Dossier Artemisia

This dossier is an information product of the department Information & Library Services of the Royal Tropical Institute. It is a copy of an archived version of the former web document that was last updated in 2010. Some weblinks may no longer be valid. An overview of all ILS dossiers on health, gender, local governance, culture, and sustainable economic development can be accessed at http://www.kit.nl/4733.

Editor: Henk van Dam
Last update: 16 September 2010

Table of Contents

Scope

Malaria still claims many victims in the developing world. An additional problem is that the parasite that causes the disease has become resistant to many of the commonly used anti-malarial medicines. Now there is an alternative: artemisinin, derived from a plant native to China, Artemisia annua (known as *alsem* or *Absinth* in Dutch). However, the production and distribution of this 'wonder drug' is encumbered for several reasons.

This Dossier focuses on the issues and questions raised in the Artemisia D-group. This virtual community is intended for malaria experts, policy-makers, NGOs, producers, researchers and distributers of ACT, with representatives from across the world. One-hundred-and-seventy-five participants have already joined the group and it is expected that this group will form the basis for an evolving network.

In-Depth

Artemisinin is a natural substance and an excellent alternative to existing malaria medicines. It is extracted from the artemisia annua plant, works fast and has few side-effects. The substance is used in combination with another anti-malarial drug (e.g. Nivaquine) to prevent the development of resistance. This so-called ACT (Artemisinin-based Combination Therapy) is currently the best treatment against malaria. One drawback, however, is that the medicine is still relatively expensive and ACT is proving troublesome to introduce.
There are 6 topics:

- Obstacles for market access of small (Artemisia) producers, especially in Africa
- The current production capacity of Artemisia worldwide
- Cultivation/processing/extraction and distribution channels
- Development of Artemisinin resistance of the parasite
- The retail price of (qualified) ACT and quality of ACT
- The best way of funding the development of ACT

The different steps in the production to consumption chain of Artemisia

Production

Artemisia annua production in China is expanding rapidly. An estimated 15 000- 20 000 ha has been planted in 2006 (MD), of which some 30-40% is smallholder production. The smallholder production is both collection and cultivation. The larger extraction and manufacturing companies (KPC, Holley Group) have all gone into production in the Sichuan Province (bordering Vietnam). In 2005 some 3000 MT of dry leaves moved into Vietnam. Vietnam claims that it can produce enough artemisinin for 100 million treatments.

• Quality and artemisinin content remains a big issue. The content is claimed to very low and variable in China (0.4 %). Higher contents are obtained in East-Africa and Madagascar.

• A major problem is the lack of reliable laboratory protocols/monographs for the determination of the artemisinin content (six different labs gave six different results for one sample).

• Post-harvest technology is not being given due attention. Stooking e.g. is claimed to raise the content, while timing of harvesting in relation to flowering is still an issue. In India one started hedgerow growing and cutting, as with tea beds. The question is raised whether Artemisia leaves can be processed wet?

• Seed quality and seed availability is still an issue. Mediplant does open its books. Field visit planned later this year by M2S2. MMV and BMG Foundation support testing of new varieties in the UK.

Extraction

Key findings of 5 extraction methods:

• Hexane extraction (hexane-ethyl acetate mixed solvent) is still the most widely used extraction method. It is still the cheapest, has environmental risks and health hazards. Are replacements possible?

• Supercritical CO2 (scCO2), is the best, but is hardly used, Experience exists in Hong Kong, Korea and India with other medicinal plants. TanzART is having its artemisinin extracted in Australia by a New Zealand company both through hypercritical CO2 and Hexane, for comparison in large quantities (8 MT dry leaves each).

• HFC-solvent (hydro fluorocarbon HFC-134a) is a method used in Canada (TFTL). The solvent has a stability problem and hence a safety problem. The method is used in France for the extraction of essential oils.

• Ionic liquids, promising new method, being tested in the UK. Still very expensive, although with different prices for different types

• Ethanol is a traditional method not very efficient

The overall challenge is to have a good extraction method (close to 100%) which economically feasible and sustainable without health risks. This could possibly lead to a multi-purpose extraction plant (as could be the case with the HFC methods and use of Ionic liquids).

Another overall challenge in relation to extraction is the lack of confidence in the extraction process. Building trust of investors in extraction, purchases of the final product, farmers who deliver the raw material, is a complicated process, further complicated by the lack of independent information on extraction methods and the lack of testing facilities.

Artemisinin content testing

Quality determination is one of the key problems in opening up the market. As there is no independent quality control and certification of either the raw material or the API, the interaction between actors in the chain is to be based on trust.

TanZart intends to sell its product (after extraction and purification) on the open market (after testing in Switzerland), but it is argued that there is a risk. An urgent need exists for international standards, quality certification and independent testing labs. Another issue is the effect of the raw product (Artemisia leaves) on the final product. Testing of the API content of Artemisia leaves is another constraint, also as it involves the trust of the producers, that are paid based on the content.

Artemisinin purification

Extraction is one thing, but has to be followed by further purification. Good purification can significantly reduce costs of the final product. An urgent need also exists for consistent quality standards; presently the artemisinin on the market is too variable in standards.

Pre-qualification

Only COARTEM is fully certified by WHO. This was facilitated by the fact that SwisMed has it certified

initially. Co-blisters prequalification dossiers have stopped. Several ACTs are open and are in phase 3 of clinical testing, including also the synthetic artemisinin OZ. Complication is the fact that some resistance has been found against amodiaquin (5-10%)

Newly pre-qualified ACTs (there are several) have the problem with the Phase 3 clinical tests, which involve bio equivalence testing. The latter is complicated as there are no standards.

No monographs exist for the clinical testing; no standard exists for the API. Only in Guelin-China an API monograph for Artesunate has been developed recently.

Also in Nigeria (where ACT is produced) some sort of standardization has been developed.

The WHO/GMP operate with a shortlist of suppliers, that produce prequalified ACTs. One of the main problems is to beyond this step. Bio equivalence being the main hurdle, the band is too narrow and there is lack of experience. . (Artemisinin products one in the bloodstream are being sucked up by parasites, which leads to a very variable artemisinin content in human blood). The

Processing

Artemisinin price on the open market has been fluctuating heavily from 400 USD/kg two years ago to 1700 USD/kg last year and now back to 400 USD/ka. Vietnam will not produce/sell below 300 USD/kg. In China the price was still 500-700 USD/ka in May-July period.

Artemisinin and its derivates are rather hygroscopic and unstable under humid conditions. This requires good quality packing material and results in some 75% costs of the total products. The drug itself accounts for only 25% of the costs.

The Bill and Melinda Gates Foundation (BMG) is key financier of several initiatives for the 'artificial' production of artemisinin.

Documents

- Artemisinin extraction study presentation
- Artemisia Agriculture and Malaria
- Artemisia Social benefit
- Artemisia Processing questionnaire
- Artemisia Generalized Roles
- Artemisia Annua Processing Benchmarking Study

KIT's involvement

Malaria: improving access to artemisinin-based combination therapy

Recent research by KIT on the 'wonder plant' Artemisia which is being used to combat malaria has been greeted with great enthusiasm. There is now an online community where the study can be augmented and where interested parties from a variety of backgrounds can meet to exchange views.

At the request of the Dutch Ministry of Foreign Affairs/Development Cooperation, KIT surveyed the state of affairs regarding bottlenecks in the production and distribution of what some consider to be a wonder drug. The results of this study have been reproduced in the publication *The World of Artemisia*

in 44 Questions. The publication also offers concrete proposals for solving the problems. *The World of Artemisia in 44 Questions* outlines the potential as well as the limitations of using Artemisia and producing ACT to combat malaria. Following the many reactions to the publications, KIT recently decided to set up an online community devoted to Artemisia with the aim of optimizing the further exchange of knowledge. To effectively bridge regional and institutional boundaries, KIT chose the medium of D-Groups.

Publications

- The world of Artemisia in 44 questions

Projects

- Artemisia
- PhD study in the field of malaria
- Novel magneto-optical Biosensors malaria diagnostics (MOT-Test)
- Feasibility study for sustainable production of artemisinin for Artemisia-based Combination Therapy (ACT)

News

- Answers to questions about the 'wonderdrug' against malaria
- Malaria: improving access to artemisinin-based combination therapy
- Diagnosing malaria without blood sampling

Resources

Websites

- Roll Back Malaria (RBM)
- ACT Malaria
- Center for Global Development's new blog
- Network of the Henry J. Kaiser Family Foundation
- Medicines for Malaria Venture
- ACT Vietnam
- World Health Organization (WHO)
- CNAP Artemisia Research Project

KIT Library Queries

- Artemisia

Facts & Figures

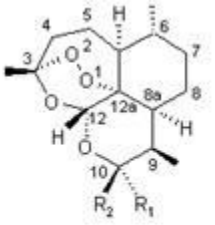
- Today approximately 40% of the world's population mostly those living in the world's poorest countries is at risk of malaria.
- Malaria is not just a disease commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development.

- Malaria causes more than 300 million acute illnesses and causes between one and three million deaths annually
- Ninety per cent of deaths due to malaria occur in Africa south of the Sahara mostly among young children.
- Malaria kills an African child every 30 seconds.
- Many children who survive an episode of severe malaria may suffer from learning impairments or brain damage.
- Pregnant women and their unborn children are also particularly vulnerable to malaria, which is a major cause of perinatal mortality, low birth weight and maternal anaemia.
- Artemisinin amounts increase during the whole life cycle of a leaf (W. Lommen)
- Artemisinin concentrations are generally higher when leaves grow old (W. Lommen)
- Artemisinin concentrations are higher in later formed leaves because of higher trichome densities on these leaves and a higher production of artemisinin per trichome; (W. Lommen)
- Artemisinin precursors and post-harvest increases in artemisinin. (W. Lommen) Willemijn Lommen

Glosssary

ACT

Artemisinin-based Combination Therapy. According to the WHO Artemisin-based Combination Therapy - based on the Artemisia Annua plant provides the most promising therapy against resistant malaria.



1a R_1,R_2= O, artemisinin; **1b** R_1= H, R_2= OH, dihydroartemisinin; **1c** R_1= H, R_2= OMe, artemether; **1d** R_1 = H, R_2 = OEt, arteether; **1e** R_1= $OC(O)CH_2CH_2CO_2Na$, R_2 = H, sodium artesunate.

Antimalarials

Antimalarial drugs are designed to prevent or treat malaria. There are many of these drugs currently on the market. Here is a partial list.

1. Antimalarial drugs currently used for treatment
• amodiaquine
• artemisinin/artemether/artesunate (Artemisinine based on the Artemisia plant)
• atovaquone
• chloroquine (Nivaquine®, Aralen®, Damaral® etc.)
• fansidar (pyrimethamine, sulfadoxine)
• lumefatrine
• mefloquine (Lariam ®)
• quinine/quinidine (quinine is derived from the bark of the tropical cinchona tree)

2. Antimalarial drugs currently used for prophylaxis
• chloroquine
• doxycycline
• hydroxychloroquine (Plaquenil)
• mefloquine
• proguanil
• pyrimethamine (daraprim) -sulfadoxine (Fansidar®)
• Halofantrine (Halfan®)

3. New medicines
• Malarone
• DNA/MVA malaria vaccin (under development)

4. Repellents
• DEET is available as lotion or DEET-spray

5. Mosquito nets

Artemisia annua

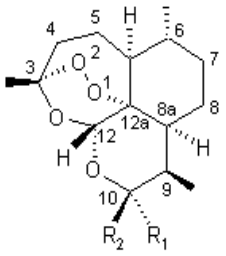
(Binomial name) also known as Sweet Wormwood, Sweet Annie, or Chinese wormwood is a common type of wormwood that grows throughout the world. It has fern-like leaves, bright yellow flowers, and a camphor-like scent.

Scientific classification; Kingdom: Plantae; Division: Magnoliophyta; Class: Magnoliopsida; Order: Asterales; Family: Asteraceae; Genus: Artemisia; Species: A. annua

Artemisinin

is a drug used to treat multi-drug resistant strains of falciparum malaria. The compound (a sesquiterpene lactone) is isolated from the shrub Artemisia annua long used in traditional Chinese medicine. Not all shrubs of this species contain artemisinin. Apparently it is only produced when the plant is subjected to certain conditions. It can be synthesized from artemisinic acid.

Formula : $C_{15}H_{22}O_5$



1a R_1,R_2= O, artemisinin; **1b** R_1= H, R_2= OH, dihydroartemisinin; **1c** R_1= H, R_2= OMe, artemether; **1d** R_1 = H, R_2 = OEt, arteether; **1e** R_1= $OC(O)CH_2CH_2CO_2Na$, R_2= H, sodium artesunate.

Coartem

is the commercial name of artemether–lumefantrine, a drug effective in treating malaria, developed by the Ciba and Sandoz laboratories in 1996. Subsequent to their merger, the patent now belongs to Novartis. It was added to the WHO essential drug list, showing a success rate above 95 %. A dose of Coartem now costs 55 cents (USD) for a child up to age 3.

Malaria

Malaria is a common and serious tropical disease. It is a parasitic infection transmitted to humans through the bites of infected female mosquitoes. Malaria is a curable disease if promptly diagnosed and adequately treated.