

# **Fighting malaria in Africa and *Artemisia annua* L. infusion**

## **2<sup>nd</sup> International Conference**

organized by ICEI (Istituto Cooperazione Economica Internazionale) and Piattaforma  
Artemisia

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### **Opening greetings by Cecilia D'Elia**

Vice-President Rome Province's and Province Councilor for Culture

It is important to all work together and overcome prejudices. The Province of Rome has made the premises available for this meeting. In future we need to improve the impact of this debate beyond specialists. The domination of market forces must be stopped from hindering the right to health.

### **Alfredo Somoza**

ICEI President - ICEI Presentation

ICEI believes it is worthwhile devoting time to discussing this topic. ICEI has always tried to work on practical projects and to listen to a variety of viewpoints in order to put together a common platform to assist people in developing countries. ICEI is also working on migration, food security, agriculture, and the impact of Genetically Modified Organisms. GMOs also require more chemical input. The approach on *Artemisia annua* is to establish a platform for scientists to discuss the way forward. There are few resources for decentralized cooperation, so the aid given by local authorities is very important in Italy. The debate on research can also be addressed, which is more difficult with large funders. Local communities in malaria endemic areas have also become involved. We must consolidate south-south, not only north-south relations.

### **Franco Borelli**

Director of ICEI Strategy, Research and Development office – Conference introduction

Last year's meeting launched this initiative with one main goal: to develop a virtual network of competence and knowledge into a real network. We thought this was essential to deal with the challenge of the use of *Artemisia annua*, and the different opinions expressed by researchers, scientists etc, in order to discuss matters face to face. The question was whether Artemisia can be as effective as drugs in the treatment of malaria. There are still a number of questions to be tackled and we need to understand progress on evaluating the scientific progress behind this treatment. There are some interesting and tangible results especially in Sub-Saharan Africa, characterized by empirical practices. There are a number of governments that support this process as well as missionaries, NGOs and others. However we must be aware that the issue is to fight a disease which has a huge impact on economies. Some parties have been reluctant to use this

treatment. There can be risks with using the tea, causing side-effects if it is not used at the right dosages, and if it is not grown in adequate conditions. These difficulties are exploited by those who oppose the use of the tea. Unless there is a systematic approach there can be negative spin-offs. ICEI is a small Italian cooperation institute with limited resources. We have attempted with these to promote an adequate network to pool resources. WHO is reticent and not willing to talk about this. Brazil had proposed a programme but nothing has come of this. Gates and the Global Fund have not supported these initiatives. Nobody has undertaken to support this battle which requires considerable funding. 25<sup>th</sup> Malaria is world malaria day, and no reference is made to *Artemisia annua*, so there is no debate on this possible treatment, so we're not getting anywhere despite the efforts made by participants at this meeting. There is no tangible sense of unity or of a common approach which could lead to a campaign in support of this treatment with WHO and NGOs which exclusively promote drugs. Drugs are not available to 70% of families with malaria. Insecticides and bednets are not effective because they have to be renewed constantly.

The concrete proposal is to establish a European platform of universities, NGOs, and experts. This would be an effective way of achieving our goals. These establishments have great credibility and we hope WHO would listen to them. ICEI cannot continue to support initiatives without a deadline.

## 1<sup>st</sup> SECTION: **Medical and scientific aspects**

Moderator: **Zeno Bisoffi**

Centre for Tropical Diseases, Sacro Cuore Negrar Hospital, Verona

### Clinical efficacy and safety of herbal *Artemisia annua* preparations: an update

**Merlin Willcox**

Honorary Secretary of RITAM (Research Initiative on Traditional Antimalarial Methods), University of Oxford

The systematic review of clinical trials on *Artemisia annua* herbal preparations has been updated to include two new clinical trials. The overall conclusion remains unchanged, that *Artemisia annua* preparations are safe and well tolerated in adults, but there is no published data on children or pregnant women. High-dose ethanolic extracts (tablets or capsules) seem to be the most effective but this needs to be replicated in Africa, in patients with falciparum malaria. Aqueous infusions clear parasites in about 70-80% of patients but there is recrudescence in 35-40% by day 28. Increasing the dose from 5g to 9g per litre has no effect.

Pilot pharmacovigilance and evaluation studies of Anamed projects were conducted in Uganda and Kenya in 2009. These showed that *Artemisia annua* preparations are safe and well tolerated except in the first trimester of pregnancy, when several miscarriages were reported. It is therefore recommended that *Artemisia annua* should be contraindicated in the first trimester of pregnancy. All projects should include evaluation and an ongoing system of pharmacovigilance for partners to report any adverse effects.

## Metabolic Profiling of Pharmacologically Active Plant Extracts

**F. Paolo Fanizzi**

Department of Biological and Environmental Science and Technology, (Di.S.Te.B.A.), University of Salento

We are researching *Artemisia* on behalf of a company. In Puglia, Italy, 40 000 hectares of tobacco are cultivated. This needs to be stopped because the CAP no longer gives subsidies for tobacco. *Artemisia* is one of the possible alternative crops which will receive EU support. Experimental fields in Puglia are growing *Artemisia annua*. We are developing extraction facilities to establish the list of ingredient compounds of *Artemisia annua* which can be used to study synergy. The physiology unit has studied embryotoxicity in zebrafish, showing that *Artemisia annua* at low doses in early pregnancy can produce fetal malformations: affecting the heart and blood vessels.

The cell culture unit studies in vitro efficacy, and so can test combinations for synergistic activity. The infusion has a stronger activity against chloroquine resistant parasites ( $IC_{50} = 0.87$  mcg/ml) than against chloroquine sensitive parasites ( $IC_{50} = 1.1$ mcg/ml).

Metabolomics is the simultaneous examination of a pool of metabolites by MS and NMR. MS is more destructive and NMR is less sensitive but it is possible to improve sensitivity. We base the "finger print" of artemisinin on the H13 signal in NMR. A huge number of metabolites have been identified which may or may not act synergistically (Liu et al, 2010. JEP 128: 230-235: Metabolites of *Artemisia annua* and *Artemisia afra*).

## Working actions for a clinical trial on *Artemisia annua* infusion to malaria treatment

**Pedro Melillo de Magalhães**

Researcher at Department of Agrotechnology, CPQBA-UNICAMP, Brazil

### 1. Raw Material

It is important to have plant material with standardized high artemisinin content (>1%) produced by a breeding programme, such as in Brazil and York (UK). The product should be registered and standardized. Last year the quantity of *Artemisia annua* produced was enough for 10 clinical trials. Unfortunately the ethical committee was very slow to approve the clinical trials. Pedro can provide plant material for other clinical trials if other groups wish.

### 2. Clinical Protocol

The clinical protocol is based on WHO protocols. *Artemisia* tea will be compared to Co-Artem. The RITAM report on the safety of *Artemisia annua* was also used

as a background for the clinical trial. Other important background documents. Included the papers by Mueller et al (2004) and Rath et al (2004).

There is a new trial from Cameroun conducted by Dr Emilien Fouda. Parasite clearance was achieved in 93.7% of patients. This used *Artemisia annua* from IFBV which contained only 0.2% artemisinin.

Recently CNPq and FAPESP have agreed to sponsor a clinical trial on *Artemisia annua* tea in Brazil costing \$150 000.

### 3. In vitro anti-inflammatory activity

The infusion was tested on the secretion of IL-8 from CACO-2 cells. This may help to reduce intestinal inflammation and improve absorption of compounds. An *in vitro* model was used to simulate the intestinal lining (CACO-2 transport model). The IC50 of the blood was more effective after absorption of the tea than after absorption of artemisinin in this model.

Discussion: There is a likelihood that the planned trial in Brazil will show that *Artemisia annua* is inferior to Co-Artem because of the high recrudescence rate with Aa infusion.

In Mozambique a number of clinical trials have been done but the government doesn't support it.

## On the quality and stability of *Artemisia annua* herbal drug

**Anna Rita Bilia**

Department of Pharmaceutical Science, University of Florence

Studies have been conducted on analysis of plants from different parts of the world, at different development stages, the activity of crude extracts, improving biopharmaceutical properties of Artemisinin, and looking at combinations of ACTs with synthetic molecules, natural constituents and plant extracts.

In China *Artemisia annua* is not used alone, it is used in combinations with 7-8 other plants. Some may increase bioavailability and change pharmacokinetics, whereas others may affect pharmacodynamics. This has led to the assumption that other plants may also be added, from traditional Chinese medicine.

Atemnkeng et al (2009) showed that the tea was more effective in mice than the equivalent dose of artemisinin, but is less effective than the WHO recommended dose of artemisinin. Mueller et al (2000) showed that the artemisinin content of a tea depended on the amount of material used per litre of water. Extraction efficiency is 20-40%. Also see Bilia et al Nat Prod Comm (2006); 1(12).

The content of artemisinin and flavonoids both vary extremely according to the cultivation conditions (Lapenna, Bilia et al, Nat Prod Comm (2008) 3:2003-6). Artemisinin concentrations range from 0.01% to 1.55%. Anamed and Mediplant concentrations vary from 0.2% to 1.5% due to environmental conditions.

Water solubility of pure artemisinin is c. 9mg/l, but in the plant extract it is 100mg/ml using 10g leaves per litre water (10x more).

Stability of Artemisinin in dried plant leaves after storage. WHO (2001) reports that the amount may degrade up to 12.8% in 3 months. Stability studies on Pedro's aluminium foil sachets: stored at 30°. Confirms they are stable for 6 months. Pedro monitored the artemisinin content over one year, it was stable for this time in the foil envelopes. Without the envelopes the content decreased over 3 months.

Conclusions from research:

1. Need to study what is the artemisinin content in tropical Africa and after cultivation, drying and storage in local conditions
2. How much artemisinin is contained in a tea prepared by local methods from the plant material?
3. Could the tea be considered as a "first aid" in the preliminary stages of the disease?
4. Can the treatment be improved by combination with other antimalarial drugs? Studying combination with dry Pawpaw leaves *in vivo*.
5. The University of Florence can contribute by doing analytical studies:
  - a. From different parts of the world
  - b. At different development stages
  - c. Of different preparations
  - d. To test stability
  - e. To evaluate artemisinin, its metabolites, flavonoids and other constituents in plasma.

[www.unifi.it/phytolab/mdswitch.html](http://www.unifi.it/phytolab/mdswitch.html)

Discussion:

If producing a standardized phytomedicine according to GMP etc as in Brazil, what is the advantage of this over another antimalarial drug – as there will be the same distribution problems.

Perhaps the objective should be to produce a first aid treatment, giving patients the access to proper drugs as early as possible. Perhaps the plant could be kept alive and used fresh rather than trying to dry and store it. However after flowering there is an immediate decrease of artemisinin content. The plant can be grown twice a year.

## Challenges in malaria treatment in children

### **Maurizio Bonati**

Manager of Public Health Department, "Mario Negri" Research Institute - Member of Global Health observatory (oISG)

88% of malaria deaths are in children in Africa (WHO 2008). Incidence is decreasing, but it still the third most important cause of death in children.

Epidemiological studies show differences in malaria incidence even between individual villages, so it is important to target interventions. Mosquito nets are an essential method but usage levels remain too low in affected areas.

ACTs are only available in the public sector in 27 of 44 African countries. No more than 63% of children can access ACTs (Malaria & Children report, Unicef). ACTs are also not used much in the private sector (Affordable medicines for malaria facility report). There are also many fake drugs on the market.

Co-artem is now available in a preparation for children (Lancet 2008; 372: 1819-27). Pre-referral rectal artesunate helps to prevent death in severe malaria (Lancet 2009; 373:557-66). But has anyone studied what happens to drugs sent to Africa?

The new WHO guidelines recommend ACT use. WHO supports cultivation of *Artemisia annua* (and has published guidelines) but most large-scale growers are in China, Kenya, Tanzania, and Vietnam. Kenya and Tanzania are the countries where distribution of bednets is the least effective. Kenya and Tanzania are growing the plant and sending it for extraction but people are still dying of malaria. We need to do something in practice if the ideal cannot be provided.

Mueller et al (2004) showed that *Artemisia* tea is effective, but recrudescence occurs. It is fine for first aid but it cannot be presented as a long-term treatment because of recrudescence. Recrudescence also occurs after ACTs.

*Artemisia annua* sachets from Pedro in Brazil were taken to Instituto Mario Negri. Tea was made in usual conditions, but other preparations were also made: biscuits and porridge.

Extraction efficacy was 40.2mg/l for 5g in 1l infused for 5 mins, and 44mg/l after 30 mins. *Artemisia* powder was mixed with millet flour to make biscuits and cooked at 200°C for 30 mins – the amount of artemisinin was 27mg if 5g leaves were mixed with with 40g flour. In porridge, 5g leaves were mixed with 50g millet and 100ml boiling water. The resulting porridge (150g) contained 53.2 g artemisinin. This quantity is more feasible for a 6m old child than a large volume of tea.

In order to provide therapeutic dose of artemisinin: (500mg/d for adult, 100mg/d for child), one would need:

- 12.5l of tea for adult or 2.5l for a child

- 18 biscuits for an adult or 4 for a child
- 1410g porridge for an adult or 282g for a child.

You need to think of different options which are feasible to provide the adequate amount of artemisinin

Discussion:

Sigma-Tau representative: opposes this approach.

## Research of active ingredient on a controlled cultivation applied to *Artemisia annua*

**Giordana Marcozzi**

Department of Basic Applied Biology, University of l'Aquila

Dr Marcozzi tried to develop a project together with Dr Paulo Monti. The aim is for local mission hospitals in Burundi to be autonomous, using local plants and pharmacopoeia. Three hybrids are available with high artemisinin content: Artemis, Campinas, Anamed.

They also studied *in vitro* micropropagation of *A. annua* cv Anamed. A simple *in vitro* system has been developed to identify the best possible soil. Unfortunately the equipment for this was damaged in the earthquake. The artemisinin concentrations in Anamed plants' glandular trichomes is greater than in wild-type plants.

A new method was developed for determining the concentration of artemisinin combining two existing methods (Reale et al, Nat Prod Res 2008). It is very fast and effective – chromatography and MS.

Chloroform extraction results in the following artemisinin extraction:

Fresh leaves – 0.3-0.4% fresh weight

Dry leaves after 2 wks: 1.4-1.5% of dry weight

Dry leaves after 1 year: 1.1-1.3% of dry weight

Regenerated plant: 0.6-0.8% of dry weight after 2 months

Extraction with aqueous infusion results in artemisinin extraction of 1.0-1.1% dry weight of dried leaves after 1 year. The maximum level was obtained with an infusion of 10g dried leaves in 1l boiling water.

Other formulations could be important in Africa: biscuits, porridge, tinctures. The drug could be produced in Africa, with a small-scale factory and laboratory to control quality. Need to network between people working on this. Also for clinical trials.

Prof Bisoffi supports establishment of multidisciplinary task force through an e-mail network.

## 2nd SECTION: What is happening in Africa?

moderator

**Franco Francesco Vincieri**

Department of Pharmaceutical Science, University of Florence

### Experience and best practice in the Centre for Research and Development on Ethnobotany

**Bela Adelaide Agostinho**

Ministry of Science and Technology -Maputo Ethnobotanical Research and Production Centre (IA), Mozambique

Studies on *Artemisia annua* were stopped last year because we were working on establishing the centre for Research and Development on Ethnobotany in Maputo. Secondly the protocol was developed for funding but the funding is still awaited. The plant is still being grown and provided to healers. The centre aims to develop technology transfer. The institution is autonomous, under the Ministry of Science and Technology. It was inaugurated last year by the Prime Minister. There are three working groups: the council, scientific board, and advisory board.

The centre's mission is to promote scientific research, dissemination of results, and development of process for the creation of goods based on native plants. The institution aims to recover and validate traditional knowledge; to promote coordinate and implement scientific ethnobotanical research. Dissemination includes making information available to communities.

Plant research is conducted on native foods, medicinal plants, and ornamental plants. This involves botany, agro-technology, development of methods for quality control of plants, pharmacognosy, pharmacology, toxicology and pharmaceutical technology. Training is being offered including in phytotherapy, and also for a post-graduate curriculum in ethnobotany. Quality control is also being developed. Main projects include creation of a nutritional table with data on native plants to mitigate malnutrition. Clinical studies on the tincture of *Artemisia annua* and techniques for the quality control of *Artemisia annua* are being developed. New products are being developed based on this research. The partners is the Faculty of Pharmacy in the University of Lisbon. Other partners include the National Institute of health, PROMETRA and AMEDO.

### Burundi, an example of best practice: cultivation and knowledge of *Artemisia annua*

**Paolo Monti**

FImAC – Italian Foundation of Physicians for Central Africa, Artemisia project in Burundi

Partners: University of L'Aquila; FIMAC (info@fimaconlus.it )

Burundi is a small country with 17 provinces. It is still affected by the aftermath of the massacre, although the war officially ended over 10 years ago. It is impossible to determine how many people live in the country. Malaria is responsible for up to 60% of all outpatient visits and up to 50% of deaths in health facilities are in children aged <5. Since 2009 healthcare has been provided free to pregnant women and children aged <5 years. Most of the population are rural farmers, and are at high risk from malaria. The resources are not fully able to meet the need of the affected areas. There are low-lying areas near lake Burundi. There are also highland areas with less malaria but a low population density with forests, and soldiers are still in hiding there.

The project began growing *Artemisia annua* to see if the concentration of active compounds was the same as in other places. It was grown around health centres. Cuttings were used as the propagation system. The government of Burundi has decided to include in its health plan the use of traditional plants. FIMAC has tried to promote the use of the plant growing in various areas. The project had to follow traditional approaches. Each province had unique practices. A nursery has been developed centrally. The soil around seedlings is covered with hay to preserve humidity in the soil. People were not confident in plants without an established value. Other plants were grown such as *Ricinus communis*. The plants are sensitive to variations in temperature and humidity, and need a cool environment, which is improved by *Ricinus*. We are planning to use low cost fluorescence tests to control Artemisinin content in the field (developed by Bernard Michels, IFBV). The focus should be on small health centres so that health workers can develop a relationship. Each health centre could therefore collect data on the use of Artemisia. Other forms of administration are being developed. The plant will be processed according to traditional processes, to provide an income for local people.

In Burundi Artemisia is also combined with other plants. It is used widely, but not yet accepted by the government.

## Fighting malaria and dysentery in Cameroon and Senegal with *Artemisia annua*: recent results

### **Pierre Lutgen**

Vice-president of IFBV – Iwerliewen fir bedreete Volleker

Resistance to conventional drugs has increased. ACTs have a lot of side-effects (Hutagalung et al 2005, Malaria J 4: 48).

The dose of *Artemisia annua* recommended by IFBV is 50g of leaves spread over at least 20 cups of fresh tea for 7 days to avoid recrudescence. IFBV will stop working with partners who cannot guarantee that the patients take the medicine for 7 days.

Artemisinin kills plasmodium through OH radicals in the Fenton reaction in combination with iron. Polyphenols and flavonoids are also active against malaria

and synergise with artemisinin (K Chiung Sheue et al, Plant Cool Reports 1992 11).

In Luxembourg the plant is dried in an oven at 35°C over 3 days. Drying: Ferreira et al J Agric Food Chem 5/1/2010.

A recent clinical study in Cameroun in 72 patients showed 95% efficacy at d14, but recrudescence after this, using tea from Luxembourg containing 0.2% artemisinin. It may be a waste of time to produce tea containing higher levels of artemisinin. Rosine Desiree Chougouo also conducted a clinical in Cameroon showing 100% adequate clinical response. In Dakar *in vitro* studies were conducted. A partner in Ghana claimed to have “cured” 40 children with 8 bags of tea, a dose intended for 8 patients.

There has been no research on the gametocytocidal effect of *Artemisia annua* tea. Artesunate alone is better than amodiaquine alone (Sowunmi 2007).

## **Malaria control**

Dr Vincenzo Racalbuto

Dr Racalbuto is a specialist in tropical diseases and started working in Africa in 1983 in Benin, in a mass chloroquine administration programme, which resulted in spreading resistance. He now works in the Directorate of Foreign Aid at the Italian Foreign Ministry.

Antimalarial policies in Africa in the last 30 years

Indoor residual spraying was used to eradicate malaria in Italy in the 1950s.

Prof Coluzzi and Prof Annette (Camerino) took part in a trial in Burkina Faso to look at the use of ITNs in 1994. The use of mosquito nets reduced child mortality. This was 6 years before the launch of the global fund in 2000. In Ethiopia the deaths from malaria have reduced from 2005 to 2007, mainly due to ITNs. ACTs were not consistently or widely available because of poor supplies, frequent stock-outs etc. This is one reason for using the tea. Uganda had a peak of malaria cases in 2005, then reduced in 2006.

The Global Fund manages \$10m. Malaria competes for funding with HIV/AIDS and TB, which receive 70-80% of the expenditure. Malaria receives <7-8% of the global fund budget. In Uganda HIV has the lion's share of funding, almost all from the USA.

Lancet 2004: Malaria only causes 8% of childhood deaths (worldwide), but more than this in Africa. Therefore all health services, not only malaria-specific ones, need to be prioritised.

## Malaria impact on clinical trials in a rural African hospital

**Giuseppe Meo**

CCM – medical Collaboration Commette, Artemisia project in Sudan

[www.ccm-italia.org](http://www.ccm-italia.org)

CCM was founded in Turin 40 years ago and has been in Sudan since 1983. Now CCM has a number of primary healthcare complexes in two states in Sudan. Mosquito nets are widely used. Africa bears 24% of the global health burden but only 1% of the global health expenditure.

Sudan household health survey 2006: 14-33% of children sleep under a mosquito net. 50% of children aged <5 had fever in last 2 weeks, only 3% received treatment in last 24 hours. Malaria is 60% of the caseload at the local hospitals. Adults also get severe malaria. Cerebral malaria is the main cause of death in children aged <5 years. Only 5-10% of the population have access to medication. Child mortality in Sudan is 250-320 per 1000.

They tried growing *Artemisia annua* in arid areas, with 6 months of drought. The state is Warab state, a remote rural state. The hospital is in Turalei. It is close to the oil wells which were the cause of a military clash. The plant seemed to grow OK, but needs to be tended carefully. A pharmacist went to a training course in Kenya with Anamed, but afterwards he was arrested and tortured (in Egypt) and disappeared.

The plant could be grown at community level with unskilled health workers. Many deaths can be prevented. 11% of deaths can be treated by surgery. Surgery should be part of primary health care (vaginal fistulae, caesarian sections etc). Dental caries are not treated so progress to become worse.

## The case of Rwanda between light and shade: the state of the art

**Paola Conti**

Share Human life Project, Artemisia project in Rwanda

“Share” is a totally self-funded association funded by private donors, done by volunteers.

Rwanda has a climate which is very suitable for growing Artemisia. It also has a high population density so it is difficult to find land to grow Artemisia rather than food. Large scale farms are not possible, only small plots of land can be found. Permission for this project was given by the Ministry of Health in Rwanda. Children helped growing the plants. Larger plants are grown to protect seedlings from the sun. The plants which did best had an artemisinin content <1%.

A clinical trial was supposed to start in 2009, for which herbal medicine was sent from Brazil. However the Minister of Health changed and health centre staff became scared to collaborate in the project. The doses from Brazil expired. There is huge institutional control in Rwanda, it is not possible to ignore this.

Coartem is the only drug permitted since 2007 in Rwanda. It is provided presumptively to all febrile children. There is no monitoring of adverse effects. There is no second line option, all other antimalarials are banned. Co-artem however is often unavailable. People would be willing to use herbal medicines in rural areas.

Discussion: It would be better to run this project in remote areas with no health facilities. It could be considered as a "first aid" where no other treatments are available.

Pierre Lutgen: IFBV does Artemisia projects through the back door in Peru etc, without official approval, because governments are not supportive.

## Watinoma Association: experience of Artemisia cultivation in Burkina Faso

**Daive Losa**, Watinoma onlus, Artemisia project in Burkina Faso

Watinoma was founded in Burkina in 1987. The object is the promotion of local culture, particularly music. Deforestation is one of the most important problems in BF. Artemisia cultivation has been tried with ICEI support in Burkina Faso since 2008. Watinoma has distributed 1000 ITNs to mothers with young children. The women confirm that their children are less likely to get malaria and have observed that this is effective. Malaria is responsible for 57% of deaths in children aged <5 years. The main ACTs used are Coartem and As/Aq. Access to drugs and treatment are a problem for most of the population.

The main difficulties in cultivation have been due to errors in fertilizing the soil and excess sun. Some seedlings died. Straw mats were placed above the plants to provide shade. The climate is drier than in Rwanda / Burundi. However the plants were not used medically, only cultivation was tried. If all goes well they would like to repeat the cultivation on a larger scale.

## Agricultural and biochemical evolution of *Artemisia annua* in Spain

**Carmen Gonzalez Ramos**

CTAEX Research manager – Technological and Food Farming Centre Extremadura, Spain  
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CTAEX is a national nonprofit agriculture organization in SW Spain and Portugal. It has experimental farms. There is also a food technology dept, analytical services, and an engineering department. Priority sectors: tomatoes, medicinal and aromatic plants, tobacco, olives, soft cheeses, meats. Here also it is being used as an alternative crop to tobacco. Research has been done on AA cultivation and adaptation in the Mediterranean region.

Studies have been done on the antimalarial active principles from *A. annua* and *Azadiractha indica*. Aa was cultivated, harvested mechanically and sun-dried. Varieties grown were Artemis (Mediplant), Sweet Annie, Cramers "Yardstick" and Cramer's cousin Annie (Johnny's seeds, USA), Vietnamese, and Chinese. Studies have been done on sowing, transplantation, fertilization, irrigation, weed control (mechanical), crop monitoring, harvesting, and drying.

Yield: 4488kg per hectare of dried pellets. Artemisinin content was 0.8% (Mediplant F1), 0.8-1.2% (Chinese).

Artemisinin pills were developed as was an insect repellent based on *A. indica*. Collaboration has been developed with the Angolan government to develop cultivation in Angola.

Discussion: It is not possible to grow other crops (e.g. tomatoes) after growing AA because it releases chemicals into the soil. It also contains some anti-nematode compounds. It has strong allelopathic activity (artemisinin was studied in Switzerland for this). In Brazil there have never been these problems, perhaps because the temperature is higher and destroys the allelopathic compounds.

### **Conclusion: Franco Borelli, ICEI**

This year there seems to be greater agreement between scientists. Last year a number of clinicians warned against this approach. There is still a question about whether we can go ahead and start or whether more research first needs to be done. Malaria is endemic in 45 countries. There are large scale productions which only address the needs of pharmaceutical companies, and also small scale cultivation. There are many contradictions between and within countries. It is not easy to look at things in a comprehensive fashion. However institutions are relatively unwilling to consider this approach as being possibly effective. We are not suggesting this is an alternative to replace drugs or other preventive measures. AA is a complementary measure, and has fewer side-effects. We cannot do this alone, we want to establish a platform of institutions, researchers, Drs, NGOs, field workers, local governments etc. The Italian Cooperation has difficulties. At present energy and resources are being wasted and duplicated. WHO funds trials on effectiveness of drugs which we already know are effective, but no funds go on clinical trials of Artemisia tea. We need everyone's support to act together.