The Potential and Complexity of Artemisia

by

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IFBV-IDAY
We started with this hypothesis

Artemisinin, the active substance in the plant, is an organic peroxide.

It kills Plasmodium through OH radicals in the Fenton reaction in combination with iron. It is a chemical, not a biological process,
which was confirmed by the following experiment

Research people in Luxembourg discovered that Artemisia annua sterilizes water
We first
1. retrieved in the scientific literature papers documenting the efficiency of *artemisia annua* tea infusion
2. and then accumulated our own clinical trials and field experiences
The Vietcong lost more soldiers to malaria than to weapons. Ho Chi Min turned to China for help. Researchers at the Chinese Institute of Material Medicine found a region of China that reported no malaria cases, and when they investigated, they discovered that its people drank a decoction of Artemesia annua at the first sign of malarial symptoms.

CJ Puotinen, NEHA Journal, Winter 2003
Artemisia annua clinical studies

A 100% cure rate was achieved in 485 cases of vivax malaria treated with the tablet of dilute alcohol extract of the herb in doses spread over 3 days.
The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects.

Mueller MS, Karhagomba IB, Hirt HM, Wemakor E.

Hopital Nebobongo, Nebobongo, Congo. 2000

The plant Artemisia annua L. (Asteraceae) is listed in the Chinese pharmacopoeia as a remedy for various fevers including malaria, and contains the well-established antimalarial compound artemisinin. In this study, a hybrid form of A. annua was successfully cultivated in Central Africa. The aerial parts of the plant contained 0.63-0.70% artemisinin per dry weight, and approximately 40% of this artemisinin could be extracted by simple tea preparation methods. Five malaria patients who were treated with A. annua tea showed a rapid disappearance of parasitaemia within 2-4 days. An additional trial with 48 malaria patients showed a disappearance of parasitaemia in 44 patients (92%) within 4 days. Both trials showed a marked improvement of symptoms.
Results obtained by Anamed in 2000 in different locations of Zaïre

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Patients</th>
<th>Negative Parasitemia after 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebobongo</td>
<td>48</td>
<td>44 (92%)</td>
</tr>
<tr>
<td>Bukavu/Lwiro</td>
<td>91</td>
<td>86 (95%)</td>
</tr>
<tr>
<td>Kinshasa</td>
<td>21</td>
<td>19 (91%)</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>149 (93%)</td>
</tr>
</tbody>
</table>
Regional health center Lwiro, Bukavu, 1999.

« 91 patients with positive plasmodium blood smears were treated with artemisia annua tea for 5 days. After treatment 95% of the patients were free of parasites. »

www.sextocontinente.org/apoyohumano/a-a-anamed...
A proof-of-concept study, which commenced in June 2004 and ended in February this year, has yielded encouraging results. Clinical studies involving 48 patients with uncomplicated malaria have shown the whole-leaf drug to have impressive efficacy in treating the disease with no significant side effects.

Source: ‘New Agriculturist’ online, Naftali Kure, Kenya
In order to compare the antimalarial activity of artemisinin from Artemisia annua and other antimalarial drugs: artesunate and artesunate + amodiaquine in 3 villages from 2 regions (125 people). The results of the comparative study showed a significantly higher sensitivity of artemisia annua concoction (0 % of Echec Thérapeutique Tardif ETT) compared with that of artesunate (12.5% of ETT) and the artesunate combined with amodiaquine (14.30% of ETT). The concoction intake for 7 days was 0% of ETT, significantly lower than that of 5 days intake (28.5%). The RTPA is above 80% for the 3 protocols indicating the absence of warning according to WHO criteria. The concoction of Artemisia annua is a good treatment of malaria seeing the results. To improve its effectiveness, it must be taken for at least 7 days or in combination with other antimalarial drugs.
OPTIMIZING THE TREATMENT OF UNCOMPLICATED MALARIA USING TEA OF HYBRID ARTEMISIA ANNUA

Adelaide Bela Agostinho, Ariadna Vlyalko, João Massingarela and João Fumane

Roma, 13th Mar 2009

On 160 volunteers in Mozambique
Summary of results (by PL)

• Average decrease of fever in 3 days for *A. annua* tea and for artesunate-fansidar control
• Average decrease of parasitemia by 97% in 3 days
• One or two cases of relapse
• TEA EQUIVALENT TO ACT
Clinical trials, Dr E Fouda, Yaoundé, Cameroon, January 2010
74 patients (financed by LBMCC and IFBV Luxembourg)

Percentage of parasites eliminated in function of time
« Overall the number of children treated was at least 250. They reported that all the children treated had recovered completely”.

(Average artemisinin content of plants: 0.3%)
Trial done by medical doctors in India

Comparative study done in Two villages with MP positive cases

• **Jero Village** (treated with AAA tea)
  - 35 Patients were given AAA tea for 7 days.
  - All of them improved within 3 days of treatment except one child who did not take, died.
  - Every one came back to their normal health within a few days.
  - Test was done on 15/10/10

• **Dumiduar Village** (treated with allopathy Medicine)
  - 20 Patients were treated with Chloroquine, primaquine & other antimalarials.
  - Their improvement was quite slow and are still recovering to their normal health.
  - Test was done on 15/10/10
Essais Artemisia annua de Luxembourg au dispensaire privé catholique de Dagana
Sœur Elke Steinacher
En collaboration avec Gembloux. U de Liège

La liste suivante reprend les noms des personnes atteintes du paludisme et soignées durant le mois de septembre 2011.
L'Artemisia a été tamisée et mélangée avec une pate arachide pour en enlever l'amertume. Par jour, 7g de poudre ont été ainsi administrés aux enfants et ceci durant 7 jours.
Des tests de TDR (Test Diagnostic Rapide) ont vérifié que les personnes étaient atteintes du palu et soignées à présent.

<table>
<thead>
<tr>
<th>Nom</th>
<th>Age</th>
<th>Température °C</th>
<th>Etat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokhna Diara Sy</td>
<td>2 ans</td>
<td>38</td>
<td>guéri</td>
</tr>
<tr>
<td>Adéle Sene</td>
<td>11 ans</td>
<td>39</td>
<td>guéri</td>
</tr>
<tr>
<td>Fabine Sow</td>
<td>10 ans</td>
<td>37,8</td>
<td>guéri</td>
</tr>
<tr>
<td>Malick Sow</td>
<td>11 ans</td>
<td>38,3</td>
<td>guéri</td>
</tr>
<tr>
<td>Boubakar Khonte</td>
<td>9 ans</td>
<td>39</td>
<td>guéri</td>
</tr>
<tr>
<td>Aminata Niarem</td>
<td>9 ans</td>
<td>38,6</td>
<td>guéri</td>
</tr>
<tr>
<td>Melanmine Mane</td>
<td>12 ans</td>
<td>39,7</td>
<td>guéri</td>
</tr>
<tr>
<td>Moussa Fall</td>
<td>10 ans</td>
<td>38,8</td>
<td>guéri</td>
</tr>
</tbody>
</table>

De même un total de 34 enfants pour les mois de octobre et de novembre

Similar results are available from our partner Kachoré in Benin on 120 children
Community sensitization for the production and use of Artemisia tea in The Gambia

Adults and children
- 35 people used as curing malaria using the 5g/liter@4 doses/day for 7 days (equals to 35g of dried leaf biomass)
- Recovery seen (72%) within 5 days & (98%) within 7 days
CHIMIOSENSIBILITE IN VITRO DE PLASMODIUM FALCIPARUM PAR RAPPORT A LA TISANE D’ARTEMISIA ANNUA ET ACTION STERILISANTE DE LA MEME TISANE SUR LES EAUX POLLUEES

Thèse de doctorat de Omar Gueye financée par ArcelorMittalFoundation et IFBV

“En conclusion les tests ex vivo* sur les souches de P. falciparum montrent que la tisane luxembourgeoise serait efficace. Cette efficacité démontrée contre P. falciparum, malgré une teneur en artémisinine faible, nécessite des études plus approfondies qui vont surtout porter sur la concentration des autres substances (polyphénols, huiles essentielles, polysaccharides, scopoletine....) sur les lymphocytes, le système immunitaire...”

* DELI test sur 57 échantillons sanguins de personnes infectées
Concernant les études faites, je pars au Bénin le 13 janvier et espère avoir des résultats plus officiels, mais pour le moment, ceux obtenus avec la tisane (en curatif) sont assez concluants. Avec l'extrait brut, le nombre de patients n'est pas encore suffisant pour pouvoir donner un résultat fiable.

Joëlle Leclercq
UCL
Le Dr Yves Saint Hillier de Besançon a fabriqué 20 000 gélules contenant pour les plus gros 1 gr de poudre d’artemisia annua moulue.

Aucun échec thérapeutique ou effet négatif n’a été rapporté pour les essais qu’il a fait sur des centaines d’adultes et d’enfants au Mali. Ils permettent l’application rectale en cas de malaria sévère. Les résultats étaient spectaculaires chez les enfants.

Hannelore Klabes also uses capsules in Burundi and received the Bundesverdienstkreuz for this.

Wan YE and Zang QZ had already made similar gelatin capsules in 1992: 100 % cure rate for plasmodium vivax.
• [Studies on the antimalarial action of gelatin capsule of Artemisia annua].
• Wan YD, Zang QZ, Wang JS.

The cure rate for Plasmodium berghei and P. vivax infections was 100%,
Based on the medical records of over 48,000 women treated over a period of more than 20 years, the team at the Shoklo Malaria Research Unit at the Thai-Burma border concludes:

The study provides a level of reassurance regarding the potential risk associated with artemisinin exposure in early pregnancy, compared with the established risk of malaria.

http://www.shoklo-unit.com/
What we have learned so far

Tea of *Artemisia annua*

- Efficiency >95%
- No side effects*
- Low cost
- No resistance shown up til today

But this needs to be confirmed by large scale clinical trials in accordance with the WHO protocol.
Because there are disturbing facts which came up during recent years
Anti-inflammatory effect on CACO-2
P de Magalhaes, UCL, 2009

Inhibition of IL-8 secretion from CACO-2 inflamed cells by Artemisia annua teas & its pure compounds

Why would the tea from Luxembourg be different or even better?
45 times more artemisinin is delivered into the bloodstream via plant material than via artemisinin pure powder

Pamela Weathers et al., Phytochem Rev 07 Mar 2010
Pure artemisinine is pro-inflammatory and immuno-depressive

Results from LBMCC, Luxembourg

Up to now our analysis showed that artemisinin is definitely not responsible for the antiHIV activity
Fr. Van der Kooy, Leiden, personal communication
Leishmaniose

La tisane d’artemisia annua luxembourgeoise administrée par voie orale à une dose de 100 mg par kg de poids corporel pendant 20 jours conduit à une guérison de 100% telle que mise en évidence par une cicatrisation totale des ulcères chez les hamsters infectés.

Dr Ivan Velez
PECET
Expert OMS Genève pour la Leishmaniose
15 Aug 2010
Tea from Luxembourg

Tea from Venezuela
Cytotoxicity test run by the CRP-Santé at Luxembourg (Dr Ning Wang) showing that the tea from Luxembourg is equivalent to the tea of Brazil
J.M. Michels and P. Lutgen, Luxembourg, 2010, unpublished
Based on results obtained by Dr Rosine Chougouo at the LNS in Luxembourg by analyzing 20 varieties of artemisia annua.

The tea from Luxembourg is also very rich in essential oils (limonene, 1.8-cineol…)
Tea of Chinese origin sold in Luxembourg contains a lot of stems rich in scopoletin.
Artemisinin, scopoletine 1.8 cineol...
Artemisia is a unique plant which contains **sulfated polysaccharids** which

- Reduce the mobility of sporozoites interfering with CS
- Prevent the sporozoites injected by the mosquito to enter the liver
- and the erythrocytes by a heparan sulfate interference
- Reduce the concentration of glucose in the blood, starving thus plasmodia
- Prolongate dormancy
Artemisinin-induced parasite dormancy: a plausible mechanism for treatment failure.

Codd A,

But a new research field has opened: Certain polysaccharides or peptidoglucans prevent excystement of dormant plasmodia.
Artemisia annua also has strong *gametocytocidal* properties, inhibiting thus the transmission from man to mosquito (WHO/MAL/98.1086).

It stimulates the *immune system* and drinking a few cups per week prevents the malaria infection as it was demonstrated in 80 schools in Kenya and for 2000 farmers in Uganda in 2011.
Malaria can be eradicated with artemisia annua tea in a few years as shown in Ugandan villages (P.E, Ogwang, Ministry of Health, Kampala)
In Uganda for improved health effect of the *artemisia annua* they remove the artemisinin from the infusion.

In China, some 2000 years ago, it was claimed that *artemisia apiacea* (containing no artemisinin) was better than *artemisia annua*.

In South Africa *artemisia afra*, not containing artemisinin either, is a strong antimalarial
Limonene, 1.8 cineol and the precursors arteannuin-B and artemisitene have cytotoxic effects on cancer cells similar to those of artemisinin.

T. Efferth et al., Phytomedicine, 18. 2011. University of Mainz
The artemisia annua plant could only stay efficient by mobilizing an entire cocktail of substances and among these several have an antiplasmodial effect. Artemisia annua infusions are thus ACTs. All this might explain why artemisinin avoided resistance despite a consumption at low and irregular doses during 2000 years.

JvE RBM-WHO
Anti-inflammatory effect and modulation of cytochrome P450 activities by Artemisia annua tea infusions in human intestinal Caco-2 cells

Pedro Melillo de Magalhães Yves-Jacques Schneider
Institut des Sciences de la Vie & UCLouvain Belgium

Our results highlight the advantage of drinking A. annua infusions for their potent antiinflammatory effect which could synergise their antimalarial activity.
Artemisinin contained in the tea does not metabolize into dihydroartemisinin, a very reactive molecule present in ACTs. Artemisinin has a much slower and longer action.
Culture of *Artemisia annua*

at Walferdange-L to be packed at “Téi vum Séi”

We have plantations in a dozen countries and reach in a few regions a production volume which requires the implementation of a distribution and marketing system (FANGA project)

**Our objective:** see artemisia growing in every African garden
Artemisia annua plants around a house or a school are an excellent repellent for mosquitoes.

Also burning the dry herb in a dormitory.
The sterilization and antibacterial power of *artemisia annua* was confirmed by the Universities of Bangui (this graph), Medellin, Gent, Dakar.
IFBV has developed a worldwide partnership

IDAY-International

Belherb (Association for the promotion of herbal medicine) from Belgium-Luxembourg is a group of 10 doctors and university researchers who closely work with universities in Senegal, Benin, Gambia, Kenya, Uganda, Cameroon, Congo, Central-Africa, Colombia, Brazil, Venezuela, Peru

And numerous associations in the North and the South
A good friend of mine, Dr. Kris Demeyer, is Professor at the university of Brussels and working on Artemisia annua, one of the best known herbs in malaria treatment because of the presence of artemisinin. However, he found out that even low doses of the compound have an effect provided the other components of the herb are present in the preparation. This is of utmost importance as we have to avoid the use of pure or purified artemisinin in order to avoid the development of resistance against the molecule. This can be achieved in using a cocktail of compounds all working via different mechanisms. He is doing research on that topic.

Luc Delmulle
Concerns raised by ACTs
Shelf life of Predosed Plates Containing Mefloquine, Artemisinin, and Artesunate

S. Houzé et al., Laboratoire de Parasitologie, Paris

The shelf lives of preserved antimalarial agent-predosed plates according to the type of wrapping and the temperature of storage were studied by measuring the 50% inhibitory concentrations of drug for Plasmodium falciparum 3D7. The shelf life of mefloquine was 8 weeks at 25°C; and those of artesunate, artemisinin, and dihydroartemisinin were a minimum of 24, 12, and 8 weeks, respectively, at 4°C.

At 37°C, whatever the conditions of packaging or the drug used, the plates were no longer valid after 1 week.

The artemisia annua herb however conserves its properties for many years if stored in dry ventilated area.
50% of ACT pills sold on the market are counterfeit.
A crime and a disaster.

Newton PN, et al. (2006) Manslaughter by Fake Artesunate in Asia—

Genuine (left), Counterfeit (right). Artesunate, Cameroon.
But for tea infusion we have a control tool…

Research people in Luxembourg discovered that the only fluorescent tea under UV light is *artemisia annua*.
Artemisia annua tea never caused side effects, ACTs do (red: lumefantrine, black mefloquine)

R.Hutagalung et al., Malaria Journal, 4, 48, 2005
Hepatotoxic and hemolytic effects of acute exposure of rats to artesunate


At doses which are lower than those prescribed by WHO/MAL/98.1086: 20 mg/kg as loading dose followed by 10 mg/kg for 6 consecutive days
In African countries the access to ACTs remains low: 3%

0.1 % in Gambie to 13 % in Zambia.

*World Malaria Report. Sept 2008*

In several countries resistance to artesunate or artemether has developed.
Of major concern to WHO and MSF
Today’s demand for the drug artemisinin is being met by the surplus from a past production boom, but a larger and more reliable supply will be required to meet future needs.

*One tonne gives about two million doses of artemisinin-based combination therapy.

Source: Boston consulting group
Resistance to ACTs, not only in Asia but also in Africa
Figure. Percentage of positive cases on day 3 after ACT

Circles represent data before November 2010 and triangles data after November 2011.
In Kenya declining responsiveness to ACTs on 474 children
S Borrmann et al., PlosOne, 6(11) 2011
A team of researchers from Canada and the United Kingdom studied parasites from travellers who returned to Canada with malaria after trips abroad between April 2008 and January 2011. They found that 11 of the 28 parasites grown in the laboratory had a mutation that made them resistant to artemether, one of the artemisinin group of antimalarials. All 11 came from Africa (from Angola, Cameroon, Congo, Ghana, Kenya, Liberia, Nigeria and Tanzania), the researchers reported last month (27 April) in Malaria Journal.
The high potential for resistance is known since 5 years!

Recurrence rate for ACTs in Uganda, H.Bukirwa et al., PlosClinicalTrials, May 2006

AQ+AS: amodiaquine + artesunate
AL: artemether+lumefantrine
Or 7 years

TK Mutabingwa et al

By day 28 the parasitological failures were 40% for artesunate–amodiaquine and 21% for artemether-lumefantrine on Tanzanian children
Or 10 years ago

In M'rimp, Senegal, even though a decline in the incidence rate of uncomplicated malaria was observed between 1998 and 2002, it was slight and the impact of ACT (ASAQ) introduction could not be clearly established.

S Sarrasat et al., Malaria Journal 7, 2008, 215
Our results suggest that that combination with mefloquine is not the ideal way of protecting the usefulness of artemisinin and its derivates.
Qinghaosu (artemisinin) resistance in rodent malaria

A.N. Chawira,
•D.C. Warhurst,
•W. Peters
Dept. of Medical Protozoology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT U.K.
Accepted 25 October 1985.
ACTs may increase oocysts in mosquitoes and retransmission to humans

BJ Huho, Malaria Journal, April 2012
FIGURE A5.1. Areas of the world in which oral artemisinin-based monotherapies are known to be produced

Source: WHO 13 Jan 2012
Figure 8. Estimated funding required for both malaria control and artemisinin resistance containment

Source: WHO 13 Jan 2012.

Global Malaria Action Plan (GMAP) implementation costs include diagnosis and treatment (ACTs, RDTs and severe case management), monitoring and evaluation, malaria programme (including community health workers, training, infrastructure and institutional strengthening) and prevention.
Cost per treatment per patient per year

° HIV/AIDS: 800 €
° TB: 100 €
° Malaria (A annua): 1 €*
° Dysentery (A annua): 0.5 €
With 1000 € we can save the lives of 1000 children
..The two systems of traditional and Western medicine need not clash....they can blend together in a beneficial harmony

Dr Margaret Chan, Beijing declaration Nov 2008