CULTIVATION OF *ARTEMISIA ANNUA* IN AFRICA AND ASIA

Antony Ellman, Natural Resources Institute, in the first of two articles on this important anti-malarial describes the potential of *Artemisia annua* cultivation for artemisinin production in the fight against malaria. In the next issue Elspeth Bartlett will describe efforts to increase the yield of the drug in the crop

Keywords: *Artemisia annua*, smallholder cultivation, artemisinin extraction, malaria control, China, East Africa

Introduction

The malaria parasite *Plasmodium falciparum* is one of the world's most lethal pests, accounting for over a million deaths per year. 90% of cases are in Sub-Saharan Africa, 85% in children under five. For over 50 years the main tool for controlling the malaria parasite[1] has been chloroquine, a synthetic derivative of the plant-based extract quinine. Chloroquine acts as both prophylactic and cure and has the advantage of very low cost ($0.10 per treatment), but unfortunately in much of Africa as well as South-East Asia it is no longer effective due to the emergence of resistant strains of the malaria parasite. The best hope for a replacement treatment lies with drugs based on artemisinin, a chemical extracted from the leaves of the plant *Artemisia annua*.

Artemisia annua is an annual shrub indigenous to China, but able to grow in a wide range of sub-tropical and temperate environments. Its use in treating malaria has been known in China for over 2000 years. The active ingredient, artemisinin, was isolated by Chinese scientists in 1972[2]. Derivatives which are more effective than artemisinin itself have been developed over the last 20 years. Attempts to produce synthetic and semi-synthetic artemisinin are ongoing, but the viability of this approach is not yet clear. Resistance to artemisinin drugs will inevitably appear in time, but the plant-based extract is still believed to have a useful life of at least 10 years[3].

This article describes programmes for expanding cultivation of *Artemisia annua* in Africa and Asia, and analyses prospects for extraction, manufacture and distribution of artemisinin-based anti-malarial drugs in the light of the WHO target of halving the incidence of malaria by 2015 and eliminating the disease thereafter.

History of Artemisia production and use

Traditionally *Artemisia annua* leaves in China were collected from unimproved wild stands of the plant (Figure 1), and were used as a herbal infusion to treat a range of diseases. The low water solubility of artemisinin made the infusion only marginally effective against malaria[4]. Leaf yields were low (estimated less than 500kg dry matter per ha) and artemisinin content was also low (estimated 0.03–0.3% by weight).

During the Vietnam war *Artemisia* plantations were established in North Vietnam by the Vietcong using seed supplied by the Chinese Government, to combat a rapid rise in malaria cases among army personnel. Solvent extraction of artemisinin was used (details of the methods adopted are not available). Yields of *Artemisia* leaf and artemisinin content would have been similar to those obtained in China.

Figure 1. Wild Artemisia plants, Chongqing, China

1 Management of the disease itself is of course much more complex, involving control of the mosquito vector by spraying or draining breeding sites, spraying or netting houses, and promoting the use of insecticide-treated bednets as well as chemical prophylaxis and control of the malaria parasite itself. This article addresses only chemical treatment of malaria parasites once a person has been infected.

2 A recipe for the use of *Artemisia* leaves as a herbal infusion for treating "intermittent fever" (taken to be malaria), dated to 168 BC, was found in a tomb excavated in Hunnan Province in 1972 (Qinghaosu Antimalarial Co-ordinating Group, 1979).

3 Malaria parasites with a degree of resistance to artemisinin drugs have already been reported on the Thai-Cambodian border. While these reduce the effectiveness of the drugs, intensive measures are being applied to contain the spread of resistant strains and it is expected to be several years before artemisinin drugs become ineffective (WHO, 2008)

4 An in-vitro trial on the effectiveness of artemisinin extracted by boiling *Artemisia* leaves in water, conducted by the London School of Hygiene and Tropical Medicine, demonstrated that 7 litres of the resulting bitter-tasting "tea" would have to be taken per day to obtain a dose of artemisinin sufficient to clear malaria parasites. This is not a realistic proposition (J.Steele, LSHTM 1999, unpublished data)

 DOI: 10.1564/21apr08

In the mid-1980s *Artemisia* seed reached several European locations, notably a Medicinal Plants Research Institute in Switzerland, Mediplant, which had close contacts with malaria control programmes in East Africa. Mediplant scientists initiated an *Artemisia* hybridisation programme which by 1994 had resulted in a variety giving dramatically higher yields than the wild plants: up to 2.5 tonnes of dry leaf per ha with 1.0–1.5% artemisinin content depending on growing conditions (Mediplant, 1998). Hybrid seed of this variety was tested at several locations in Tanzania and performed well. A company was established to commercialise artemisinin production in East Africa: some 5,000 small and large-scale farmers are currently contracted to grow *Artemisia* for processing in factories in Kenya, Tanzania, Uganda and Madagascar.

Over the last ten years as the worldwide demand for artemisinin has become apparent, Chinese, Vietnamese and Indian plant breeding institutes have followed Mediplant's example in developing high-yielding *Artemisia* hybrids. Factories have sprung up in all three countries to extract artemisinin and manufacture anti-malarial drugs. The East African factories currently export artemisinin to pharmaceutical factories in India and Europe where the final products are made[5]. Between 5,000 and 15,000 ha of commercial *Artemisia* are now estimated to be planted annually worldwide, the exact area following fluctuations in the price of artemisinin and hence in the viability of the enterprise both for farmers and for pharmaceutical companies[6].

Artemisia cultivation methods

East African producers were the pioneers in establishing commercial plantations of *Artemisia annua* and have more practical experience than other regions[7], though Chinese and other Asian producers are fast catching up[8]. However, *Artemisia* has not been grown for long as a planted crop so there are still many lessons to be learned.

Planting: *Artemisia annua* is a robust plant once established, but the seeds are tiny (12–14,000 seeds/gramme) and the young seedlings are very delicate so planting in the field is not easy. Hybrid seed is extremely expensive so it is always planted in a nursery prior to transplanting[9] (Figure 2). Seeds collected from wild plants or selected cultivars may be sown directly in the field, usually in rows or saucers at 0.5–1.0 metre intervals to facilitate irrigation and weeding. The process is very labour-intensive and losses are frequently high.

Transplanting: seedlings are normally transplanted from the nursery at a height of 10–12cm, approximately 7 weeks after sowing (Figure 3). The process is extremely delicate: if the taproot is bent or if the young plant is stressed in any way (especially by water shortage) it responds by flowering prematurely leading to greatly reduced yield. Some growers transplant cuttings from selected mother plants (Figure 4): these are more robust than seedlings, but the cost and labour requirement involved are very high.

Figure 2. Artemisia nursery, Madagascar

Figure 3. Transplanted seedlings, Madagascar

5 To reduce the risk of accelerating appearance of parasite resistance WHO strongly recommends that artemisinin derivatives are used only in combination with another antimalarial drug (as Artemisinin Combination Therapies or ACTs). The East African factories plan ultimately to manufacture ACTs locally, but it will take some time before they achieve the required quality standards.

6 Several other countries are experimenting with *Artemisia* cultivation – Nigeria, Ghana, South Africa, Argentina and even some countries in Europe – but with no local extraction plants and finite global demand for the end product these trials seem unlikely to prove viable.

7 A Production Manual for *Artemisia annua* cultivation based on East African experience of growing the crop was published in 2005 (East African Botanicals Ltd, 2005).

8 WHO held a consultative meeting in Guangxi China in July 2005 which brought together *Artemisia* producers from many Asian and African countries. This resulted in a WHO Monograph on Good Agricultural and Collection Practices for *Artemisia annua* (WHO, 2005).

9 Mediplant hybrids cost $75 per gramme. Many growers pellet the seeds before germination to reduce waste. Fortunately only 3–4 g/ha are required for planting

Figure 4. Cuttings of Hybrid Artemisia plants, Kenya

Figure 5. Artemisia interplanted with Ginkgo, Szechuan Province, China

Planting density: F1 hybrid seed is normally planted at a spacing of 1m × 1m (10,000 plants per ha). Non-hybrid or F2 hybrid seed has less vigorous growth and is planted more densely with a population of 20,000 or even 30,000 plants per ha. The relation between plant density and yield needs further research.

Fertiliser requirement: soil testing in each planting location is needed to assess fertiliser requirement. Nitrogen fertiliser is often required to maximise leaf growth: it is best applied as an organic manure. Its impact on artemisinin content needs study. Certain micronutrients, especially zinc, seem to be required in some soils.

Water requirement: well established *Artemisia* plantations can withstand dry conditions, but moisture stress in young plants tends to induce premature flowering and reduced yield of both leaf and artemisinin. A rain-fed crop requires at least 600–650mm of rainfall. Supplementary irrigation by flood or (ideally) drip irrigation is often needed, but over-watering can be damaging if it results in nutrient leaching or reduced root depth.

Weed control: young *Artemisia* seedlings are very susceptible to weed competition so planting into a clean field is vital. In China, *Artemisia* is often interplanted with other crops (eg Ginkgo, maize or beans, Figure 5) while in Tanzania it has been interplanted with young or recently stumped coffee: this reduces weeding cost by sharing the burden between two crops, but the yield of *Artemisia* is also reduced.

Pest and disease control: a great attraction of *Artemisia* is that until now it has had few natural enemies – in East Africa because as a recently introduced crop it still enjoys a "honeymoon period" before potential pests or diseases catch up with it, in Asia because it has not been grown for long enough in concentrated locations where pests and diseases can easily spread. Some evidence of cutworm and bacterial damage to stems has been seen in East Africa[10], but broadly pest management in *Artemisia* itself has not posed a major problem.

Harvesting and storage: plants are normally harvested just before they come into flower, as artemisinin content falls off rapidly thereafter. They can be over 2m high at this stage

Figure 6. Mature Artemisia plants, Madagsacar

(Figure 6). Non-hybrid varieties do not all mature at the same time so sequential harvesting, though labour-demanding, can add significantly to yield. The plants are cut at the base, stooked in the field for air drying, and threshed on a tarpaulin before sieving and storing the dried leaves (Figure 7). Provided the leaves are dried to a moisture content below 12% and are kept at a temperature below 40°C they can be stored for several months prior to processing.

Economics of Artemisia cultivation

As a labour-intensive crop, particularly at the planting and harvesting stages, *Artemisia annua* is in many respects ideally suited to smallholder cultivation[11]. The viability of the enterprise

[10] For a case of bacterial infection of *Artemisia* stems encountered in Uganda see Ssekiwoko (2009)

[11] The mean size of *Artemisia* holding in East Africa is less than 1.0 ha, though some commercial producers have planted as much as 10ha. Some such producers have experimented with mechanised transplanting and harvesting but they have not yet proved successful.

Figure 7. Harvested Artemisia plants, Tanzania

Box 1. Indicative Enterprise Budget for Cultivation of 1 Ha Artemisia

Item	Commercial Grower* ($ per ha)	Smallholder Production** ($ per ha)
Land Preparation	75.00	75.00
Seed/Seedlings	180.00	10.00
Nursery	–	30.00
Transplanting	30.00	30.00
Infilling	5.00	5.00
Fertiliser	60.00	40.00
Weeding	40.00	40.00
Irrigation	80.00	20.00
Pest and Disease Control	10.00	10.00
Cutting and Stooking	40.00	35.00
Threshing and Cleaning	20.00	15.00
Storage/Bags	10.00	10.00
Transport	20.00	20.00
TOTAL COSTS	570.00	340.00
SALES	1,375.00	940.00
NET REVENUE	805.00	600.00

Assumptions: * F1 hybrid seedlings purchased from central nursery, ** F2 seeds germinated in own nursery

Source: East African Botanicals Ltd, cross-checked with growers.

depends, however, on the costs and returns of *Artemisia* cultivation (Box 1 shows an indicative budget from Tanzania), and on the profitability of *Artemisia* cultivation in comparison to alternative cash crops[12].

Viability also depends critically on the current market price of artemisinin, which determines the price that processing factories can afford to pay farmers for dried leaf. Some purchasing companies have adopted a leaf pricing formula which includes a premium for high artemisinin content. Unfortunately, the difficulty and cost of measuring artemisinin content accurately has made this hard to apply on a large scale, though assay equipment for testing artemisinin content in the field is under development[13].

Just as important as the actual price of artemisinin is the extent to which it fluctuates from year to year (see below). Uncertainty over future demand discourages both farmers and extractors from making long term investments in production. Nevertheless large numbers of growers are eager to plant *Artemisia*, realising the potential it offers both for delivering a product important to health and for generating higher incomes than can be earned from traditional cash crops. To achieve this end, greater stability in the market for artemisinin and ACTs is essential.

Artemisinin drug supply chain from extraction to distribution

Until 2004 the price paid by pharmaceutical companies for artemisinin was below $300/kg and only six significant factories worldwide bought *Artemisia* leaf for extraction[14]. In the following year, $200 million became available to the Global Fund for AIDS, TB and Malaria, primarily from the Bill and Melinda Gates Foundation; this rose to $600 million in 2006/07 and reached over $2 billion in 2008/09. Much of the money was earmarked for purchase and distribution of ACTs. Some 81 countries, 44 of them in Africa, adopted ACTs as the front-line drug against malaria, and there was suddenly an acute global shortage of artemisinin[15]. The price shot up to over $1,000/kg in 2005. Unregulated factories sprang up all over China and Vietnam to manufacture artemisinin-based drugs, and large numbers of farmers were encouraged to plant *Artemisia*.

Inevitably over-production ensued and the price of artemisinin fell again to below $200/kg in 2008, a level which is uneconomic for farmers and processors. The price has since risen to around $350/kg. Such a boom-and-bust scenario has a highly negative impact both on the producers and on health outcomes. An important initiative is now under way for establishing a pre-financing facility for artemisinin extractors who supply WHO-approved ACT manufacturers[16]. The

[12] The current high price of many food crops and other export commodities reduces the competitive advantage of *Artemisia* cultivation, but it is uncertain for how long these price levels will persist.

[13] One Chinese producer claims that he can judge artemisinin content accurately by chewing fresh leaves, but this has not been verified. A more accurate procedure using a hand-held field detection kit has been developed by a UK firm (SensaPharm Ltd), but is not yet commercially available.

[14] 3 factories in China, 2 in Vietnam, 1 in East Africa.

[15] The global funded demand for ACTs is currently estimated at some 260 million treatments per year, requiring an annual supply of 130 tonnes of artemisinin. At current levels of yield and extraction efficiency this translates to the planting of 23,000 to 28,000 ha of *Artemisia annua* per year.

[16] This initiative, known as the Assured Artemisinin Supply System (A2S2) was launched in July 2009 by a group of NGOs and consulting firms and is managed by Triodos Bank (Sustainable Trade Fund).

facility is financed by UNITAID and other donors: it is intended to allow extractors to offer secure contracts and prices to *Artemisia* growers and to enter into long-term supply agreements with ACT manufacturers, thus stabilising production and keeping supply of the drugs approximately in line with funded demand.

Conclusion

Anti-malarial drugs extracted from the Chinese plant *Artemisia annua* have the potential to reduce greatly the incidence of malaria worldwide and, in combination with other approaches to pest management, to contribute ultimately to elimination of the disease. To reach this goal higher-yielding Artemisia varieties and cultivation methods are needed, together with more effective approaches to artemisinin extraction, manufacture and distribution of ACTs, and use of the drugs in a manner which delays appearance of resistant parasites and extends their useful life.

African producers pioneered the commercial cultivation of *Artemisia* in the 1990s. Since 90% of deaths from malaria occur in Africa, they also have a strong incentive to remain in the forefront of the development of artemisinin-based drugs: a locally based remedy for a locally based disease.

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Letter to the Editor

Dear Editor,

Upon reading the February issue of *Outlooks on Pest Management*, I was drawn to two errors that should be corrected in what is usually a reliable and trustworthy source of information and news. In the section on Regulatory News (page 14) the item on pet flea treatments gives the impression that it was permethrin that led to most of the complaints from pet owners, and I originally assumed that all the companies mentioned must have had their own brand of permethrin. However, Bayer's Advantage (the only product actually mentioned) contains only imidacloprid (see http://www.bayeranimal.com.au/default.aspx?Page=50&ItemId=75). This raises the question is imidacloprid also under a cloud regarding its toxicity to cats? I ask these questions because I have a cat and we treat it with imidacloprid. (The news item in question was from a PAN North America press release and it was wrong to claim that Advantage contains permethrin and that it is dangerous to use on cats apologies for this – Editor).

On another matter, in your editorial, which was a fascinating delve back in history, you mentioned that Monks Wood was still a Research Institute. However, I am afraid you are wrong there – see extract from web sites http://www.monkswood.org.uk/4.html and http://www.ceh.ac.uk/science/CorporateInformation/index.html

"A miscellaneous potted history of Monks Wood, the research station.

The woodland adjacent to the site was declared a National Nature Reserve in 1953, science staff were permanently based at Monks Wood from 1961 and the research station was officially opened in 1963. For the first decade the station and wood were both part of The Nature Conservancy. Subsequently, the station became part of the Institute of Terrestrial Ecology, then the Centre for Ecology and Hydrology. The woodland reserve became part of the Nature Conservancy Council, then English Nature and then Natural England. All science ended at the station in January 2009" (Apologies once again. I visited what I thought was the Monks Wood website via Google and the information published was as I found it. Clearly this was wrong – Editor).

Alan Dewar