Use of non-pharmaceutical forms of *Artemisia*

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WHO issued a position statement in 2012 on the effectiveness of non-pharmaceutical forms of *Artemisia annua* against malaria

In this, it is stated that “*WHO does not recommend the use of A. annua plant material in any form, including tea, for the treatment or the prevention of malaria*”

Since then, the use of non-pharmaceutical forms of *Artemisia* has received increased attention
Background

- Number of different products available, including in the form of tea or capsules
- These products are promoted for the prevention and treatment of malaria
- Mostly made from *A. annua* and, more recently, *from A. afra*
Arguments used to promote non-pharmaceutical forms of Artemisia

- Key arguments used focus on:
  - the products as a cheap and self-reliant alternative to ACTs;
  - the products as unlikely to be falsified; and
  - that due to the different compounds in a natural herb, *A. annua* cannot be considered a monotherapy

- European NGOs and faith-based organization are playing a role in the promotion. The material can include specific instructions on use:

WHO GMP has done a review of available literature for non-pharmaceutical forms of *Artemisia*

The conclusions are in-line with previous WHO statement in that WHO still *does not support the promotion or use of Artemisia plant material in any form for the prevention or treatment of malaria.*

This conclusion is based on findings regarding:

- Content
- Efficacy
- Risk of artemisinin resistance
- Other treatments available
**A. annua**

- Native to Asia, originating in temperate climates
- Now grows naturally in many countries also in subtropical and tropical areas.
- In wild samples, artemisinin concentration found is 0.02% to 1.07% of dried plant material. Hybrids have been cultivated with higher artemisinin content.
- Other compounds includes flavonoids and phenolic acids.
- A Chinese recipe from 341 A.D. prescribed *A. annua* juice produced using cold water for the treatment of fever.
- *A. annua* tea never used for malaria treatment in China (according to Prof. Tu Youyou, Nobel laurate)
A. afra

• Native to Africa, with a wide distribution in Southern and Eastern parts of Africa.
• Large variation in the chemical compounds in A. afra between geographical areas.
• A. afra does not have any significant content of artemisinin.
• Has been used in traditional medicine for a variety of ailments including asthma, diabetes and fevers.
The content of the *Artemisia* herbal remedies given for malaria treatment and prevention varies substantially.

- Plant content affected by genetics, harvesting time, temperature, nutrient availability, and from where on the plant the leaves are harvested.
- Content of final product further affected by processing, drying, storage conditions, and preparation method.

Studies done in controlled conditions using 5 or 9 g hybrid *A. annua* found that tea content varied from 8.4 mg to 117.2 mg artemisinin per liter of tea.
Efficacy

Content in Artemisia herbal remedies often insufficient to kill the parasites and to prevent recrudescence

- Too short treatments or too low blood levels of artemisinin result in failure to clear parasites or recrudescence.
- Artemisinin auto-inducts so higher levels need to be administrated after first day to achieve same blood-levels.
- No evidence that antimalarial activity of other plant constituents or synergism with artemisinin, significantly increase the efficacy of non-pharmaceutical forms of A. annua.
- A. afra does not contain artemisinin or any other compound identified as having significant antimalarial activity in vitro.
A recent in vitro study by Czechowski et al. (2019) focused on the potential effect of flavonoids.

Comparing in vitro efficacy of *A. annua* extracts with and without flavonoids showed no significant difference.

Testing extracts from *A. annua* without artemisinin showed very low to no antiplasmodial activity.

The authors concluded that the in vitro bioactivity of flavonoids against *P. falciparum* is negligible compared to that of artemisinin.
The few clinical studies completed, mostly of relatively low quality, have been conducted with few patients, included too short a follow-up period, or been poorly controlled for bias. Many studies find a recrudescence rate up to 90% by day 28 using *A. annua*.

One study stands out:

*Artemisia annua* and *Artemisia afra* tea infusions vs. artesunate-amodiaquine (ASAQ) in treating *Plasmodium falciparum* malaria in a large scale, double blind, randomized clinical trial.

Jérôme Munyangi, Lucile Cornet-Vernet, Michel Idumbo, Chen Lu, Pierre Lutgen, Christian Perronne, Nadège Ngombe, Jacques Bianga, Bayon Mupenda, Paul Lalukala, Guy Mergeai, Dieudonné Mumba, Melissa Towler, Pamela Weathers

Conducted in 2015 in the Democratic Republic of the Congo
Multi-centre, randomized, double-blind design with a follow-up of 28 days

957 patients enrolled in five different locations:
- 472 enrolled in a artesunate-amodiaquine arm, and
- 471 enrolled in the *Artemisia* arm (248 *A. annua*, 223 *A. afra*).

On day 28, Munyangi et al. reported recurrent parasitaemia in:
- 9 out of 248 patients (3.6%) treated using *A. annua*,
- 25 out of 223 patients (11.2%) treated using *A. afra*,
- 310 out of 472 patients (65.7%) treated using artesunate-amodiaquine.
Munyangi et al. furthermore reported that:

- In some treated with artesunate-amodiaquine, parasites found 14 days after the start of treatment.
- Treatment failures with artesunate-amodiaquine occurred mainly within the first 14 days.
- Artesunate-amodiaquine had higher efficacy in children (50%) than in adults (30%).

This data conflict with other available data:
- Even in areas of high drug resistance in South-East Asia, parasites never remain in patients 14 days after the administration of an ACT.
- Treatment failures with ACTs, mostly occur at the end of the follow-up period.
- Studies done by different partners in Congo consistently found ≥ 95.0% efficacy with artesunate-amodiaquine.
- Efficacy normally higher in adults.
Widespread use of *A. annua* herbal remedies could hasten the development and spread of artemisinin resistance.

- Resistance is more likely when parasites are exposed to sub-therapeutic levels of an antimalarial drug.
- If consumption of *A. annua* becomes widespread, any potential weak antimalarial activity of other compounds in *A. annua* would not be sufficient to protect artemisinin from resistance.

Artémisinin in any form does not work well as prevention against malaria

- Artémisinin has short elimination half-life, and is not promoted for use in malaria chemoprophylaxis in any form.
Affordable and efficacious treatments for malaria are available

- ACTs are still highly efficacious
- Complete treatment with an ACT can be procured for less than US$ 2.
- Countries need to strengthen their regulatory systems to protect patients from counterfeit and substandard treatments;
  - this includes any products promoted for treatment of malaria without the necessary information in terms of their content, quality, safety and efficacy.
Thank you for your attention

END MALARIA