast China [8].

During the wars in neighbouring Cambodia and Vietnam in the late 1960s, the Chinese Government began a systematic examination of plants used in traditional Chinese medicine with the aim of finding a new antimalarial agent. In 1971, the pharmacologist Tu Youyou from the Institute of Chinese Materia Medica,
China Academy of Traditional Chinese Medicine, extracted the active principle of qinghao. She used ether in her extraction and named the compound *qinghaosu*, meaning “principle from qinghao” in Chinese. *Qinghaosu* is a stable and easily crystallizable compound with a molecular weight of 282 Da and a molecular formula of $C_{15}H_{22}O_5$ [9].

**Current use of Artemisinin**

To prevent the emergence of resistant *Plasmodium falciparum*, Artemisinin is commonly used in combination with other active antimalarial drugs. Artemisinin-based combination treatments (ACTs) are generally accepted as the best treatments for uncomplicated falciparum malaria [10]. Cost is a major obstacle to ensure adequate treatment in most malaria endemic countries. Only a minority of the patients that need ACTs actually receive them. One artemisinin-based combination therapy, artemether–lumefantrine (Coartem), is currently being produced by Novartis and has a wholesale price of US $2.40 per adult treatment (reportedly with little or no profit margin), as compared with US $0.10 retail for chloroquine [11], putting Coartem out of financial reach for all but tourists, military forces and the urban elite. The expense of artemisinin has already led to the production of counterfeit drugs and black market distribution.

Fortunately international support is being mobilized to help provide ACTs to countries in need. During 2006 more than 62 million treatment courses of Coartem were delivered to over 30 African countries, helping to save an estimated 200,000 lives.

**Quinoline-related Drugs**

Within a two day intraerythrocytic cycle *P. falciparum* digest more than two-thirds of the hemoglobin, the oxygen-carrying pigment of red blood cells. Protein free hematin, the detergent-like component of hemoglobin, is toxic when it is in a highly charged and soluble $\alpha$-hematin state, but becomes insoluble and inert when bio crystallized to $\beta$-hematin. The quinoline antimalarials appear to act by preventing biocrystallization of the toxic heme. Heme biocrystallization is highly specific to the malarial parasite, and the drug target is outside the genetic control of the parasite.

For hundreds of years quinine was the only drug used in the prevention and treatment of malaria. The drug is found in the root, bark, and branches of cinchonas and other trees, which are evergreen trees originally part of the high forest (1500 – 2700 m) of the eastern slopes of the Andes Mountains from Venezuela to Bolivia [12,13]. The natives called the cinchona-bark *quinquina* (“the bark of barns”), from which came the word *quinine*. The name *jesuits’ powder* became synonymous with the bark since the Jesuits had done so much to popularize it as a remedy for malaria. At the age of 46, Francisco de Goya (1746–1828) suffered from a severe illness. An infectious disease such as meningitis, encephalitis, or malaria was the likely cause. After a few months he recuperated but was left stone-deaf forever. Toxicity associated with Quinine treatment (cinchonism) may have complicated his illness. Quinine has a well known number of unpleasant side effects such as bitter taste, tinnitus, nausea and vomiting [14].

Quinine has provided the basis for the development of synthetic counterparts such as chloroquine, amodiaquine and mefloquine [15]. Ironically, a synthetic quinine substitute, the skin-staining atebrin, developed by Bayer (“Interessen-Gemeinschaft Farbenindustrie AG”, Elberfeld, Germany) in the 1930s proved instrumental to Allied success in the Second World War when the supply of quinine from countries in the South Pacific was cut off by Japanese military conquest. Malaria parasites are susceptible to quinine and other quinoline-containing drugs only when they degrade hemoglobin and produce pigment. The pigment forming pathway in *P. falciparum* is a specialized parasite biocrystallization process with a proven history as an exploitable therapeutic target [16]. In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer.

Circulating malaria parasites catabolize hemoglobin as an important source of amino acids and to maintain osmotic stability. Template mediated crystallization (“biocrystallization” for short) of toxic heme into inert hemozoin is a vital defence mechanism that makes it possible for *Plasmodia* to consume hemoglobin. The main advantage of biocrystallization has been attributed to the fact that it is independent of energy consumption. *Plasmodia* are quite capable of mutating and have evolved sophisticated mechanisms to inactivate drug targets. The emergence and global spread of drug resistance is now threatening to undermine our ability to treat malaria. An exception is pigment biocrystallization because hemozoin biocrystallization in *P. falciparum* is a non-muta table target. Crystallization inhibitors will therefore remain a potential class of future antimalarial drugs. EM studies have shown the pigment formation as a carefully...
controlled process involving many membranes and other cell components.

**Figure 2:** Hermann Adolph Köhler 1887 plate 79 III Cinchona officinalis (Courtesy: Royal Botanic Gardens, Kew)

**Hemoglobin Metabolism**

Camillo Golgi was the first to photograph the pigments of malaria quartana in 1890 [17]. Since the report of Meckel in 1847 pigment was thought to be melanin due to its similarity to the brownish colour of the skin pigment [18]. In 1911 Brown observed that all melanins were bleaching rapidly with potassium permanganate, while with this reagent malarial pigment manifests not the slightest sign of a true bleach reaction [19]. His spectroscopic examinations of a solution of malarial pigment proved conclusively that pigment is hematin and not melanin. The low solubility of malaria pigment in mildly alkaline bicarbonate buffer was a long time puzzle which was solved in 1987 [20], hematin in malaria pigment is in a ß-hematin form. ß-hematin lost charged groups by specific coordination linkage and can be either a linear polymer or a cyclic dimer [21]. Based on EM studies and electrophoretic separations Hempelmann & Marques concluded that pigment is not produced by polymerisation but by biocrystallization [22].

**Figure 3:** Labourers sorting out cinchona bark on the Cinchona estate Tjinjroean, West-Java (1915-1930) (Courtesy: Tropenmuseum, Amsterdam. Coll.nr. 10012685).

**Conclusion**

The WHO recommended plant derived Anti Malaria compounds in combination with synthetic drugs to combat drug resistance. The choice of combination depends on efficacy, cost and resistance pattern. Drug resistance will spread and the next generation of drugs are urgently needed.

**References**


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