Photoessay

Artemisia Species: From Traditional Medicines to Modern Antimalarials—and Back Again


Artemisia annua L (Asteraceae) (Photo by Merlin Willcox).

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Introduction

The genus *Artemisia* (Asteraceae) comprises over 400 species, many of which have an aromatic, bitter taste. Some say that it is named after the Greek Artemis (Fig. 1), who was goddess of the hunt, of forests, and of childbirth.1,2 Plants of this genus, as for instance *A. absinthium*, were used to control pain in childbirth and to induce abortions. Most importantly, however, the species *Artemisia annua* L is now known worldwide for its antimalarial properties. Other *Artemisia* species have also been used for the treatment of fevers and malaria. *A. absinthium* and *A. abrotanum* were used to treat malaria in Europe, and *A. afra* in Africa.3–5

The species *A. annua* L and *Artemisia apiacea* Hance are native to China. There has been some confusion over their ancient Chinese names. In older texts, *qing hao* (blue–green herb) and *cao hao* (herbaceous herb) were used interchangeably. The polymath Shen Gu (1031–1095) of the Song dynasty described two different varieties of *qing hao*, one with blue–green leaves, the other with yellowish–green leaves in autumn. Based partly on his description, the famous physician and natural historian Li Shizhen (1518—1593), whose encyclopaedic *Classified Materia Medica* (*Ben cao gang mu*) was published posthumously in 1596, differentiated between *qing hao* (blue–green herb) and *huang hua hao* (yellow blossom herb).6 Modern botanists have identified the former as *A. apiacea*, the latter as *A. annua* (Fig. 2).

*A. annua* is so named because it is almost the only member of the genus with an annual cycle. It is a shrub, often growing over 2 m high (Fig. 3), and is native not only to China but also to Japan, Korea, Vietnam, Myanmar, Northern India, and southern Siberia through to Eastern Europe.7 It has been introduced to many other countries in Europe, North America, and the tropics.8 Seed varieties have been adapted by breeding for lower latitudes, and cultivation has been successfully achieved in many tropical countries, for example in the Congo,9 India,10 and Brazil.11–13 In contrast *A. apiacea* is less common and is rarely grown outside China.

**A. annua** and Related Species as Traditional Antimalarials

The earliest record of the medicinal use of *qing hao* dates back to 168 BC in the “Fifty-two prescriptions” (Fig. 4),14 which recommended it for the treatment of hemorrhoids,15 which were said to resemble “cow lice” (possibly ticks). In the classic of the Chinese materia medica (*Shennong ben cao jing*), which is thought to have been compiled in the first century AD but is now lost, *cao hao* is recommended as a food additive for “killing lice and lingering heat between bones and joints.”16,17

Ge Hong was the first to recommend “*qing hao*” for the treatment of “intermittent fevers” (many of which were probably malaria). His *Handbook of Prescriptions for Emergency Treatment* (*Zhouhou Bei Ji Fang*), written in 340 AD, recommends the following preparation: “Take a bunch of *qing hao* and two *sheng* (two times 0.2 L) of water for soaking it, wring it out to obtain the juice and ingest it in its entirety.”6,18

Different preparations have subsequently been recommended in different texts. The current pharmacopoeia of the People’s Republic of China officially lists the dried herb of *A. annua* as a remedy for fever and malaria, at a daily dose of 4.5–9 g of dried herb prepared as an infusion.19 This is the herbal preparation that has been used for clinical trials.

**Development of Artemisinin as a Modern Pharmaceutical**

During the Vietnam war, malaria was a problem for all armed forces, so military research institutions on both sides of the Pacific started to screen substances for their antimalarial properties. The Maoist Chinese government established a nationwide campaign called “taskforce 523,” and one of the many institutions approached was the Academy of Traditional Chinese Medicine. This employed not only tra-
only a few hours. Hence, it cannot be used as a prophylactic.

The World Health Organization now recommends the use of artemisinin combination therapies (Fig. 7) for the first-line treatment of uncomplicated malaria, to reduce the risk of parasite resistance and recrudescence. There is widespread resistance to older and cheaper drugs such as chloroquine and sulfadoxine-pyrimethamine, which have until now been the first-line treatments in most countries. Artemisinin is poorly soluble in oil or water, so is usually administered orally, although it can be given rectally and, when suspended in oil, intramuscularly.

For patients with severe malaria (who are often unconscious and so cannot swallow), the treatment needs to be given by injection or suppository (Fig. 8). Synthetic derivatives that are water-soluble (artesunate) and oil-soluble (artemether) have been developed to allow intravenous and intramuscular administration, respectively. A meta-analysis of trials, with data on 1919 patients, has shown that artemether is at least as effective as quinine for the treatment of severe malaria, and is associated with fewer serious adverse effects. The SEAQUAMAT (2005) trial has shown that intravenous artesunate is not simply equivalent, but is even more effective than quinine for the treatment of severe malaria.

Artemisinin cannot be synthesized cost-effectively, so is still extracted from A. annua aerial parts. Therefore, the science of commercial cultivation of Artemisia annua, to maximize artemisinin yields, is already well-developed.

Artemisia annua contains many different classes of compounds: at least 28 monoterpenes, 30 sesquiterpenes, 12 triterpenoids and steroids, 36 flavonoids, 7 coumarins, and 4 aromatic and 9 aliphatic compounds. Several of these have some antimalarial activity (Table 1), but the most active is undoubtedly the sesquiterpene lactone artemisinin (Fig. 5). This is found in the leaves and flowers of A. annua. Artemisinin has been found in only two other species, Artemisia apiacea and A. lancea.

Artemisinin and its synthetic derivatives (e.g., artesunate, artemether, dihydroartemisinin) are the most potent and rapidly acting antimalarial drugs ever discovered: The parasite biomass is reduced by 10,000-fold per asexual life cycle, compared to 100–1,000-fold for other antimalarials. The pharmacologic and clinical evidence is well documented. These drugs are unusual in also killing gametocytes, the sexual stage of the malaria parasite (Fig. 6), and thus reducing transmission of malaria. However, artemisinin does not kill the liver stages of the parasite, is metabolized rapidly, and remains in the bloodstream for only a few hours. Hence, it cannot be used as a prophylactic.

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ferent genetic varieties contain widely varying amounts of artemisinin, and it is believed to be important to choose a variety with a high artemisinin content (>1%) and a high biomass. One of the best is the hybrid Artemis (produced by Mediplant Inc., Conthey, Switzerland) which contains up to 1.4% artemisinin.35

However, the endproducts (the pure compound artemisinin or its derivatives) are often unaffordable for the poor, especially as they are recommended only to be used in combination with other drugs.28 Furthermore, its value makes it an attractive target for forgery. A survey in 2000–2001 in Southeast Asia found that 38% of shop-bought oral “artesunate” samples were fake and contained no artesunate,36 some indistinguishable from the genuine ones.37

Return to Artemisia annua as an Herbal Medicine

Several nongovernmental organizations (NGOs) recommend developing and perfecting A. annua as an herbal remedy. ANAMED (Action for NAture and MEDicine) is an NGO promoting the use of traditional medicines (www.anamed.org). It distributes seeds of a recently developed artemisinin-rich genetic variety of A. annua (Delabays N, 1997, unpublished thesis; De Magalhães, 1996, unpublished thesis) for cultivation and preparation as an herbal antimalarial. Two hundred and forty (240) partner organizations in developing countries are participating in this program, and their feedback has helped the organization to refine its recommendations.

The recommended doses are based on the Chinese pharmacopoeia: an infusion of 5 g dried leaves on which 1 L boiling water is poured and left to cool for 15 minutes, of which 250 mL is taken every 6 hours for 7 days. A reduced dose is

<table>
<thead>
<tr>
<th>Constituent</th>
<th>IC50 (μmol/L)</th>
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<tr>
<td>Artemisinin</td>
<td>0.03</td>
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<tr>
<td>Artemetin</td>
<td>26</td>
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<tr>
<td>Casticin</td>
<td>24</td>
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<tr>
<td>Chrysoplenetin</td>
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<tr>
<td>Chrysosplenol-D</td>
<td>32</td>
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<tr>
<td>Cirsilineol</td>
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<td>Eupatorin</td>
<td>65</td>
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recommended for children, according to weight. This method can extract up to 86% of the artemisinin into the water, whereas as little as 30% is extracted in a decoction (when the plant is boiled in water for several minutes), because artemisinin is not heat-stable. Using full fat milk rather than water can increase the proportion of artemisinin extracted. As artemisinin reacts with iron, herbal preparations should not be made in iron pots.

The Research Initiative on Traditional Antimalarial Methods (RITAM, www.gifts-ritam.org) has established an Artemisia annua Task Force, to investigate the feasibility of using a traditional formulation of Herba Artemisia annua as a more affordable and accessible option for the early treatment of malaria in poor and remote areas of developing countries.

Clinical Research on Whole Plant Extracts

Clinical trials have examined the efficacy of the whole herb for the treatment of malaria, but not of the juice expressed from the fresh plant. The best results were reported from studies in China on alcohol extracts of the plant. However, these are not practical to prepare in the field, so they are not discussed further here. Table 2 summarizes the results of studies on teas prepared from A. annua: one comparing an infusion with a decoction and one comparing infusions of different strengths.

These results suggest that the infusion is more effective than the decoction, and that there is no benefit in increasing the strength of the infusion. The apparently better results in the first trial by Mueller et al. can mostly be explained by the fact that patients had low parasite counts, and were not followed up beyond 7 days. In the 2004 study, patients all had >2000 parasites per microliter of blood, and were followed up for 28 days. Because the definition of “cure” was taken to be parasite clearance at day 7, it would have been much easier to achieve this in patients with fewer parasites. Unfortunately, clinical outcome measures were not used, so the conclusions are probably too pessimistic. Mueller et al. showed that recrudescence rates were high. However, they also showed that the A. annua infusion was significantly more effective than chloroquine in an area of chloroquine resistance.

None of the above studies adhere to an ideal design. None included children, who are at greatest risk of severe malaria and death in sub-Saharan Africa. Nevertheless, they all suggest that an herbal infusion of A. annua can be effective against malaria in humans, although its artemisinin content is much lower than the World Health Organization (WHO) recommended dosage. More research is needed to determine the optimal preparation method and dosage.

How Can the Whole Herb Be Effective?

A. annua infusion is significantly more effective than the equivalent dose of pure artemisinin for reducing parasitemia in animal experiments (Plaizier-Vercammen, personal communication). How can this be possible?

First, the oral dose of 500 mg artemisinin daily, recommended by WHO, may be unnecessarily high. The minimum concentration needed to inhibit the growth of Plasmodium falciparum in vitro is 9 ng/mL. This concentration is
present in the plasma for at least 4 hours after a dose of *A. annua* infusion.\(^{19}\)

Second, artemisinin may boost the human immune response to malaria. It stimulates the phagocytic activity of macrophages in the mouse abdominal cavity *in vivo*, and improves their destruction of infected erythrocytes *in vitro*.\(^{45}\)

Third, the whole plant contains other constituents with antimalarial activity (Table 1). The callus of the plant has some antimalarial activity even though it contains no artemisinin.\(^{46}\) The water-soluble fraction of *A. annua*, after extraction of artemisinin, has an antipyretic effect.\(^{41}\)

Some *Artemisia* species, such as *A. absinthium*, *A. abrotanum* (Fig. 9), and *A. afra* (Fig. 10), have antimalarial activity without containing artemisinin.\(^{4,47,48}\) Perhaps some of the same phytochemicals also contribute to the activity of *A. annua*.

Fourth, other constituents of *A. annua* synergize the activity of artemisinin.

There are 28 other sesquiterpenes, some in much greater concentrations than artemisinin in wild strains of the plant: arteannuin B (2–4\(\times\)) and artemisinic acid (7–8\(\times\)). Arteannuin B used alone is ineffective and toxic in rat malaria, but it potentiates the effect of artemisinin.\(^{41}\) *A. annua* also produces at least 36 flavonoids. Many of these have antimalarial activity *in vitro*, although the IC\(_{50}\) is much higher than that of artemisinin (Table 1). Five of these, artemetin, casticin, chrysoplenetin, chrysosplenol-D, and cirsilineol, have been shown selectively to potentiate the *in vitro* activity of artemisinin against *Plasmodium falciparum*.\(^{49}\) Casticin, at a concentration of 5 \(\mu\)mol/L, induced a 3–5-fold reduction in the IC\(_{50}\) for artemisinin.\(^{50}\) Chrysosplenol-D has the strongest potentiating effect, and this is also the most abundant flavone in plant material.\(^{51}\) The effect of all the flavones in combination with artemisinin has not been investigated. Other flavones, and indeed other components of *A. annua*, may have a similar effect; they have not all

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**FIG. 7.** Artesunate–amodiaquine, one of the artemisinin combination therapies promoted by the World Health Organization. (Photo by Merlin Willcox).

**FIG. 8.** Dr. Moussa Dicko prescribes intramuscular artemether for a child with severe malaria at Sikasso Hospital, Mali. This treatment is more practical than intravenous quinine because it is often difficult to find veins in severely ill young children. Furthermore, the treatment can be given once daily rather than four times a day and carries less risk of toxicity. (Photo by Merlin Willcox).
been tested, because it is difficult to purify them. The antimalarial properties of the traditional preparation of *A. annua* most probably reside in the combination of many constituents, not just artemisinin.

Modern drug combinations may unwittingly be mimicking the combinations of phytochemicals (and sometimes plant species) with synergistic activities contained in the traditional preparations of *A. annua*. Indeed, the pharmaceutical industry may find it beneficial to further investigate combinations of artemisinin with other compounds produced by *A. annua*, which may improve its antimalarial efficacy, and reduce the risk of resistance. 43

**Controversy**

There has been much debate as to whether it is appropriate to recommend the use of *A. annua* herbal teas for the treatment of malaria. At one end of the spectrum, commercial growers of *A. annua* and manufacturers of artemisinin have claimed that it would be “criminal” to promote the use of *A. annua* teas because they contain “subtherapeutic doses” of artemisinin, which in theory could lead to the evolution of parasites resistant to artemisinin. There is little evidence to support or refute this hypothesis, and further research is needed.43 Jansen51 writes that “The herbal tea approach to artemisinin as a therapy for malaria is totally misleading and should be forgotten as soon as possible.” His argument is based on the low artemisinin content of the teas and the assumption that therefore the teas cannot be effective, an assumption that may be incorrect.52 Furthermore, preliminary experimental research that tests the ancient Chinese recommendations suggests that more artemisinin can be extracted by preparing juice from fresh *A. annua* plants (Elizabeth Hsu and Colin W. Wright, personal communication).

At the other end of the spectrum, Anamed replies that it would be criminal not to provide *A. annua* to remote communities that do not have any other treatment for malaria. Health care infrastructure is lacking in most of the areas worst affected by malaria, making it impossible to distribute drugs to those who most need them. For example, in the Brazilian Amazon, patients commonly have to travel for 2 days before reaching a modern health facility. Although recrudescence can occur after treatment with *A. annua* infusion, it can still be effective as a “first aid” measure to keep the patient alive while they travel to the health center. An imperfect treatment given rapidly, to prevent deterioration

![Artemisia abrotanum](Photo by Merlin Willcox).
to severe malaria and death, may be preferable to the “gold standard” modern treatment if there is a significant delay in obtaining it.

Priorities for future research, proposed by the RITAM Artemisia task force, are summarized below.

**Priorities for Future Research on Artemisia species as Antimalarials**

Priorities are:

1. To determine the best species and genetic variety of *Artemisia* to cultivate in each region of interest (in function of its environmental characteristics).
2. To determine the most effective method of preparation (including combinations with other plants), dose, and length of treatment.
3. To test the clinical effectiveness of this preparation for treating falciparum malaria in nonimmune patients.
4. To determine whether use of this preparation increases the risk of *P. falciparum* developing resistance to artemisinin.
5. To test whether the use of this preparation reduces mortality from malaria.

**References**


**FIG. 10.** *Artemisia afra*. Its antimalarial activity is attributable to a complex mixture of flavonoids and sesquiterpene lactones, rather than to a single compound. (Photo by Merlin Willcox).


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