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In Vivo Trials on The Therapeutic Effects of Encapsulated Artemisia Annua and Artemisia Afra

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ABSTRACT

This trial took place in the province of Katanga in the RDCongo and was handled in two parts

1. 82 volunteers suffering from malaria were treated during 7 days with capsules containing powdered leaves of Artemisia annua from Luxembourg (AAL) or from Burundi (AAB) and Artemisia afra (AAF). Total dose for AAL was 15 gr, for AAB 7.5 gr and for AAF 7.5 gr. Despite these low doses all patients were free of fever after 2 days and 85% were free of parasites after 7 days for AAL, 76% for AAB and 40% for AAF.

2. 44 volunteers carrying trophozoites were treated with capsules containing Artemisia afra leaf powder from Burundi. The total dose of Artemisia afra powder administered over 10 days was 20.gr. In order to better understand the prophylactic and therapeutic effect of Artemisia herbal medicine on malaria infection it is important to assess the CD4 count and gametocyte carriage before and after treatment. It was found that on day 10 the CD4 count had on the average increased by 20% and the trophozoite carriage was reduced to zero except in a few rare cases

KEYWORDS :

INTRODUCTION

A large portion of the population consults with practitioners of traditional medicine and medicinal uses of local plants for first aid, as only choice in the absence of other remedies (Kitua a.y Malebo & HM 2004). The World Health Organization (WHO) is trying to promote traditional medicine and its integration into medical treatments (WHO Perspectives of Traditional Medicine 2014-2023). *Artemisia annua* is a major source of artemisinin, which has received considerable attention as a promising and powerful malaria drug and its rather low toxicity (Ferreira et al 1995). This active ingredient has been extracted from the plant which has been used in China to treat fever and malaria for centuries (Allahdin O et al. 2008). However, it appears that the antimalarial potential of *Artemisia annua* is not only due to artemisinin; several studies have shown that many other molecules or inorganic constituents in the plant also have their own or synergistic antimalarial activity, and it seems that the importance given to artemisinin has been overestimated (Ferreira et al 2010 ; Fouda , 2010 ; De Donno et al 2012).

In this study the main objective was to compare the therapeutic effects of *Artemisia annua* powder from two different origins to *Artemisia afra* based on clinical and biological signs.

In a second part of the trial the objective was to verify the mode of action of *Artemisia afra*, its impact on the immune system and other physiological factors and confirm the absence of side effects.

1.0 MATERIALS AND METHODS

POPULATION STUDY

The study was conducted in the Democratic Republic of Congo in the Katanga Province during a period of 8 months, from April 2013 to December 2013.

The first part of the study population included 82 young adult volunteers with uncomplicated *Plasmodium falciparum* malaria who were divided into three groups:

The first group of 20 volunteers received *Artemisia annua* from Luxembourg

The second group of 37 volunteers received *Artemisia annua* from Burundi

The third group of 25 volunteers received *Artemisia afra*

44 patients were treated with capsules containing *Artemisia afra* leaf powder from Burundi

CRITERIA FOR INCLUSION

Any single voluntary adult patient with age varying between 15 and 70 years and with non- complicated form of malaria with *Plasmodium falciparum* confirmed by a positive blood smear

EXCLUSION CRITERIA

Pregnant women, children, sick patients under other antimalarial or antibiotics two weeks before treatment.

TREATMENT

Three varieties of *Artemisia* were used :

Artemisia annua from Luxembourg (low concentration of artemisinin, capsules 1 gram) *Artemisia annua* from Burundi (artemisinin in high concentration, capsules 0.5 gram)

Artemisia afra (from Burundi without artemisinin, capsules 0.5 gr)

Each patient received 15 capsules : 3 capsules on the first day and 2 capsules on the six following days, corresponding to a total of 15 grams of *Artemisia annua* from Luxembourg, 7,5 gr of *Artemisia annua* fromBurundi, 7.5 grams of *Artemisia afra*.

Paracetamol was prescribed on the first day for patients with fever.

RESULTS PART 1

2.1 EPIDEMIOLOGY PROFILE

- The 82 patients treated with capsules of Artemisia were divided into three sub -groups:
- For the first group (20 volunteers) who received *Artemisia annua* Luxembourg, 85 % of patients healed at the 7th day and clinical signs improved in 100 % of cases within the first two days of treatment.
- For the second group (37 volunteers) who received *Artemisia annua* of Burundi, 75.6 % of patients healed at the 7th day and clinical signs improved in 100 % of cases within the first two

days of treatment.

- For the third group (25 volunteers) who received *Artemisia afra* of Burundi, 40% of patients healed at the 7th day and clinical signs improved in 100 % of cases within the first two days of treatment.

2.2 CLINICAL PROFILE

2.2.1 Group of patients given capsules of *Artemisia annua* Luxembourg (AAL)

TABLE 1: Distribution of patients by sex, age, clinical signs, and biological evolution

		Patients (n 20)	%
Gender	male	14	70
	female	6	30
Age	18 – 38	14	70
	39 – 49	6	30
Clinical indications Day 1	Feverish	3	15
	Afebrile	17	85
Clinical indications Day 7	Feverish	0	0
	Afebrile	0	0
Thick film blood smear Day1	+	7	35
	++	3	15
	+++	10	50
Day 7	-	17	85
	+	3	15
	++	0	0
General disease progression	Good progress without side effects	20	100
	Side effects	0	0

COMMENTS :

- The sex ratio is 70% of males

- The age between 18 and 38 years included 70% of cases

- 15 % of patients were febrile on the first day and 85% were afebrile.

- At J+10 a complete disappearance of clinical manifestations was observed.

- At J+1 blood smear was positive (+++) in 50 % of patients; at J+7 blood smear was positive in 15% of patients.

- No adverse events were observed on the 25 cases followed

2.2.2 Group of patients given capsules of *Artemisia annua* Burundi (AAB)

TABLE 2: Distribution of patients by sex , age, clinical signs, and biological evolution

		Patients (n 37)	%
Gender	male	15	40.54
	female	22	59.45
Age	15 – 25	6	16.21
	26- 36	15	40,54
	37-47	16	43.24
Clinical indications Day 1	Feverish	12	32.43
	Afebrile	25	67.56
Clinical indications Day 7	Feverish	0	0
	Afebrile	0	0
Thick film blood smear Day1	+	23	62.16
	++	12	32.43
	+++	2	5.40
Day 7	-	28	75.67
	+	9	24.32
	++	0	0
General disease progression	Good progress without side effects	37	100
	Side effects	0	0

COMMENTS :

- The sex ratio is 61% of males

- The age group between 37 and 47 years included 43% of cases

- 32 % of patients were febrile on the first day and 68% were afebrile.

- At J+10 a complete disappearance of clinical manifestations was observed in all cases.

- At J+1 blood smear was positive in 62 % of patients; at J+7 blood smear was positive in 24% of patients.

2,2.3. Group given capsules of *Artemisia afra* Burundi (AAF)

TABLE 3: Distribution of patients by sex, age, clinical signs, and biological evolution

		Patients (n 25)	%
Gender	male	9	36
	female	16	64
Age	18 – 28	6	24
	29 – 39	15	60
	40-49	4	16
Clinical indications Day 1	Feverish	19	76
	Afebrile	6	24
Clinical indications Day 7	Feverish	0	0
	Afebrile	0	0
Thick film blood smear Day1	+	1	4
	++	5	20
	+++	19	76
Day 7	-	10	40
	+	0	0
	++	15	60
General disease progression	Good progress without side effects	25	100
	Side effects	0	0

Comments :

- The sex ratio is 36% of males

- The age group between 29 and 39 years included 60% of cases

- 76 % of patients were febrile on the first day and 24% were afebrile.

- At J+10 a complete disappearance of clinical manifestations was observed.

- At J+1 blood smear was positive (+++) in 76 % of patients; at J+7 blood smear was positive (++) in 60% of patients.

- No adverse events were observed on the 25 cases followed

3.0 RESULTS PART 2

In the second part of the trial with *Artemisia afra* capsules an average increase of CD4 by 10 % to 20% was noticed and trophozoites disappeared at J+11, with a few exceptions.

In all patients changes in urea, creatinin, ALAT and ASAT were monitored. No significant changes were noticed.

It is difficult to summarize these results in one table. The individual data can be found in the TABLE I in the annex.

DISCUSSION

The results obtained during this preliminary comparative study between two families of Artemisia (*Artemisia annua* and *Artemisia afra*) demonstrate the therapeutic effect of the powdered leaves. It is remarkable that these results were obtained with very low total doses: 15 gr for *Artemisia annua* from Luxembourg, and 7.5 gr for *Artemisia annua* from Burundi and 7.5 gr for *Artemisia afra*. The effects are related to the disappearance of clinical and biological signs; a good evolution is evident in all patients. The efficacy of herbal tea or powder has already been demonstrated in in clinical trials in Africa (Rosine Chougouo et al, 2009. Patrick Engeu et al 2011). Our results confirm the results obtained with the *Artemisia annua* powder by Michel Onimus *in vivo*. These results also corroborate those obtained by other medical teams (Saint- Hillier, Klabes) in Africa working with capsules of *Artemisia annua* and *Artemisia afra* powder in adults and children with excellent results. High concentration in artemisinin does not appear to be a key factor. The results obtained with *Artemisia afra* confirm the antimalarial effects of other Artemisia species containing no artemisinin, as *Artemisia apiacea* in China, *Artemisia ludoviciana* in California and *Artemisia sieberi* in Iran.

The most likely hypothesis for this antimalarial activity of Artemisia plants is their strong hemozoin (beta-hematin) crystallization inhibition (M Akkawi, 2012). This had been recognized in the past as the main mode of action of quinine and chloroquine.

CONCLUSION

The present study demonstrates that the administration of *Artemisia annua* and *Artemisia afra* powder capsules is an effective way to fight malaria in Africa. The therapeutic efficacy is not dependent on high concentrations of artemisinin contained in the plant and highlights the potentiating effects of other components present in the plant. Our results confirm similar reports on the significant antimalarial efficiency of other varieties of Artemisia like *Artemisia afra* without artemisinin and this may contribute to the fight against malaria in Africa.

Our present work, as well as the clinical trials carried out in Maniema in 2015 by Dr Jerome Munya and Michel Idumbo (personal communication) show a complete disappearance of parasites and gametocytes on day 10 and further on. A breakthrough finding which could stop transmission from humans to mosquitoes and fulfill the dream of malaria eradication.

Artemisia afra is growing wild in all countries of Eastern Africa from The Cape to Addis Ababa, from Narobi to Kinshasa. In all these countries it has been widely used and continues to be used against malaria and many other diseases like tuberculosis or bilharzia. It fulfills the requirements of the "WHO Perspectives for Traditional Medicine 2014-2023". It has also shown strong anti-HIV properties (Fr Van der Kooy 2011)

Artemisia afra readily accessible to low income populations could become the flagship in the fight against malaria in Africa.

FUTURE WORK

- Evaluate more precisely the effect of the initial parasite load on the results. In the present work the initial parasite load was significantly higher for AAL and AAF groups than for the AAB group. It has been shown that if the initial parasitic load exceeds 10 000/µl 10x recrudescence can be higher (Ittarat W).

- Monitor the CD4 for different treatments.

- Check if other drugs like aspirin, paracetamol, antiretrovirals, vitamin C and E, iron supplements might explain the exceptional increase in trophozoite carriage at the end of the treatment for a few patients and treatment failure as often observed for ACTs.

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Annex 1.
BILAN BIOLOGIQUE DES PATIENTS SOUS ARTEMISIA AFRA TRIMESTRE 1/2014

PATIENT 1
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	768		920
UREE	27		24
CREATININE	0,9		0,86
ACIDE URIQUE			
GE	10 à 100 trophozoites		1 à 10 trophozoites

PATIENT 2
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1131		1295
UREE	29		25
CREATININE	0,95		0,89
ACIDE URIQUE			
GE	10 à 100 trophozoites		1 à 10 trophozoites

PATIENT 3
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1174		1265
UREE	36		28
CREATININE	1,00		0,82
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 trophozoites

PATIENT 4
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1130		1210
UREE	31		19
CREATININE	0,96		0,90
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 trophozoites

PATIENT 5
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	655		798
UREE	11		15
CREATININE	0,88		0,84
ACIDE URIQUE			
GE	10 à 100 trophozoites		0

PATIENT 6
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	850		987
UREE	27		23
CREATININE	0,83		0,86
ACIDE URIQUE			
GE	10 à 100 trophozoites		100 à 1000 trophozoites

PATIENT 7
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1288		1360

UREE	26		24
CREATININE	0,81		0,9
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATIENT 8
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	894		1020
UREE	25		26
CREATININE	0,8		0,81
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 trophozoites

PATIENT 9
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	788		930
UREE	29		23
CREATININE	0,91		0,88
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATIENT 10
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1251		1430
UREE	15		17
CREATININE	0,7		0,8
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATIENT 11
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1211		1295
UREE	24		25
CREATININE	0,83		0,8
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

|PATIENT 12
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	890		1110
UREE	28		25
CREATININE	0,92		0,87
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATEIENT 13
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1120		1340
UREE	26		21
CREATININE	0,87		0,89
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATIENT 14
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	986		1010
UREE	22		20
CREATININE	0,89		0,86
ACIDE URIQUE			
GE	1 à 10 trophozoites		1 à 10 trophozoites

PATIENT 15
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1050		1175
UREE	31		26
CREATININE	0,79		0,80
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATIENT 16
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1342		1390
UREE	27		21
CREATININE	1,0		0,9
ACIDE URIQUE			
GE	10 à 100 trophozoites		1 à 10 trophozoites

PATIENT 17
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1310		1380
UREE	18		20
CREATININE	0,76		0,7
ACIDE URIQUE			
GE	10 à 100 trophozoites		1 à 10 trophozoites

PATIENT 18
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1248		1300
UREE	21		19
CREATININE	0,81		0,82
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 trophozoites

PATIENT 19
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1292		1360
UREE	17		15
CREATININE	0,75		0,76
ACIDE URIQUE			
GE	1 à 10 trophozoites		0 trophozoites

PATIENT 20
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1120		1214
UREE	21		20
CREATININE	0,8		0,82
ACIDE URIQUE			
GE	10 à 100 trophozoites		1 à 10 trophozoites

BILAN BIOLOGIQUE DES PATIENTS SOUS ARTEMISIA AFRA TRIMESTRE 2/2014

PATIENT 21
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1254		1410
UREE	17		18
CREATININE	0.72		0.73
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 trophozoites

PATIENT 22
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	756		1010
UREE	29		21
CREATININE	0.87		0.80
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 23
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	810		1098
UREE	30		26
CREATININE	0.91		0.87
ACIDE URIQUE			
GE	0 à10 trophozoites		0 trophozoites

PATIENT 24
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1231		1379
UREE	16		16
CREATININE	0.65		0.69
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 25
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1174		1282
UREE	17		16
CREATININE	0.74		0.7
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 26
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	817		1191
UREE	26		20
CREATININE	0.9		0.87
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 27
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	637		796
UREE	14		15
CREATININE	0.96		0.89
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 28
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1015		1930
UREE	19		16
CREATININE	0.96		0.6
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 29
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1015		1230
UREE	13		13
CREATININE	0.57		0.6
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 à 10 trophozoites

PATIENT 30
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	936		1116
UREE	17		15
CREATININE	0.97		0.7
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 31
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1140		1300
UREE	26		18
CREATININE	0.97		0.8
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 32
BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1145		1345
UREE	10		13

CREATININE	1.11		0.80
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 33

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	720		980
UREE	11		11
CREATININE	0.86		0.84
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 34

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1232		1310
UREE	20		20
CREATININE	0.93		0.91
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 à 10 trophozoites

PATIENT 35

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1125		1257
UREE	14		15
CREATININE	0.61		0.6
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATI5ENT 36

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1910		1456
UREE	18		17
CREATININE	0.60		0.64
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 37

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	741		1050
UREE	26		23
CREATININE	0.87		0.85
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 38

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	756		977
UREE	28		25
CREATININE	0.88		0.87
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 39

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1096		1208
UREE	19		20
CREATININE	0.82		0.83
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 à 10 trophozoites

PATIENT 40

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	816		1081
UREE	22		24
CREATININE	0.8		0.72
ACIDE URIQUE			
GE	10 à 100 trophozoites		0 à 10 trophozoites

PATIENT 41

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	719		987
UREE	18		18
CREATININE	0.81		0.8
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 42

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	420		758
UREE	17		16
CREATININE	1.1		0.94
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 43

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	849		1108
UREE	19		16
CREATININE	0.63		0.7
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

PATIENT 44

BILAN BIOLOGIQUE

Examens para cliniques	J1	Intermédiaires	J11
CD4	1151		1265
UREE	11		14
CREATININE	0.6		0.65
ACIDE URIQUE			
GE	0 à 10 trophozoites		0 trophozoites

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