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Comparative clinical study of Mist Amen Fevermix and Edhec Malacure: two polyherbal products used for the treatment of uncomplicated malaria in Ghana against Artemether/Lumefantrine

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Abstract

The use of herbal products for the treatment of malaria, has increased globally. However, inadequate scientific studies about the safety and effectiveness of such herbal products have been raised. Also, the reduced sensitivity of the malaria parasites to artemisinin-based combination therapies is of concern. There is therefore the need for new antimalarial medications including those from alternative sources such as herbal medicinal products. In this study, a prospective, comparative parallel group randomized, clinical study was done to assess the safety and effectiveness of *Mist Amen Fevermix* and *Mist Edhec Malacure* with Artemether/Lumefantrine as control at the Tafo Government Hospital, Kumasi between July and November 2019, after Committee on Human Research, Publication and Ethics approval (CHRPE/AP/424/19). The study was conducted in accordance with Good Clinical and Laboratory Practice (GCLP) and registered with the Pan African Clinical Trials Registry with trial number PACTR202109664146698. Participant completed an informed consent form. Randomization was based on a single sequence to allocate participants to a group. SPSS version 19. One-way ANOVA test and exploratory statistics was used for data analysis. Total sample size was 150 participants with 50 on each arm of the group. Male and female patients aged 15–45 years and meet inclusion criteria with clinically established malaria were treated with *Mist Amen Fevermix* and *Mist Edhec Malacure*, at the specified doses of 45 mls (0.1063 g) and 30 mls (0.0521 g) three times daily after meals for three days. Artemether/Lumefantrine was administered at a dose of 80/480 mg/kg twice daily after meals for three days. Baseline data was taken on day 0. Patients were then followed up on Day 3, 7 and 28 to establish treatment outcomes and any side effect using a checklist for signs and symptoms and Karnofsky's scale to assess the quality of life. *Mist Amen Fevermix* was effective with a cure rate of 95.89%. *Mist Edhec Malacure* was also effective with a cure rate of 91.87%. The cure rate of Artemether/Lumefantrine was 97.25%. Kidney and liver panels were within normal reference range at the end of the 28-day study. This study supports the use of *Mist Amen Fevermix* and *Mist*

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Edhec Malacure, two multi-component products as safe and effective for the treatment of uncomplicated malaria. Both products achieved a comparable clinical treatment outcome with Artemether/Lumefantrine.

Keywords Safety, Effectiveness, Antimalarial, Treatment, Cure rate, Multi-component

Introduction

Malaria is a life-threatening mosquito-borne infectious ailment that causes hundreds of thousands of deaths every year. It is one of the globally most important infectious ailments which leads to substantial morbidity, mortality with negative socioeconomic influence, and human suffering every year [1]. Globally, the World Health Organization (WHO) states that approximately 228 million cases of malaria was estimated to have occurred in the year 2018 leading to about 435,000 deaths, the majority, 93 per cent, occurred in Africa and over 405,000 deaths have been recorded in children under age 5 years, which account for 67 per cent of all deaths [1].

Treatment of malaria and strategies aimed at terminating the infection, preventing the spread of infection, treatment of clinical manifestation, eradication of the parasites from the liver and prevention of recurrence in the future, has been investigated for hundreds of years and continues up to the present day. However, *Plasmodium* parasites have become resistant to the previously known and therapeutically potent antimalarial agent and many of the existing antimalarial medicines including amodiaquine and sulphadoxine-pyrimethamine. The current gold standard treatment is the use of the fixed-dose artemisinin combination therapy consisting of derivatives of artemisinin and a longer-acting antimalarial agent. However, there are emerging signs of resistance and treatment failure to artemisinins, with patients taking longer period to clear their fever and parasite [1].

Despite the various claims for the benefits of herbal medicinal plants and products in the treatment of various disease conditions including malaria, concerns have been raised regarding their safety and efficacy [2]. Safety related to less side and adverse effects linked with the use of the herbal medicinal products is essential to minimize toxicity. Herbal therapies should be effective for the disease or condition indicated. There is therefore the need to clinically validate such herbal products. There is little evidence to support the claim of safety and efficacy of herbal medicinal products. Such studies are essential today to ensure that polyherbal products are well researched into. But there is inadequate significant preclinical and clinical research when it comes to the scientific safety of herbal products. Hence, it is important to gather whatever scientific data that is available to substantiate the use of herbal medicines to treat different pathologies. Also, the effectiveness of most of the herbal products are unproven by standard scientific methods [3]. Currently, there is a need to undertake clinical studies of herbal medicines. This is because clinical studies can provide valuable data on the effectiveness and potential risks of herbal medicines. This can help to establish their role in healthcare and to ensure that the trial drug is tested for batch-to-batch consistency and quality [26]. Safety and efficacy depend on the indications of the therapy. A therapy has no clinical value if it is safe but lacks efficacy or if it is active on a relevant therapeutic target but its use is unsafe [4]. There has been a successful report of a Phase II pilot trial to evaluate the safety and efficacy of CoBaT-Y017 against uncomplicated *falciparum* malaria versus Artemether-Lumefantrine in Benin Subjects. Physical and laboratory examinations did not show any significant changes in vital signs, biochemical, and haematological parameters [5].

Mist Amen Fevermix is a finished herbal product, a decoction, prepared from the stem bark of *Morinda lucida* Benth (Family: Rubiaceae) and the stem bark of *Parinari robusta* Oliv. (Family: Chrysobalanaceae) [6]. The product has been registered with the FDA, Ghana, since the year 2008 and is on the 'Recommended Essential Herbal Medicines List (EHML)' for primary healthcare services of the Ministry of Health and used in the Herbal Medicine Units of Ghana Health Service [7]. Currently, there is availability of preliminary safety and effectiveness data on *Mist Amen Fevermix* but no comparative study with standard treatment for malaria [6]. *Edhec Malacure* is also, a finished herbal product and a decoction prepared from the stem bark of *Morinda lucida* Benth (Family: Rubiaceae), leaves of *Cleistopholis patens* Benth. Engl. and Diels (Family: Annonaceae), and stem bark of *Mangifera indica* Linn. (Family: Anacardiaceae). Currently there is inadequate data on *Edhec Malacure*. It is therefore important to undertake a comparative clinical study and to validate the safety and effectiveness of the two multicomponent herbal products with Artemether/Lumefantrine used in the treatment of uncomplicated malaria.

Materials and methods

Study site

The study was conducted at the Herbal Medicine Unit of the Tafo Government Hospital, Kumasi, between July and November 2019. The Hospital serves about 261,584 people in Manhyia North sub-metro which constitutes 16 per cent of the population of the Kumasi Metropolis [8]. The Hospital was established in 1976, as the Tafo Urban Health Centre and upgraded to hospital status in the year 2000 [9].

Study design

The research design employed is a prospective, comparative parallel group randomized clinical study and data was collected using a structured questionnaire. All data were collected and written in a case record form (CRF) of the Herbal Unit of the Tafo Government Hospital between July to November 2019.

Patients selection criteria and monitoring for Malaria

Patients were recruited and managed as outpatients in a normal clinical setting, and they had to satisfy both inclusion and exclusion criteria to be selected. The selection criteria included the following:

Inclusion criteria

- Gender: Male and female.
- Age: 18 to 45 years.
- Disease state: Uncomplicated malaria.
  - Absence of severe anaemia.
  - Presence of axillary temperature ~ 37.5 and < 39.5 °C at visit.
  - Headache.
  - Muscle pains.
  - Nausea and vomitting.
- Informed consent of participants.
- Patient able and willing to return for follow up [6].

Exclusion criteria

- Participants with anaemia (haemoglobin < 8 g/dl).
- Confusion.
- Coma.
- Focal neurologic signs.
- Respiratory difficulties.
- Hypogylcaemia.
- Hyperparasitaemia (> 250,000 ml or > 5%).
- Haemoglobinuria (dark urine).
- Patients on treatment with orthodox antimalarial.
- Any disease condition such as type 1 and type 2 diabetes, heart disease and obesity, hepatitis viruses etc.,which might compromise the renal, hepatic or any other body system.
- Intake of any medication such as antimalarial, antidiabetics, antihyperlipidemics within 14 days before the start of the study.
- Presence of clinically significant abnormal laboratory results (LTF, RFT) during screening.
- Pregnant and lactating mothers.
- Use of any recreational drugs or a history of drug addiction.
- Presence of any chronic and communicable disease condition [10].

Recruitment of participants

During out-patient department's (OPD) herbal medicine clinic hours, an announcement was made on the public address (PA) system of the Hospital to inform patients about the Herbal Medicine Unit and invited clients who were willing to use the services of the unit. The participants who volunteered and presented with malaria signs and symptoms were informed about the study. They were examined by a physician specialist and made to undergo laboratory tests to confirm the presence of malaria parasites or otherwise. Those with uncomplicated malaria were made to do the following laboratory investigations; renal and hepatic panel tests, and full blood count (FBC).

A total of 150 participants were recruited with 50 in each arm of the test products and 50 in the control group of study. The participants were briefed and enrolled with their consent. The participants were randomly selected [6].

Withdrawal from study

The withdrawal criteria for participants involved in the study were recorded as persons who were unable to comply with the protocol and those who developed any reaction to the test samples such as skin rashes, diarrhoea, dizziness and tachycardia were withdrawn from the study and referred to the OPD to be attended to.

Sample size calculation

The total sample size calculated was 150. Since there was 3 arms of the study, the population size of 50 participants (males and females) on each arm of the study was used. This was based on total attendance for 2017 and 2018. The sample size was determined according to Pocock's formula for the sample size for a dichotomous or continuous response [11].

$$n = \frac{[P1\ (1-P1) + P2\,(1-P2\,)]}{(P1-P2)^2} \times\ \ (Z\alpha\ /2 + Z\beta\ )^2$$

Where:

n required sample size.

$\boldsymbol{P_1}$ estimated proportion of study outcome in the exposed group.

$\boldsymbol{P_2}$ estimated proportion of study outcome in the unexposed group.

α is the level of statistical significance.

$\mathbf{Z_{\alpha/2}}$ represents the desired level of statistical significance (typically 1.96 for 95% for α = 0.05).

Z_β represents the desired power (typically 0.84 for 80% power).

n for each group *2=total sample (i.e., for the two groups).

Ethical consideration

Recruitment of participants was done after approval for the study was obtained from the Committee for Human Research, Publications and Ethics (CHRPE), Kwame Nkrumah University of Science and Technology, School of Medical Sciences and Komfo Anokye Teaching Hospital (CHRPE/AP/424/19). The study was conducted in accordance with the protocol and Good Clinical and Laboratory Practice (GCLP) to ensure the protection of all aspects of the ethical rights and welfare of study participants [12]. An emergency team headed by a medical officer with a public health background was constituted as required for ethical clearance during the study period. This was to ensure that participants who may experience any adverse reactions would be attended to. The study has been registered with the Pan African Clinical Trials Registry with trial number PACTR202109664146698.

Informed consent forms

Participants were asked to complete an informed consent form. The details of the clinical study were explained to participants in the local dialect or the language of choice by the principal investigator before forms were signed or thumb printed.

Artemether/Lumefantrine, *Mist Amen Fevermix and Edhec Malacure* Administration

Mist Amen Fevermix and *Edhec Malacure* were dispensed according to recommended dosing for seven days. Each participant was given three and two bottles each of the product, making a total of one hundred and fifty (150) bottles for participants on *Mist Amen Fevermix* and (100) bottles for participants on *Edhec Malacure*. Also, tablet Artemether/Lumefantrine (80/480 mg) was dispensed according to recommended dosing for three days. Each participant was given one pack containing six tablets of the product, making a total of fifty (50) packs.

Dosing

Mist Amen Fevermix was dispensed at the recommended dose of 45 mL (0.1063 g) thrice daily after meals and *Edhec Malacure* at 30 mL (0.0521 g) thrice daily after meals for three days. Artemether/Lumefantrine was dispensed at the recommended dose of (80/480 mg) twice daily after meals for three days.

Monitoring participants for Malaria

Baseline data was taken on day 0. Patients were then monitored and reviewed on days; 3, 7, and 28. During the review period, the history was retaken and assessment was made to establish treatment outcomes and any side effect noted. Examination of blood films for malaria parasites was also done at the review.

On the days 3 7 and 28 visits, clinical evaluation of the patients, remission of signs and symptoms; using

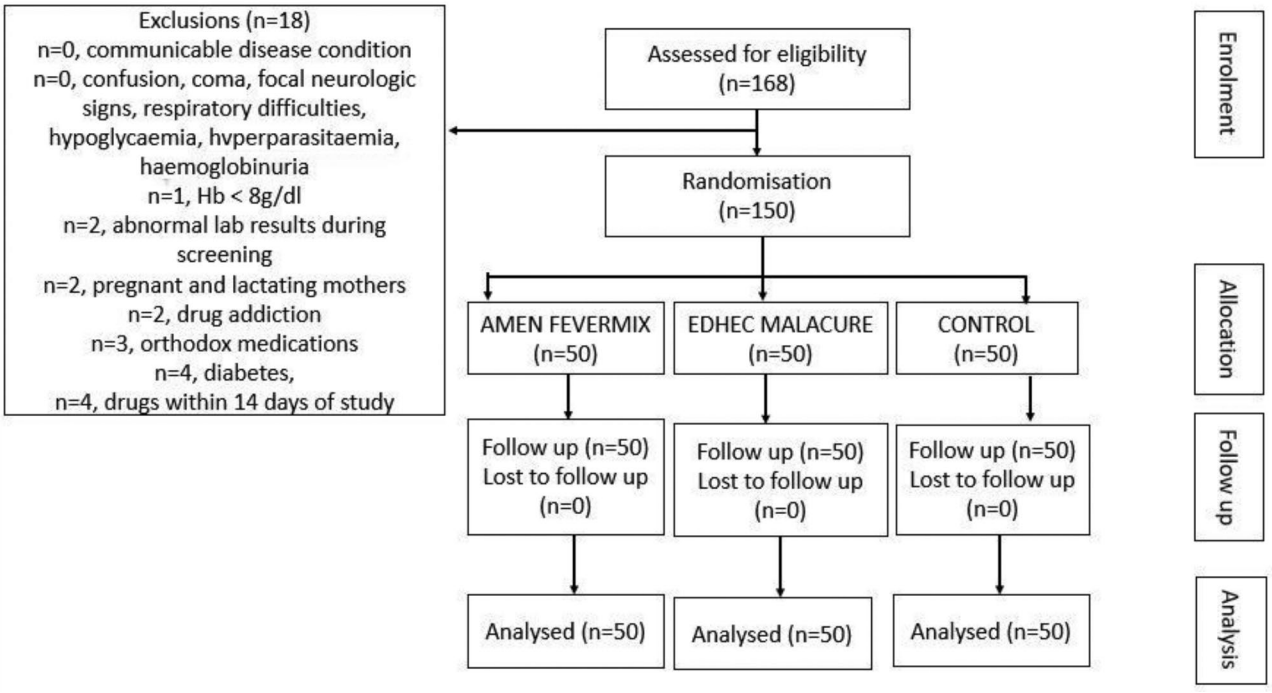

Fig. 1 Schematic representation of clinical study

a checklist for signs and symptoms or otherwise were noted: full blood count to check for malarial parasites, liver and kidney panel tests were conducted and any side effects recorded.

Data collection

Demographic data (age, gender, marital status, and education) of participants were captured and entered the moment they were enrolled in the study. Codes were given to participants to ensure their identity was anonymous. Adverse reaction, recurrence of signs and symptoms, and quality of life assessment using Karnofsky's scale were also recorded accordingly.

Clinical assessment of the effectiveness of Mist amen Fevermix and Edhec Malacure

The efficacy of *Mist Amen Fevermix* and *Edhec Malacure* were assessed based on the clinical outcomes after the duration of treatment (laboratory outcome). Treatment was measured by the clearance of parasite at the end of the study.

Clinical assessment of the safety of Mist amen Fevermix and Edhec Malacure

The reagents (Tridem Eng., Italy) for the tests (LFT, KFT, and FBC) were all purchased from Tridem Chemicals, Kumasi, Ghana.

The following vital signs, parameters (Blood pressure, temperature, body weight) of all participants enrolled in the study were taken on days (0, 7 and 28). On day 0, baseline data was taken. Haematological tests were done by using Abacus 5 Differential Haematology Analyzer (Diatron MI Zrt, Hungary) and the hepatic function and renal function tests were done by using Faith Mindray BS-230 Auto Clinical Chemistry Analyzer (BS-120/BS-200/BS-240, China).

Hepatic and renal panel test and FBC baseline parameters were compared at the end of the study. This was done in relation to the reference range and, any significant change in a parameter, whether below or above the accepted reference range was considered to have compromised the integrity of the said parameter.

Table 1 Reduction in parasite counts after administration of all test samples

Comparison	Drug	Mean	Std. Deviation	Min.	Max.
First	Control (AL)	14268.68	18167.06	-250	53,320
	MEM	3069.81	4233.36	120	21,374
	MAF	2072.38	2212.71	320	9374
Second	Control	392.20	413.37	0	1080
	MEM	249.71	590.53	-434	2090
	MAF	85.14	151.23	0	370
Third	Control	0	0	0	0
	MEM	0	0	0	0
	MAF	0	0	0	0

Key: MAF-Mist Amen Fevermix, **MEM**-Edhec Malacure

Study outcomes

Primary outcome of the study is total clearance of parasite at the end of the study. Secondary outcome of the study is safety of test drugs on kidney and liver panels, FBC and effect of test samples on health indices.

Data analysis

Data on the safety and effectiveness studies of Mist Amen Fevermix and Edhec Malacure were statistically analysed using IBM Statistical Package for the Social Sciences (SPSS), version 19. One-way ANOVA test and exploratory statistics were computed to measure the frequency distribution, central tendencies and dispersions of the data. The mean variables in both liver and kidney panel were calculated and statistically tested against the control range; a hypothesis was postulated. Paired sample t-tests of the mean variables over the three subsequent visits was performed to test the difference between the first visit and the second visit and then that of the second and the third.

Results

Safety and effectiveness assessment

Age and gender distribution

A total of one hundred and fifty (150) participants took part in the study. Most of the patients (62.2%) were aged between 18 and 33 years with the average age being 31.1 (SD=8.23) years. Cumulatively the majority of respondents belonged to the age bracket of 18–33 years. This constitutes a very youthful age. There was three arms of the study. All the arms of the study had an equal number of participants taking part in the study. Out of the total sample population of 150 patients, 90 (60%) are female, whereas 60 (40%) were males. There were three female respondents to every two male respondents taking part in the study. The disparity between male and female proportions was a recurring trend in all the arms of the study.

Assessment of the comparative effectiveness of test samples

The initial parasite counts before administration of the study samples was [14268.68, SD=18167.06] for the control, [3069.81, SD=4233.36] for MEM and [2072.38, SD=2212.71] for MAF. As compared to the test samples after the administration of the medications after the second visit, there was marked reduction in the parasite counts to [392.20, SD=413.37] for the control group, [249.71, SD=590.53] for MEM and [85.14, SD=151.23] for the MAF group. However, on the third visit, there was total clearance of all parasites for the test samples and the control Table 1.

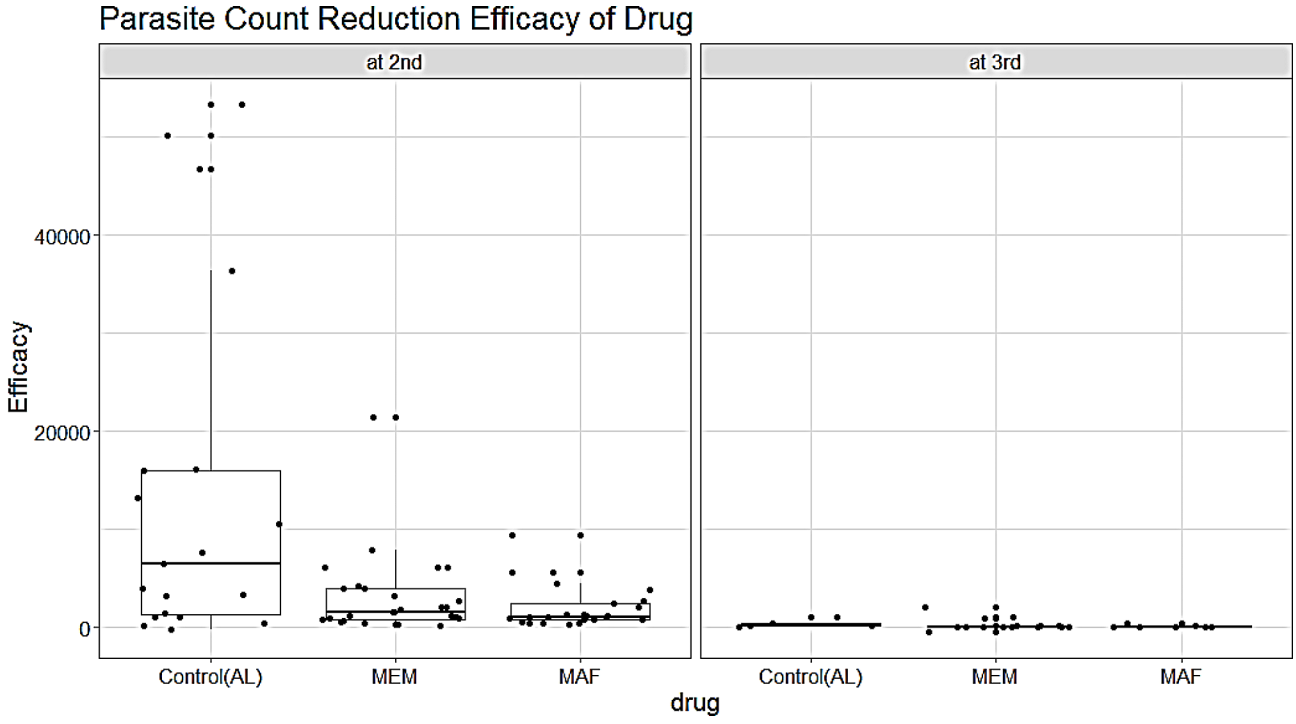

Fig. 2 Reduction of parasite count due to effectiveness of test samples

Table 2 % suppression of parasites after administration of test samples (effectiveness assessment)

Sample	Cure Rate (% suppression)
AL	97.25
MAF	95.89
MEM	91.87

Keys: AL: Artemether/Lumefantrine; MAF: *Mist Amen Fevermix; MEM: Edhec Malcure*

The outcome of a one-way ANOVA test, comparing the *Control (AL), Edhec Malacure* and *Mist Amen Fevermix* showed significant differences in parasite count (number of resolved parasites) of the three study samples at second visits [$F(2, 67) = 9.75$, $p < .001$] (Fig. 2). No difference in effectiveness was shown for the three study samples at the third visit [$F\ (2, 26) = 0.58$, $p = .568$]. Post-hoc analysis for reduced parasite count at second visit, using Dunnett's *t* test (a 2-sided *t*-test), revealed higher effectiveness of the Control drug (AL) when compared to *Edhec Malacure* ($p = .001$), and to *Mist Amen Fevermix* ($p < .001$). The control drug artemether/lumefantrine (*AL*) was most effective in reducing the parasite counts as the mean reduced parasite count with a cure rate of 97.25% at the end of the study. The cure rate in terms of effectiveness of *Mist Amen Fevermix* was 95.89%. Also, the cure rate of *Mist Edhec Malcure* was 91.87% (Table 2). Results of the post-hoc analysis of the test drugs (*Edhec Malacure* and *Mist Amen Fevermix*) to control drug is as shown in the ANOVA effectiveness outcome Fig. 2.

Table 3 Effect of *Mist amen Fevermix* on kidney function

Parameter	Range	0 Day (Baseline)	Day 7	Day 28	-*p*-value
		χ±s	χ±s	χ±s	
Potassium (K)	3.5–5.5	4.17 ± 0.51	4.18 ± 0.5	4.15 ± 0.45	0.913
Sodium (Na)	135–155	140.14 ± 2.82	140.21 ± 2.65	139.01 ± 2.05	0.909
Chloride (Cl)	96–110	100.18 ± 2.92	100.27 ± 2.67	98.35 ± 1.09	0.805
Urea	2.1–7.1	4.67 ± 1.42	4.74 ± 1.28	4.55 ± 2.22	0.817
Creatinine	M = 61.88– 123.8 F = 61.88–106.1	87.66 ± 15.59	87.32 ± 16.96	88.41 ± 15.41	0.915
eGFR	> 60mL/min/1.73m^2	95.47 ± 2.92	95.37 ± 2.65	95.09 ± 2.41	0.888

Results are Mean ± S.E.M

Table 4 Effect of *Edhec Malacure* on kidney

Parameter	Range	0 Day (Baseline)	Day 7	Day 28	-*p*-value
		χ±s	χ±s	χ±s	
Potassium (K)	3.5–5.5	4.14 ± 0.54	4.18 ± 0.52	4.05 ± 0.24	0.723
Sodium (Na)	135–155	139.64 ± 2.53	136.9 ± 15.26	134.09 ± 1.21	0.234
Chloride (Cl)	96–110	99.81 ± 0.73	100.2 ± 2.45	98.09 ± 2.17	0.314
Urea	2.1–7.1	4.87 ± 1.39	6.85 ± 10.08	4.96 ± 1.31	0.194
Creatinine	M = 61.88–123.8 F = 61.88–106.1	96.95 ± 17.5	95.41 ± 15.42	98.33 ± 12.98	0.546
eGFR	> 60mL/min/1.73m^2	95.53 ± 2.42	95.27 ± 2.71	94.32 ± 2.97	0.607

Results are Mean ± S.E.M.

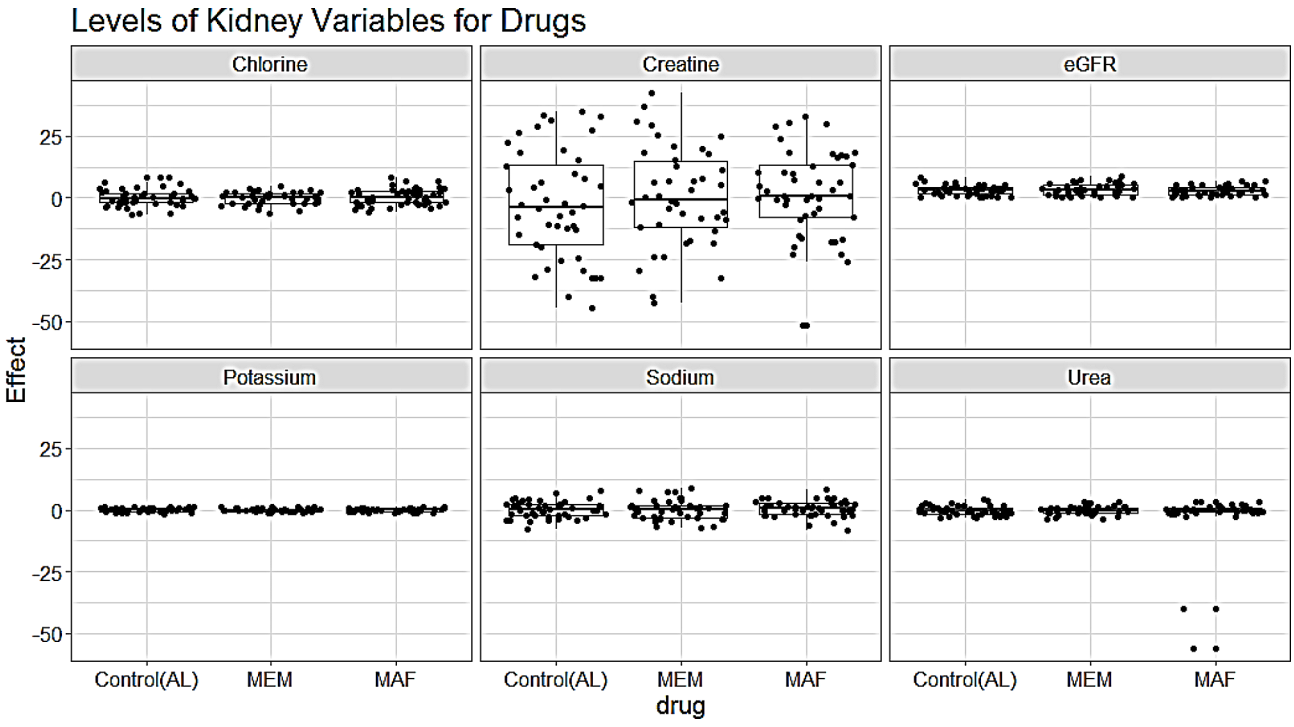

Fig. 3 Levels of kidney variables for all the drugs

Assessment of the safety of test samples Mist *Amen Fevermix* and *Mist Edhec Malacure*

Assessment of the safety of Mist amen Fevermix on renal panel

The difference in the levels of Potassium was [$t(24) = -0.110$, $p = .913$]; Sodium [$t(24) = -0.116$, $p = .909$]; Chlorine [$t(24) = -0.249$, $p = .805$]; Urea [$t(24) = -0.232$, $p = .817$]; Creatinine [$t(24) = 0.108$, $p = .915$]; and eGFR levels[$t(41) = 0.142$, $p = .888$]. This was before and after the administration of the *Mist Amen Fevermix* Table 3.

Assessment of the Safety of *Edhec Malacure* on renal panel

The levels of the differences recorded between Potassium was [$t(45) = -0.357$, $p = .723$]; Sodium [$t(45) = 1.207$, $p = .234$]; Chlorine [$t(45) = 1.019$, $p = .314$]; Urea [$t(45) = -1.319$, $p = .194$]; Creatinine [$t(45) = 0.609$, $p = .546$] and eGFR [$t(45) = 0.518$, $p = .607$]. This was before and after the administration of *Edhec Malacure*. There was no significant difference Table 4.

Comparative assessment of the safety of artemether/lumefantrine on renal panel

The control drug (*AL), Mist Amen Fevermix* and *Edhec Malacure* on patient's kidney, showed no significant differences in the levels of Potassium [$F(2, 130) = 0.124$, $p = .884$], Sodium [$F(2, 130) = 1.195$, $p = .306$], Chlorine [$F(2, 130) = 0.98$, $p = .378$], Urea [$F(2, 130) = 1.361$, $p = .26$]; Creatinine [$F(2, 130) = 0.648$, $p = .525$] and eGFR [$F(2, 130) = 0.834$, $p = .437$] after first visits. Post hoc analysis was not needed as there was no significant differences warranting the test. Results of comparative analysis of drugs on the test variables of kidney is as shown in Fig. 3.

Table 5 Safety of *Mist amen Fevermix* on participants' liver

Parameter	Normal range	Day 0 Baseline	Day 7	Day 28
		χ±s	χ±s	χ±s
Albumin	18–51	34±10.25	34±10.47	34±8.99
ALP	0–240	120±68.09	132±69.02	130±64.54
ALT	0–40	22±12.03	23±10.28	20±12.65
AST	0–31	17±8.94	14±9.31	17±8.56
Direct Bilirubin	0–8.67	5±2.65	5±2.38*	5±2.66
GGT	7–32	20±7.41	21±7.19	20±7.4
Globulin	25–40	33±4.83	33±4.12	32±4.83*
Indirect Bilirubin	0–17.33	10±4.58	9±5.49	9±5.89
Protein	66–87	10±4.58	9±5.49	9±5.89
Total Bilirubin	0–26	12±8.01	14±6.84	11±7.71

* Significantly different from previous value *(p < .05)*. Results are Mean±S.E.M

Table 6 Safety of *Edhec Malacure* on participants' liver

Parameter	Normal range	Day 0	Day 7	Day 28
		χ±s	χ±s	χ±s
Albumin	18–51	34±9.37	33±9.8	37±9.81
ALP	0–240	104±65.44	135±69.85	108±63.64
ALT	0–40	20±12.34	22±11.26	21±12.65
AST	0–31	18±9.19	15±9.75	17±8.6
Direct Bilirubin	0–8.67	4±2.69	5±2.47	4±2.78
GGT	7–32	20±7.92	21±6.68	18±7.26
Globulin	25–40	34±4.34	79±5.83	77±6.02
Indirect Bilirubin	0–17.33	8±4.32	9±5.16	8±5.42
Protein	66–87	74±3.91	74±4.22	74±3.94
Total Bilirubin	0–26	12±7.67	14±8.41	14±8.38

Results are Mean±S.E.M

Table 7 Effect of *Mist amen Fevermix* on Health indicators

Parameter	Day 0	Day 7	Day 28	*p*-value
	χ±s	χ±s	χ±s	
Body weight	53.19±9.91	52.55±12.72	52.25±10.05	0.726
Systolic	118.33±10.1	118.9±11.49	119.21±9.07	0.766
Diastolic	79.43±8.33	77.6±10.8	78.53±9.43	0.224
Body Temperature	38.79±0.55	37.1±0.48	37.01±0.01	0.000

Results are Mean±S.E.M

Assessment of the safety of *Mist Amen Fevermix* on liver function

The test of the three visits for *Mist Amen Fevermix* revealed that statistically, there was no significant differences in levels of Albumin, ALP, ALT, AST, GGT, Indirect Bilirubin, Protein and total Bilirubin. However, Globulin [t (41) = -39.12, $p<.001$] and Direct Bilirubin [t (41) = -2.75, $p<.01$] were shown to have been reduced after use of *Mist Amen Fevermix* on the second and third tests respectively. The result of this analysis is as shown below in Table 5.

Table 8 Effect of *Edhec Malacure* on health indicators

Parameter	Day 0	Day 7	Day 28	*P*-value
	χ±s	χ±s	χ±s	
Bodyweight	56.11±8.89	56.65±10.58	56.59±8.55	0.531
Systolic	119.67±10.13	116.43±8.77	117.59±9.22	0.041
Diastolic	79.04±8.77	76.09±8.82	80.02±12.19	0.030
Body Temperature	38.95±0.66	36.95±0.62		0.000

Results are Mean±S.E.M

Assessment of the safety of *Edhec Malacure* on liver function

The test of the three visits for the effect of *Edhec Malacure* on patient's liver, showed significant differences between the levels of Albumin, ALP, ALT, AST, Direct Bilirubin, GGT, Globulin, Indirect Bilirubin, Protein, Total Bilirubin on the second visits Table 6.

Assessment of health indices after the use of *Mist Amen Fevermix*

The assessment of the health indices revealed statistically, no significant differences between levels of body weight [t (41)=0.352, $p=.726$]; systolic [t (41)=−0.300, $p=.766$]; and diastolic [t (41)=1.234, $p=.224$] blood pressure before and after the administration of *Mist Amen Fevermix*. However, body temperature [t (41)=2.50, $p<.001$] was shown a statistically significant difference after the utilization of *Mist Amen Fevermix* Table 7.

Assessment of health indices after the use of *Edhec Malacure*

The assessment of the health indices revealed statistically, no significant differences between levels of body weight [$t(41)=-0.63$, $p=.531$] before and after test, whereas systolic [$t(41)=2.11$, $p=.041$] and diastolic [$t(41)=2.25$, $p=.03$] blood pressure. however, there was a statistically significant reduction in body temperature [$t(41)=15.02$, $p<.001$] before and after the administration of *Edhec Malacure* Table 8.

Comparative assessment of health indices after the use of test samples

Comparative assessment of health indices after the use of test samples revealed the following, body weight [F (2, 132)=0.351, $p=.704$] and diastolic [F (2, 131)=0.553, $p=.576$] after the test. Meanwhile, significant differences were evident for systolic [F (2, 132)=3.422, $p=.036$] and body temperature [F (2, 125)=74.13, $p<.001$] after test. Post-hoc analysis using Dunnett's t-test showed higher effectiveness of *AL* on systolic when compared individually to *Edhec Malacure* ($p=.028$) whereas AL and *Mist Amen Fevermix* ($p=.099$) were not statistically different. For body temperature AL was found to have higher

Table 9 Results of quality of life using Karnofsky's scale between Baseline Day 0 and Day 7 for *Mist amen Fevermix*

Days	Karnofsky's Scale	Level of Significance
0	80.0 ± 5.0	
7	95 ± 5.0	$p > .0001$

Results are Mean ± S.E.M

Table 10 Results of quality of life using Karnofsky's Assessment between Baseline Day 0 and Day 7 for *Edhec Malacure*

Days	Karnofsky's Scale	Level of Significance
0	85.0 ± 5.0	
7	92.5 ± 2.5	$p > .0001$

Results are Mean ± S.E.M

Table 11 Effect of *Mist amen Fevermix* on FBC

Parameter	Day 0	Day 7	Day 28
	χ±s	χ±s	χ±s
HB	12.15 ± 2.11	12.6 ± 1.68	12.75 ± 1.56
WBC	7.2 ± 2.87	7.55 ± 3.22	7.56 ± 3.25
RBC	5.02 ± 0.36	4.92 ± 0.4	6.73 ± 8.32
Neutro	59.06 ± 17.33	58.51 ± 15.32	50.79 ± 20.96
Lympho	33.73 ± 16.69	27.37 ± 18.06	24.35 ± 16.1
Monocy	3.44 ± 2.14	3.33 ± 2.14	3.47 ± 2.26
Ecosi	0.48 ± 1.24	0.3 ± 0.33	0.35 ± 0.42
Baso	12.15 ± 2.11	12.6 ± 1.68	12.75 ± 1.56

Results are Mean ± S.E.M

effect than both *Mist Amen Fevermix* ($p < .001$) and *Edhec Malacure* ($p < .001$).

Assessment of quality of life using the Karnofsky's scale of performance

Assessment of the quality of life was done using the Karnofsky's scale of performance. On day zero (0) before the administration of *Mist Amen Fevermix* the mean quality of life was 08.00 ± 5.0. This improved to 95 ± 5.0 with a p value of > 0.0001 at the end of the study on day seven (7). Also, after the administration of *Edhec Malacure* on day zero (0), 85.0 ± 5.0 was the mean quality of life, this also improved significantly on day seven (7) to 92 ± 2.5 with a p value of > 0.0001 Tables 9 and 10.

Assessment of full blood count after use of *Mist Amen Fevermix*

Assessment of full blood count after the administration of *Mist Amen Fevermix* showed that, there was no statistically significant differences between these parameters; HB [$t(43) = -1.052$, $p = .299$]; WBC [$t(43) = -1.125$, $p = .267$]; Neutrophils [$t(43) = 0.485$, $p = .63$]; Monocytes [$t(43) = 0.350$, $p = .728$]; Eosinophils [$t(43) = 1.051$, $p = .299$]; and Basophils [$t(43) = 1.014$, $p = .316$] before and after the administration of *Mist Amen Fevermix* at first test. Two variables RBC [$t\ (43) = 2.381$, $p = .022$]; and Lymphocytes [$t\ (43) = 2.678$, $p = .01$] were shown to have significant differences in levels before and after the use of *Mist Amen Fevermix* Table 11.

Table 12 Effect of *Edhec Malacure* on FBC

Parameter	Day 0	Day 7	Day 28
	χ±s	χ±s	χ±s
HB	12.89 ± 2.07	13.07 ± 1.84	13.19 ± 1.75
WBC	10.84 ± 13.37	9.4 ± 10.85	10.37 ± 12.44
RBC	5.05 ± 0.39	4.88 ± 0.45	5.69 ± 5.77
Neutro	59.94 ± 14.47	56.8 ± 13.33	57.82 ± 13.74*
Lympho	34.84 ± 15.26	34.76 ± 14.47	35.17 ± 14.59
Monocy	3.83 ± 6.48	4.35 ± 7.23	3.65 ± 5.73
Ecosi	3.15 ± 3.36	3.21 ± 3.66	3.13 ± 3.65*
Baso	0.34 ± 0.87	0.26 ± 0.21	0.26 ± 0.16

Results are Mean ± S.E.M

At the second test of effectiveness of *Mist Amen Fevermix*, the FBC parameters revealed that, Hb [$t(43) = -1.306$, $p = .199$]; WBC [$t(43) = -052$, $p = .959$]; RBC [$t(43) = -1.454$, $p = .153$]; Lymphocytes [$t(43) = 1.518$, $p = .136$]; Monocytes [$t(43) = -0.514$, $p = .610$]; and Basophils [$t(43) = -0.740$, $p = .463$] exhibited no statistical differences between the two visits. Neutrophils [$t\ (43) = 2.681$, $p = .01$]; and Eosinophils [$t\ (43) = 3.098$, $p = .003$] reported statistically significant differences between the second and third visits after use of *Mist Amen Fevermix*.

Assessment of full blood count after use of *Edhec Malacure*

There were no statistical significant differences between levels of WBC [$t(55) = 1.351$, $p = .182$]; Lymphocytes [$t(55) = 0.125$, $p = .901$]; Monocytes [$t(55) = -1.136$, $p = .261$]; Eosinophils [$t(55) = -0.244$, $p = .81$]; and Basophils [$t(55) = 0.702$, $p = .485$] before and after use of the *Mist Amen Fevermix*. On the other hand, Hb [$t\ (55) = -3.651$, $p = .001$], RBC [$t\ (55) = 3.132$, $p = .003$]; and Neutrophils [$t\ (55) = 4.208$, $p < .001$] showed differences at the first and second visits Table 12.

At the second test of effectiveness of AL, no statistical differences were recorded for HB [$t(55) = -1.552$, $p = .126$]; WBC [$t(55) = -0.955$, $p = .344$]; RBC [$t(55) = -1.047$, $p = .30$]; Neutrophils [$t(55) = -1.148$, $p = .256$]; Lymphocytes [$t(55) = -1.402$, $p = .166$]; Monocytes [$t(55) = 1.503$, $p = .139$]; eosinophils [$t(55) = 1.221$, $p = .227$]; and Basophils [$t(55) = -0.157$, $p = .876$].

Comparative assessment of the effect of test samples on full blood count

Analysis of variance of effectiveness of *AL*, *Mist Amen Fevermix* and *Edhec Malacure* on each of the indicators showed no significant differences in their effect on Hb ($p = .737$), WBC ($p = .15$), RBC ($p = .529$), Neutrophils ($p = .098$), Monocyte ($p = .518$), Eosinophils ($p = .328$) and Basophils ($p = .645$) after first visits. However, differences in effect of the three drugs on Lymphocytes ($p = .003$) were recorded after the first visit. Post-hoc analysis

showed effects of *Edhec Malacure* to be lower than the effects of Control (AL) on levels of Lymphocytes in the patients.

Discussion

The increasing utilization of finished multi-component herbal products for the management and treatment of different kinds of ailments found in developing and developed countries poses a public health challenge. This is due to the number of clinically untested herbal preparations. Since time immemorial, products obtained from medicinal have been used to promote optimal health and well-being. These products are known to contain various phytochemicals which possess pharmacological activities [13, 14]. There is, therefore, the need to, harness the potential clinical use of herbal products as alternative therapies or options to conventional drugs. This has many benefits to the population who rely on herbal products for their primary health care needs as it improves the quality of life of consumers.

Mist Amen Fevermix and *Edhec Malacure* have been used in clinical practice in Ghana since 2011 to date for the treatment of uncomplicated malaria [15]. However, there is paucity of data from clinical studies that compare the safety and effectiveness of these herbal products with standard conventional medicines to justify their utilization. Thus, it is desirable to undertake a comparative clinical study of the two multi-component herbal products against artemether/lumefantrine using standard scientific methods to clinically evaluate the antimalarial activity for their benefits in humans. Quality control of the two herbal products including the in vitro and in vivo antiplasmodial activity have been undertaken [15, 16]. The selection of the two FDA registered multi-component herbal antimalarial remedies was based on acceptance, patronage and their subsequent utilization at the Herbal Medicine Unit of the Tafo Government Hospital.

The study revealed that, about 62.2% of the patients were aged between 18 and 33 years. This implies that participants for the study constitutes a very youthful age. However, this is not in line with a study which revealed that the use of herbal products among youth is not as common as it is among adults [25]. Also, there were more females (60%) than males (40%).

Comparatively, on the initial visits, parasite counts on the control arm of the study was [14268.68, SD=18167.06], that of *Mist Amen Fevermix* was [2072.38, SD=2212.71] whereas *Edhec Malacure* was [3069.81, SD=4233.36]. However, on the second and third visits, there was a marked to no parasite counts respectively Table 1. The % Suppression of parasites after administration of study samples to assess effectiveness revealed that, AL (control) % suppression was 97.25%, *Mist Amen Fevermix* 95.89% and *Edhec Malacure* 91.87% respectively. Therefore, the outcome of the study indicates that the control (*AL*) was most effective in reducing the parasite counts Table 2. Also, one-way ANOVA test, comparing the control and the test samples, showed significant differences in effectiveness Fig. 3. The outcome of the study supports a similar study where 87.9% suppression of parasitaemia was observed against 96.9% for Artesunate-Amodiaquine combination [17]. Comparatively, some multi-component herbal products have been confirmed to be very effective in the treatment of wide variety of diseases [18, 19]. The multi-component herbal products; *Mist Amen Fevermix* and *Edhec Malacure* achieved a comparable treatment outcome to the reference control medication artemether/lumefantrine. The two herbal products could therefore be considered as viable alternatives to the allopathic treatment with artemether/lumefantrine. Using the Dunnette's *t* test (a 2 sided *t* test), there was a statistical significance of $P<.001$. This indicates the effectiveness of the control as compared against the test samples. This is similar to a study which showed there was a complete treatment of malaria infection in patients treated with an antimalarial phytomedicine against artemether/lumefantrine [17, 20].

The safety of the test samples on renal function panel revealed that all the parameters were maintained within the normal limits in both study arms. This indicates that *Mist Amen Fevermix* and *Edhec Malacure* did not impair the renal function of the patients (Tables 3 and 4). The outcome of a one-way ANOVA test, comparing the effect of the test samples revealed that there was no alteration to renal function. This outcome is similar to clinical trials and experimental studies where it was demonstrated that a polyherbal formulation, did not cause any renal impairment after administration [21]. On the safety of the test samples on hepatic function, there was no statistically significant differences in levels of renal function parameters in patients who used *Mist Amen Fevermix.* However, globulin and direct bilirubin were slightly high Table 5. Also, the effect of *Edhec Malacure* on patient's liver, showed no significant differences between the levels of Albumin, ALP, ALT, AST, Direct Bilirubin, GGT, Globulin, Indirect Bilirubin, Protein, Total Bilirubin on the second visits Table 6. This supports a similar study where various herbal medicines have been used without affecting hepatic function. Some have even shown promising results in the treatment of hepatic disorders [22].

The evaluation of health indices from the one-way ANOVA test comparison of the effectiveness of AL, *Mist Amen Fevermix* and *Edhec Malacure* on health indicator variables showed no significant differences. However, there was a statistically significant ($p>.001$) decrease in body temperature (Tables 7 and 8). This implies that the test samples showed an antipyretic effect. This finding can be compared with the herbal product *Pyrexol*, which

showed a significant reduction in yeast-induced elevated temperature as compared with that of standard drug paracetamol [22, 23].

Malaria is known to cause several changes in full blood count (FBC) parameters, of which the most prominent are anaemia and thrombocytopaenia1. Full blood count should be routinely carried out in people infected with malaria in order to diagnose and monitor the incidence of anaemia. There was no significant differences shown between levels of the full blood count Tables 11 and 12. But Mist Edhec Malacure exhibited a statistically significant differencesin RBC [$p=.003$] and Neutrophils [$p<.001$] between the first and second visits Table 11. This is similar to a study where no changes in haematological parameters was observed after the administration of a herbal product [5].

The quality of life using the Karnofsky's scale of performance, which refers the standard of health, comfort, and happiness experienced by an individual was assessed in participants. There was a statistically significant improved quality of life from 80.00±5.0 to 95±5.0 with a p value of >0.0001 at the end of the study on day seven (7) involving *Mist Amen Fevermix*. Also, after the administration of *Edhec Malacure* on day zero (0), 85.0±5.0 was the mean quality of life, this also improved significantly on day seven (7) to 92±2.5 with a p value of >0.0001 Tables 9 and 10. This is similar to a research where the utilization of herbal therapy did improve the quality of life of patients who used it [24]. After 28 days of follow-up, no significant differences between the mean values of the different biological parameters in the two treatment groups was observed.

Conclusion

This study has validated and provided scientific evidence on the clinical safety and effectiveness profile of the antimalarial properties of *Mist Amen Fevermix* and *Edhec Malacure*, which justified their use as herbal antimalarial products. The multi-component herbal products; *Mist Amen Fevermix* and *Edhec Malacure* achieved a comparable treatment outcome to the reference control medication artemether/lumefantrine. The two herbal products could therefore be considered as viable alternatives to the allopathic treatment with artemether/lumefantrine.

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Data availability
The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Conflict of interest
The authors declare that they have no conflicts of interest.

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