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Clinical Evaluation of the Effectiveness and Safety of Mist Amen Fevermix, a Ghanaian Bi-Herbal Product, Used in the Management of Uncomplicated Malaria

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Abstract
Medicinal plants and products have been used all over the world throughout the history of mankind. Over time in some countries, they have been integrated into the public healthcare system but in the case of Ghana, integration is at the pilot stage. However, questions related to the effectiveness and safety of these medicinal plants and products have been raise and become the bone of contention between orthodox and traditional medicine practitioners. Malaria is a public health problem and continues to be a major cause of morbidity and mortality in most tropical and subtropical countries. The influx of fake medicines and drug counterfeiting have led to malaria parasites becoming resistant to allopathic medicines and have led to an urgent need for new effective antimalarials from medicinal plants. This research was to determine the effectiveness and safety of *Mist Amen Fevermix* which is a decoction of the stem bark of *Morinda lucida* and *Parinari robusta* at the Tafo Government Hospital, Kumasi after Committee on Human Research, Publication and Ethics approval.Clinically established malaria in male and female patients aged, 15-60 years were treated with *Mist Amen Fevermix*, at the specified dose of 45 mls (0.45 g) three times daily for six days. Parasitaemia clearance was 82.35% within the first three days in clients who responded positively to treatment. There was a statistically significant difference between the mean levels of malaria parasite load recorded at the first visit and those recorded at the second visit, t (34) =12.20, p=.000. Similarly, there was statistically significant difference between the malaria parasite load recorded on the second visit and that of the third visit, t (24) = 2.50, p=.022. This shows a significant effectiveness of *Mist Amen Fevermix* in the treatment of malaria. Kidney and liver function tests were within normal range at the end of the study as well as full blood count.The main findings of the study are that *Mist Amen Fevermix* produced by Amen Scientific Herbal Hospital, Kumasi is an effective and safe finished herbal antimalarial product when used as specified by the manufacturer.
Keywords: Malaria; effectiveness; herbal; integrated; antimalarial: parasitaemia.

INTRODUCTION

Malaria is a mosquito-borne disease caused by infection with unicellular parasites belonging to the genus Plasmodium. These parasites are transmitted through the bite of infected female Anopheles mosquitoes. The main symptoms of uncomplicated malaria are fever, chills and headache and if left untreated could lead to severe consequences including death.

Malaria is one of three globally important infectious diseases, including tuberculosis (TB) and HIV/AIDS which cause substantial morbidity, mortality, negative socioeconomic impact, and human suffering (WHO, 2010). The World Health Organization (WHO) estimates 3.3 billion people are at risk of infection worldwide, resulting in about 500 million clinical cases and around one million deaths per year. Malaria is currently endemic in tropical and sub - tropical regions of the world including: Africa, Asia, Latin America, the Middle East and some parts of Europe. However, majority of the malaria related deaths occur in sub - Saharan Africa where it is the leading cause of mortality for children under the age of five years and pregnant women (WHO, 2008). Therefore, immediate diagnosis, appropriate and effective treatment of the disease is deemed urgent in the fight against malaria.

In Ghana, malaria is hyper-endemic and remains a major public health problem, requiring focused interventions including immediate and effective case management and has also been a major cause of poverty and low productivity accounting for about 32.5 percent of all out- Patient Department (OPD) attendances and 48.8 percent of under five years admissions in the country (NMCP/ MOH, 2009). It also resulted in 36.9 percent of hospital admissions in 2009 for all ages with more than 80 percent among children alone in Ghana (MOH, 2009).

As per the WHO estimates, at least 80 percent of the population in most developing countries of the world rely on traditional medicine for their primary health care needs. Considering this fact and also that, modern healthcare system alone could not meet the health needs of the global community; the WHO launched the policy, 'Health for All by 2000' (Alma-Ata Declaration of 1978) urging its member states to promote and integrate traditional medicine into their national health care systems (Ene *et al.,* 2010). The important contribution traditional knowledge and practices have made to orthodox medicine can be attested to by the fact that more than 40 percent of commonly prescribed medicines throughout the world find their origin directly or indirectly from plants or animals (Ene *et al* 2010).

It is known that about 70 percent of Ghanaians depend on herbal medicinal products for their primary health care needs. This is due to the fact that, the herbal products are mostly cheap, easily available and thought to be very effective and safe as compared to allopathic medicines. Many of such products have been used in Ghana for the treatment of malaria. One of such products is *Mist Amen Fevermix,* produced by Amen Scientific Herbal Hospital, which is on the recommended essential herbal medicines list of the Ministry of Health and used throughout the pilot Herbal Medicine Unit in Ghana.

Mist Amen Fevermix is an herbal decoction prepared from: *Morinda lucida* Benth. (Family: Rubiaceae) and *Parinari robusta* Oliv., synonym of *Maranthes robusta* (Oliv.) Prance ex F. White (Family Chrysobalanaceae) *(*www.theplantlist.org).

Morinda lucida is a tropical West Africa rainforest tree also called Brimstone tree. http://plants.jstor.org/specimen/linn-hs345-3). It is an evergreen shrub or small to medium-sized tree up to 18-25 m high. (Abbiw, 1990). The leaves are used to prepare infusions which are used not only for the treatment of malaria but also as a general febrifuge and analgesic. All parts of the plant are used as laxative. A weak decoction of the stem bark is administered for the treatment of severe jaundice often characterized by haemoglobinuria and haematuria (Oliver-Bever, 1986).

Parinari robusta is a small to medium-sized deciduous tree with characteristic habitats of swamp-forest. It occurs in drier types of semi-evergreen rainforest. It grows up to 13 m high and low-branching in coastal areas, or to 35 m or more inland with a cylindrical bole up to 1.70 m girth. (Keay *et al*., 1960; Taylor, 1960). The plant occurs in West Africa, from Côte d'Ivoire to Nigeria. (Aubréville, 1959). Bark decoction and pounded leaves are applied as anodyne. Pregnant women take a decoction of the bark as a tonic (www.prota4u.org) (www.plants.jstor.org).

Although *Mist Amen Fevermix* has been successfully used in the treatment of uncomplicated malaria, there is no available empirical clinical data to support this claim. The aim of the study was therefore to clinically evaluate effectiveness and safety of *Mist Amen Fevermix* in the treatment of uncomplicated malaria in humans.

MATERIALS AND METHODS

Design of study

The study design was based on an open, prospective, non-comparative clinical trial in 50 patients with clinically established malaria, and confirmed by laboratory investigations. Study commenced after ethical approval by the Committee on Human Research, Publication and Ethics in June 2014.

TREATMENT AND DURATION OF STUDY

A decoction of Mist Amen Fevermix is dispensed in a dose of 45mls (0.45g) three times daily after meals for a period of six days.

PATIENTS SELECTION CRITERIA AND MONITORING FOR MALARIA DISEASE

Inclusion criteria

Patients were recruited and managed as out- patients in a normal clinical setting. The selection criterion included the following;

- Gender: Male and females
- Age: between 15 and 60 years
- Health status:
    - Absence of anaemia
    - Absence of severe malnutrition
    - Absence of general signs of severe and complicated malaria
    - Presence of axillary temperature ~37.5 and < 39.5°C at first visit
- Ability to come for the stipulated follow-up visits

Exclusion criteria

- Febrile conditions caused by diseases other than malaria
- Patients on current treatment with orthodox medicines
- Inability to come for the stipulated follow-up visits

- Any disease condition which might compromise the renal, hepatic or any other body system function
- Intake of any medication within 14 days before start of the study
- Pregnant women
- Use of any recreational drugs or a history of drug addiction

MONITORING FOR MALARIA

Patients were reviewed and monitored on following days: 3, 7, 14 and 28. Remission of signs and symptoms or otherwise were noted. Blood films were taken to check for malarial parasites on the review dates as above. Liver and kidney function tests were done on days; 7, 14 and 28.

RECRUITMENT OF PARTICIPANTS

During out-patient departmental (OPD) herbal medicine clinic days, an announcement was made using the Public Address (PA) system of the Hospital to inform patients about the Herbal Medicine Unit and invite clients who want to use the services of the unit. Interested patients were examined and those determined clinically to have malaria were made to undergo laboratory tests to confirm the presence of malaria parasites or otherwise. Mist Amen Fevermix was then dispensed according to standard dosing for six days. Patients were to report for review purposes on day three, seven and twenty-eight after dispensing of the medicines. During the review period, the history was retaken. An assessment was made to establish if there was compliance with their medication, and any side effect was noted. Blood film examination for malaria parasites was done on the 3rd, 7th, 14th and 28th day visits..

DATA ANALYSIS

Data on the effectiveness and safety of Mist Amen Fevermix was statistically analyzed using IBM Statistical Package for the Social Sciences (SPSS), version 19. Exploratory statistics were computed to measure the frequency distribution, central tendencies and dispersions of the data. These were presented in tables and bar charts. The mean amount of liver enzymes and urea and creatinine in both liver and kidney were calculated and statistically tested against the control range. A hypothesis was postulated to determine the safety of the product.

- The null hypothesis was that the mean amount of liver and kidney function parameters tested after every visit was in the range of the control.
- The alternate hypothesis being that there is an increase or decrease in the liver and kidney function parameters tested at every visit.

A paired sample *t*-test of the mean amount of elements over the three various visits was performed to test the difference between the first visit and the second visit and then that of the second and the third. To this, a hypothesis was postulated.

- The null hypothesis was that the mean amount of liver and kidney function parameters tested at various visits was no different from each other.
- The alternate hypothesis being that the amounts of liver and kidney function parameters tested over the visits are not equal.

RESULTS

Age - Sex Distribution

A total number of 50 patients was enrolled in the study, thirty 30 (60%) of the participants were females and twenty, 20 (40%) were males. The modal age group of the study was below twenty-three (23) years represented by twenty-eight percent (28%). The age groups of the participants showed normal distribution; twenty-two percent (22%) of participants was between 23-32 years and 20% each between 33-42 years and 43-52 years respectively, while ten percent (10%) constituted the least age group of 53 years and above. The age distribution of participants is as shown in Figure 1.

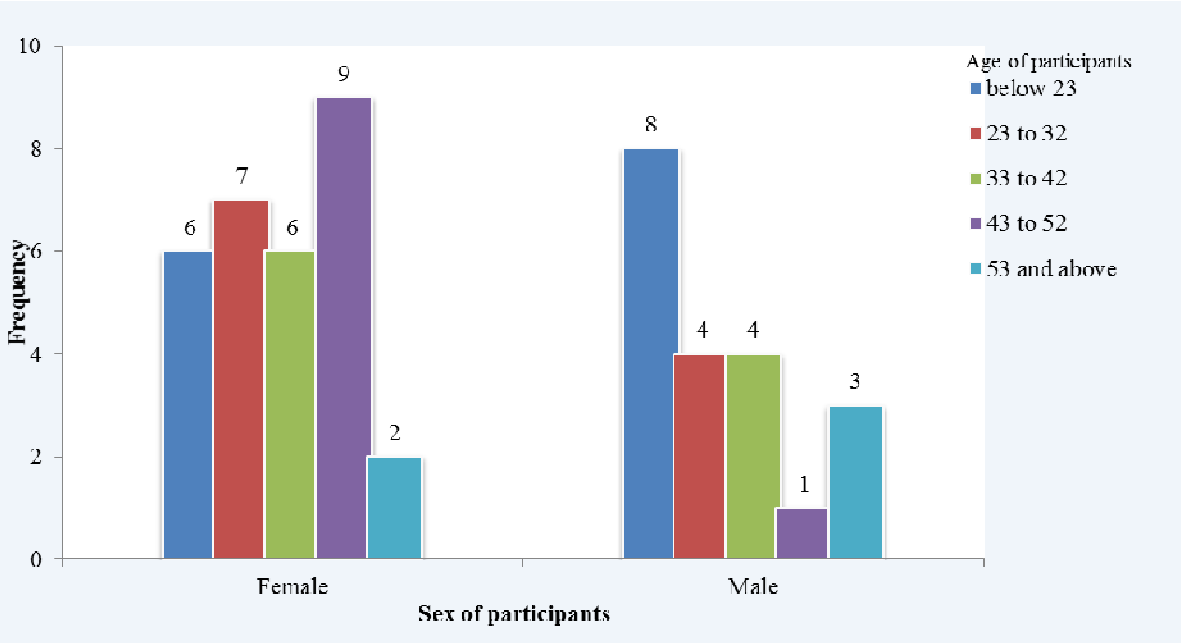

Figure 1. Age-sex Distribution

EFFECTIVENESS OF MIST AMEN FEVERMIX

The results are shown in Figure 2; a paired-sample t-test was performed to test the difference between the results of test for parasite load at first visit against the second visits, the second against third visits and third against fourth visits. The null hypothesis for the pairing of first visit and second visit test is that, the mean levels of malaria parasite load are equal. The alternate hypothesis was stated that the first visits' level of malaria parasite load is not the same as the second visit. Similarly, the null hypothesis for the pairing of the second visit and third visit was stated that there are equal level of malaria parasite loads and the alternate states there is a difference. Finally, the null hypothesis for the pairing of the third and fourth visit states that there is equal level of malaria at the both visit while the alternates state otherwise.

The test indicates a statistically significant difference between the mean levels of malaria parasite load recorded at the first visit and those recorded at the second visit, *t (34) =12.20, p=.000.* Similarly, there was statistically significant difference between the malaria parasite load recorded on the second visit and that of the third visit, *t (24) = 2.50, p=.022*. This shows a significant effectiveness of *Mist Amen Fevermix* used by the patients. The third and final pairing test was not possible as a result of the incalculability of the value of *t* and its correlations.

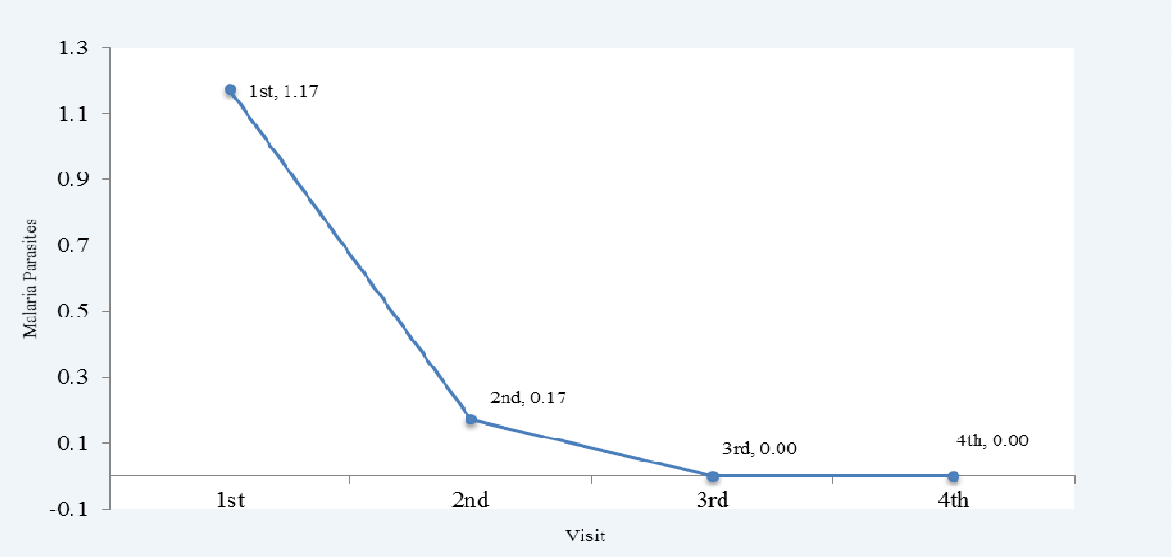

Figure 2.Mean Levels of Malaria Parasites per review.

SAFETY ASSESSMENT OF *MIST AMEN FEVERMIX* ON PATICIPANTS' KIDNEYS

The results of safety on the kidneys and liver showed no effect an indication that the product is relatively safe. Table 1 below shows the effect of *Mist Amen Fevermix* on participants' kidney, while Table 2 shows the effect of *Mist Amen Fevermix* on participants' livers.

Table 1. The effect of *Mist Amen Fevermix* on participants' kidney (n=37)

	Normal Range	1st χ ±s	2nd χ ±s	3rd χ ±s
Potassium (K)	*3.5 – 5.5*	*4.38 ± 0.72*	*4.32 ± 0.7*	*4.24 ± 0.69*
Sodium(Na)	*135 – 155*	*141.21 ± 4.82*	*140.55 ± 4.75*	*141.33 ± 4.67*
Chloride(Cl)	*96 – 110*	*98.94 ± 2.49*	*96.6 ± 13.34*	*99.41 ± 3.28*
Urea	*2.1 – 7.1*	*4.61 ± 1.21*	*6.28 ± 11.91*	*8.6 ± 16.48*
Creatinine	*M = 61.88 – 123.8* *F = 61.88 – 106.1*	*75.07 ± 12.94*	*76.16 ± 14.21*	*76.82 ± 14.11*

SAFETY OF MIST AMEN FEVERMIX ON PATICIPANTS LIVER

Table 2. SAFETY OF MIST AMEN FEVERMIX ON PATICIPANTS' LIVER (n=37)

	Normal Range	1st *χ ±s*	2nd *χ ±s*	3rd *χ ±s*
Protein	*66 – 87*	*73.67 ± 6.02*	*73.79 ± 6.05*	*72.74 ± 6.44*
Albumin	*18 – 51*	*30.36 ± 11.46*	*29.35 ± 9.7*	*28.44 ± 10.26*
Globulin	*25 – 40*	*30.82 ± 3.34*	*31.81 ± 5.05*	*31.06 ± 2.93*
ALT	*0 – 40*	*24.71 ± 9.7*	*24.3 ± 9.62*	*24.34 ± 10.01*
GGT	*7 – 32*	*17.6 ± 10.67*	*16.93 ± 6.63*	*16.88 ± 7.12*
AST	*0 – 31*	*18.82 ± 6.66*	*22.74 ± 23.24*	*19.48 ± 5.62*
ALP	*0 – 240*	*155.48 ± 57.1*	*155.23 ± 58.09*	*169.94 ± 46.76*
Total bilirubin	*0 – 26*	*16.11 ± 8.01*	*15.61 ± 7.12*	*16.20 ± 6.30*
Direct bilirubin	*0 – 8.67*	*5.11 ± 2.72*	*5.26 ± 2.6*	*4.63 ± 1.77*
Indirect bilirubin	*0 – 17.33*	*11.26 ± 3.19*	*11.43 ± 3.27*	*11.70 ± 3.58*

The vital signs parameters inclusive of body weight and blood pressure did not show significant difference after treatment. However, body temperature showed a significant difference after treatment P<0.05 (Table 3).

Table 3: vital signs parameters of patients before and at end of treatment (n=37)

Parameter	Before Treatment	After Treatment	Level of Significance
Body Weight	58 ± 9.68	55.71 ± 8.79	.401
Temperature	37.87 ± 0.51	36.56 ± 0.93	.000
Blood Pressure(systolic)	111.24 ± 14.58	113.32 ± 14.49	.549
Blood Pressure(diastolic)	71.53 ± 8.55	72.82 ± 7.89	.536

Among the haematological parameters, the haemoglobin, RBC, neutrophils, lymphocytes, monocytes and eosinphils counts remained more or less constant. The WBC counts showed improvement by end of treatment with statistical significant at P< 0.05 (Table 4)

Table 4: Haematological Findings for Assessment of Safety (n=37)

parameter	At screening	At end of treatment	Level of significance
Hemoglobin (g/dl)	13.53 ± 1.745	13.09 ± 1.5	*.311*
RBC ($x10^9$)/L	5.32 ± 0.73	4.70 ± 1.09	*.007*
WBC ($x10^9$)L	11.68 ± 2.74	8.18 ± 3.4	*.000*
Neutrophils (40-70)%	61.03 ± 8.7	58.18± 8.54	*.121*
Lymphocytes (20-50)%	36.3824 ± 8.79	36.4412 ± 8.68	.981
Monocytes (2-10)%	6.2647 ± 1.5	6.0588 ± 1.35	.566
Eosinophils (1-6)%	3.2353 ± 1.39	2.6176 ± 1.3	.079

ADVERSE EFFECT OF MIST AMEN FEVERMIX

A checklist for possible side-effects indicated there was no report of any adverse effects or side effect.

DISCUSSION

This study sought to validate the claim for the clinical effectiveness and safety of *Mist Amen Fevermix* in the management of uncomplicated malaria in human.

This study was undertaken as a prospective one with open-ended questionnaire in which an attempt was made to treat malaria patients with *Mist Amen Fevermix* a bi-herbal antimalarial product so as to assess the effectiveness and safety. The diagnosis of malaria was established by using microscopic examination of blood, utilizing blood films on the day of visit. Different parameters, that is, age, sex, duration of signs and symptoms, and other clinical signs and symptoms base line was studied and compared during the 3rd, 7th, 14th and 28th visits at base line and end of the dispensing of *Mist Amen Fevermix*. Safety assessment was also done

The clearance of the malaria parasite may be due to the presence of *Morinda lucida* which is known to possess antimalarial properties. (Mshana *et al*, 2000). The result corresponds with the study by Obih, *et al* (1985) 'Investigation of the stem bark extracts of *Morinda lucida*' for antimalarial actions that had a promising result with 96.4% clearance of parasitaemia.

The phytochemical analysis of *Mist Amen Fevermix* revealed the presence of saponins, tannins, alkaloids, the active principle responsible for the antimalarial activity of the formulation is not known. These findings are very significant as *Mist Amen Fevermix*, like many antimalarials could serve as a potential substitute.

The vital signs parameters inclusive of body weight and blood pressure did not show significant difference after treatment. However, body temperature showed a significant difference after treatment $P<0.05$ (Table 3).

Haematological abnormalities which are the hall mark of malaria, the haemoglobin, RBC, neutrophils, lymphocytes, monocytes and eosinphils counts remained more or less constant. However, WBC counts showed improvement by end of treatment with statistical significant at $P< 0.05$ (Table 4).

This result proves contrary to the fact that, renal failure and hepatic diseases presented at the hospitals as being caused by herbal products usage as been held by physicians. It can be inferred from the study that not all herbal products have toxic effects on the body's physiology especially on the kidneys and liver.

CONCLUSION

The outcome of the clinical studies indicated that *Mist Amen Fevermix*, a FDA registered antimalaria product proved to be an effective herbal treatment for the management of uncomplicated malaria in human. Its ability to clear the *Plasmodium* parasites makes it a potential useful antimalarial agent with no observed adverse effects.

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