

# Clinical Evaluation of the Safety and Effectiveness of *Adutwumwaa Malamix*: A Polyherbal Product for the Treatment of Uncomplicated Malaria in Ghana

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## ABSTRACT

Antimalarial medications remain one of the major interventional tools for the global malaria control efforts. One of the most popular Ghanaian herbal antimalarial agent is the product sold under the trade name '*Adutwumwaa malamix*'. This product is registered with the Food and Drugs Authority (FDA) of Ghana as treatment of uncomplicated malaria. In this study, the safety and effectiveness of the product '*Adutwumwaa malamix*' for the treatment of uncomplicated malaria was clinically evaluated based on disease-oriented and patient-oriented evidence. A total of 42 subjects were recruited for the study. Complete cure was achieved for 35 (83.33%) of participants by day 7 of the study. Partial efficacy was also achieved for 7 (16.66%) of subjects. Patient reported symptoms such fever, chills and abdominal pains were also significantly improved by day 7 and absent by day 28. The safety parameters assessed did not show any clinically significant change among the study population during treatment. The outcome of the study indicates that the Ghanaian herbal antimalarial agent '*Adutwumwaa malamix*' may be an effective herbal treatment for the management of uncomplicated malaria.

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## INTRODUCTION

Malaria is a disease condition caused by the plasmodium parasite and transmitted by the bite of an infected female anopheles mosquito. *Plasmodium species* that cause malaria in humans are *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and more recently *P. knowlesi*. Among these species, *P. falciparum* is the most prevalent and the most virulent (Singh,

2011). Clinical manifestations can include headache, periodically recurrent fever (every 48 to 72hours), chills, myalgia, sudoresis, hepatosplenomegaly, prostration and anaemia (Singh *et al.*, 2011). The role herbal medicines play in the management of malaria cannot be ignored. The current conventional treatment of choice; quinine used in complicated and cerebral malaria and the artemisinin-based products, have their roots from medicinal plants (Biamonte *et al.*, 2013). There are 1200 plant species from 160 families used to treat malaria (Cui *et al.*, 2012). According to the World Health Organization (WHO), more than 3.5 billion people in the developing world rely on medicinal plants as components of their healthcare (Sasidharan *et al.*, 2011).

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In Africa, up to 60% of the population use traditional medicine and it is the first choice of healthcare treatment for most of the populace who suffer from fever and other common ailments (Bekalo *et al.*, 2009).

The National Malaria Control Programme in 2007 reported that 70% of Ghanaians used herbal medicines in treating malaria (Siaw, 2011). This is due to the fact that, the herbal products are generally cheaper, easily available and believed to be effective and safe, as compared to allopathic medicines. Many of such products have been used in Ghana for the treatment of malaria (Turkson *et al.*, 2015). The World Health Organization has stated that global eradication of malaria is not possible and recommends a stance where parasites and their resistance to drugs are kept under control (WHO, 2009). The malaria parasite has developed resistance against most malaria drugs including the popular Artemisinin-based Combination Therapy (ACT) in some region (Cui *et al.*, 2012). The rapid spread of resistant parasites, makes it imperative to search for effective herbal antimalarial agents as resistance is may be generally low with botanical medicines (Graz *et al.*, 2010). In Ghana, there are numerous herbal products available for use as antimalarial agents. One of these products is 'Adutwumwaa malamix' which is registered with the Food and Drugs Authority (FDA) of Ghana for the treatment of uncomplicated malaria. The product is a polyherbal decoction prepared from *Vitex grandifolia* Gurke (Family: Verbenaceae), *Anthocleista nobilis* G. Don (Family: Loganiaceae) and *Phyllanthus fraternus* G L Webster (Family: Euphorbiaceae).

Traditionally, the bark of *Vitex grandifolia* Gurke is used to treat diarrhoea, bronchial complaints, rickets, sores and fever (Burkill, 1997). The Ezza people in Nigeria use the bark of *Anthocleista nobilis* as a worm expellant and as antimalarial remedy (Ngwoke *et al.*, 2015). In Ghana, the plant extract of *Phyllanthus fraternus* G L Webster is reported to be a strongly diuretic and taken to allay spasms, such as griping in dysentery, it is also used as a laxative and to treat gonorrhoea and fever (Oudhia, 2008). The herbal product, 'Adutwumwaa malamix' has been on the Ghanaian market for over eight years, it is patronised for use in the treatment of uncomplicated malaria, but currently lacks empirical clinical data to support this claim. This study was therefore setup with the aim of evaluating the clinical safety and effectiveness of 'Adutwumwaa malamix' in the treatment of uncomplicated malaria based on disease-oriented and patient-oriented evidence.

## MATERIALS AND METHODS

### Ethical Considerations

Ethical approval for the study was obtained from the Committee for Human Research, Publications and Ethics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology and Komfo Anokye Teaching Hospital, Kumasi in January, 2016 (SMS/KATH, CHRPE/ AP/016/16) and the research committee of the Kumasi South Hospital also gave their approval prior to the commencement of the research. A written informed

consent was also obtained from all the participants involved in the study after the purpose of the study and guarantees of anonymity and their rights had been explained to them in either English or one of the local Ghanaian languages they could comprehend. The study and its protocols were in accordance with the Helsinki declaration for Good Clinical Practice.

### Study design

The study was an open label, prospective, non-comparative clinical trial in patients with uncomplicated malaria confirmed by a thin and thick blood film. During consultations, patients with established classical signs and symptoms of malaria (i.e. headache, fever, general malaise, chills, bitter taste in the mouth, easy fatigability and loss of appetite) were made to undergo laboratory tests to establish a positive blood film for malaria parasite and full blood count. Upon recruitment, blood was also drawn for baseline kidney and liver function tests as well as other safety parameters. A structured questionnaire was then used to collect data from the subjects who were diagnosed with malaria at the herbal clinic of the Kumasi South Hospital. Information gathered included the patient's demographics (age, weight, height, and gender), educational levels, cell phone number, contact persons' cell phone number (for follow up), residential address, signs and symptoms presented.

### Inclusion and Exclusion Criteria

Participants included in the study comprised male and females between the ages of 15-60 yrs with parasitaemia in the range of 20 to 50,000 asexual parasites per  $\mu$ l and an axillary temperature  $>37.5^{\circ}\text{C}$  but  $<39.5^{\circ}\text{C}$  at the baseline. Subjects were also recruited if they had no history of ingestion of any known anti-malaria product within the past 14 days, able and willing to return for follow up, willingness of the subject/guardian to sign an informed consent to take part in the study and ease of access to the health facility. Exclusion criteria comprised individual with complicated malaria i.e. evidence of cerebral involvement (meningitis or encephalopathy), hypertension, dehydration, excessive vomiting, renal involvement, the severely malnourished, febrile illness from other causes other than malaria, pregnant or breastfeeding women, haemoglobin of less than 8g/dl, patients with liver and/or renal disease(s) and comorbidities which might compromise the renal, hepatic or any other body system.

### Interventional Product

A decoction of the product 'Adutwumwaa malamix' packaged in 500ml amber colored bottles was dispensed according to the recommended dose of 60ml to be taken three times daily for six (6) days by the participants.

### Participant Follow-ups

A diary card for the study was also provided for subjects to assess drug compliance. Patients were asked to report for follow-up visits at the hospital; on days 3, 7 and 28 after commencement of therapy. On day 14 and 21, patients were called

on phone to assess whether or not the symptoms presented were improving or getting worse, so as to provide the relevant clinical advice, determine possible adverse drug reactions and side effects of the herbal product. On day 3 and 7, full case history and examination were conducted. Subjects were assessed for drug compliance on the diary card, laboratory investigations on blood film for malaria parasites and full blood counts were done. On day 28, patients were made to undergo clinical assessment to verify whether or not the subject's treatment has been successful or if there was any form of recrudescence. Laboratory investigations such as blood film for malaria parasites, full blood count, kidney and liver function tests were repeated. Participants with residual parasite by day 7 and 28 were referred to the orthodox healthcare unit for further treatment.

### Assessment of Product Effectiveness

Primary assessment of the effectiveness of the product was defined by its ability to totally clear parasites by the day 7 of the study. Participants achieving this outcome were defined as having a complete cure. Partial efficacy was said to have occurred if participants were able to clear more than 50% of initial parasite count by day 7 and treatment failure when less than 50% of the parasites were cleared. Subjects who recorded a partial efficacy or treatment failure were referred to receive the conventional antimalarial treatment after which the blood film was repeated.

### Safety Assessment

Participants were evaluated for drug related toxicity using a biochemical assay of the liver and kidney, and a haematological analysis. Adverse reactions were also monitored using the standardized WHO questionnaire.

## RESULTS

### Study Population

A total of 50 participants were recruited for the study, 2 of the participants withdrew voluntarily at the initial stages because of reasons which were undisclosed, 6 other participants were not able to comply with the trial protocol and were thus withdrawn. In all 42 participants were able to comply with the protocol and complete the study. The dropout rate for the study was thus 14.28%.

### Mean Age and Gender of Participants

The study participants comprised 26 (61.90%) females and 16 (38.10%) males. The mean age of the participants was 35.69 ( $\pm 12.35$ ) and 39.50 ( $\pm 12.57$ ) for the male and female participants respectively.

### Safety Assessment of Participants

#### Effect of the treatment on renal function

Renal function was measured using the blood urea and creatinine levels. Creatinine levels for all participants were found to be within the physiological range on day 1. A non-significant

decline in this parameter was observed on day 28. The level of urea was however unaffected at the end of the study. The results of the renal function are presented in Table 1.

#### Effect of the treatment on liver function

The assessment of the effect of *Adutwumwaa malamix* on the liver (Table 1), indicated that all the parameters measured: proteins, albumin, globulin, alanine transaminase (ALT), gamma glutamyl transferase (GGT), aspartate transaminase (AST) and alkaline phosphatase (ALP) were not significantly affected after the treatment. Although baseline measurements were different from the end of the study these variations were established to be clinically and statistically non-significant.

**Table 1:** The effect of the herbal product '*Adutwumwaa malamix*' on the renal and liver function of participants. Results are presented as Mean ( $\pm$ SD) (n=35).

	Baseline	End of Study
Proteins	76.73 (5.54)	75.38 (6.57)
Albumin	34.56 (7.48)	33.82 (8.45)
Globulin	30.87 (6.56)	29.53 (4.47)
ALT	27.35(4.35)	27.03(4.77)
GGT	30.72 (2.07)	28.03 (2.38)
AST	26.76 (4.05)	26.50 (4.11)
ALP	153.24 (41.78)	154.33 (39.48)
Creatinine (Umol/l)	61.17 (11.36)	60.00 (8.96)
Urea (mmol/l)	3.84 (0.79)	3.97 (0.79)

\*Alanine transaminase (ALT), Gamma glutamyl transferase (GGT), Aspartate transaminase (AST) and Alkaline phosphatase (ALP).

### Haematological Findings

Haematological indices for the various parameters were all found to be within the reference range for all participants at baseline with the exception of RBC's which was lower than the reference limits. This report remained unchanged even after the treatment (Table 2). Statistical testing did not indicate any significant difference in RBC's. The treatment did not also appear to affect any of the parameters assessed.

**Table 2:** The effect of the herbal product '*Adutwumwaa malamix*' on the renal and liver function of participants. Results are presented as Mean ( $\pm$ SD) (n=35).

Parameter	Baseline	End of Study	P-value
Haemoglobin	13.06 (1.61)	13.19 (1.27)	0.29
RBC	$2.08 \times 10^9$ ( $6.13 \times 10^9$ )	$1.95 \times 10^9$ ( $5.36 \times 10^9$ )	0.17
WBC	$2.69 \times 10^9$ ( $2.10 \times 10^{10}$ )	$1.83 \times 10^9$ ( $9.69 \times 10^{10}$ )	0.32
Haematocrit	42.04(20.60)	42.07 (7.85)	0.95
Platelets	$319.2 \times 10^3$ ( $8.39 \times 10^8$ )	$292.1 \times 10^3$ ( $6.97 \times 10^8$ )	0.15

### Monitoring of Participants Health and Disease Indices

#### Body Weight and Temperature

A marginal increase in the mean body weight of participants was recorded (Table 3) at the termination of the trial. This result obtained were not statistically significant. Mean body temperature recorded for the participants at the baseline was 37.89°C ( $\pm 0.25$ ) a decline was observed throughout the follow up period. A comparison of the baseline temperature to the end of study showed a statistically significant difference ( $37.17 \pm 0.14$ ;  $p < 0.05$ ) (Table 3).

**Table 3.0:** Summary participant health and disease indices at baseline and after treatment. Results are presented as Mean ( $\pm$ SD) (n=35)

Parameter	Before Treatment	After Treatment	p-value
Body Temperature ( $^{\circ}$ C)	37.89 (0.25)	37.17 (0.14)	$2.22 \times 10^{-13}$
Body Weight (kg)	65.97 (8.46)	66.20 (7.64)	0.366
Systolic Blood pressure (mmHg)	130(15.72)	123.79(12.93)	0.0009
Diastolic Blood pressure (mmHg)	80 (11.38)	77.93 (8.61)	0.147

**Table 4.0:** Mean parasitaemia of the complete cure and partial efficacy groups at the baseline and at the end of the study.

Parameter	Baseline	Day 7	p-value
Partial Efficacy (count/ $\mu$ L)	2730.50 ( $\pm$ 21.79)	161.83 ( $\pm$ 9.69)	0.000
Complete Cure (count/ $\mu$ L)	302.76 ( $\pm$ 17.91)	0.00	0.000

**Table 5.0:** Assessment of Patient-Reported Symptoms on Day 7

SYMPTOMS	Number of Subjects (n)	No Improvement n (%)	Mild Improvement n (%)	Moderate Improvement n (%)	Maximum Improvement n (%)
Fever	35	-	3 (8.57)	4 (11.43)	28 (80.0)
Chills	32	-	-	1 (3.57)	31 (96.43)
Abdominal pain	9	-	-	5 (57.14)	4 (42.86)
Dizziness	10	-	8 (80.0)	2 (20.0)	-
Headache	35	-	2 (5.88)	6 (17.65)	27 (76.47)
Loss of Appetite	14	-	11 (80.0)	3 (20.00)	-
Oral bitterness	35	3 (8.82)	26 (76.47)	6 (14.71)	-

### Blood Pressure

Blood pressure among the participants were recorded at baseline and during follow up. It was observed that there was a significant decline in systolic blood pressure (SBP) measurements. Post treatment SBP was  $123.79 \pm 12.93$ ; ( $p < 0.05$ ) over the period. Diastolic blood pressure (DBP) measurements during the study were however not statistically different with mean DBP at the end of the study recorded as  $77.93 \pm 8.61$ ; ( $p > 0.05$ ). Results are summarized as Table 3.

### Monitoring of Harms and Adverse Effect

A checklist for possible side-effects was employed during the follow up period (WHO, 2004). Using this standardized checklist, none of the participants reported of any side or adverse effects during administration of the product.

### ASSESSMENT OF EFFECTIVENESS

The mean parasite count for participants declined significantly during the first 7 days of treatment. Baseline parasite count was  $671.1 (\pm 177.0) / \mu\text{L}$  which on follow up declined to  $29.42 (\pm 12.79) / \mu\text{L}$  on day 7. This response comprised 35 (83.34%) who attained the primary outcome of complete cure and 7 (16.66%) who recorded a partial efficacy. None of the participants had a treatment failure. Participants who recorded a partial efficacy had a higher mean parasite count at the baseline than the group that attained the complete cure (Table 4). A comparison of the parasite count recorded on Day 1 and Day 7 of visits showed a significant difference ( $p < 0.05$ ) for both the partial efficacy and complete cure groups as reported in table 4.

### Symptomatic Response to Treatment

Generally, all the participants reported with the classical symptoms of malaria: fever, chills, headaches, loss of appetite and

oral bitterness at the start of the study. These symptoms were followed up for improvement over the 28day period. Upon review of the study subjects on day 7, a total of 28 (80%) participants reported of maximum improvement/or an absence of the fever initially presented. Reports of chills were also absent in 33(96.43%), other symptoms such as abdominal pains and headaches recorded a maximum improvement for 15 (42.86%) and 27 (76.47%) participants respectively (Table 5). At the end of the trial (Day 28) all the subject reported that their symptoms had resolved.

### DISCUSSION

The treatment of malaria aims to interrupt the blood schizogony that causes the pathogenesis and clinical symptoms of the infection (Derbyshire, *et al.*, 2011). Prompt and effective treatment is probably the most cost-effective method of malaria control. Early treatment prevents progression to the severe state of the disease and its resultant complications. If the medicine is safe and effective, a decrease in overall malaria-related morbidity and mortality may be achieved.

Medicinal herbs continue to play an integral role in the efforts at controlling malaria (Thomford *et al.*, 2014). This fact is even more true for developing countries like Ghana. Currently, there are numerous herbal antimalarial products on the Ghanaian market. Most of these products lack scientific data to support their widespread use and acceptance. It is against this background that the current study was undertaken to establish a scientific basis for the use of the product.

This study provides both disease-oriented evidence; based on surrogate markers of health such as temperature, blood pressure, haematological, liver and kidney indices and patient-oriented evidence that addresses real-life questions of whether patients' condition actually improved or aggravated.

The herbal product 'Adutwumwaa malamix' after evaluation was shown to be safe at the current dosage and treatment regimen. The various safety parameters did not show any significant change from the baseline and at the end of the study as evidenced by the normal liver and renal function tests. Significantly, the level of gamma glutamyl transferase (GGT) which is a very important indicator of drug induced hepatotoxicity was normal. The risk of harms due to the use of herbal medicines is a very important public health issue and therefore such reports about safety of products should always be made available for the consumer. The product did not also induce any adverse reactions or side effects. None of the participants reported of any symptoms that could have been associated with the use of *Adutwumwaa malamix*. All complaints which were typical symptoms of malaria resolved during the follow up.

Haematological abnormalities which are a hall mark of malaria, were normal in the subjects used for the study. This situation is quite common in malaria endemic regions where some form of immunity develops due to recurrent exposure (Menendez *et al.*, 2000). The absence of any clinically significant change in haemoglobin, red blood, white blood cells and other haematological indices could also be interpreted as confirming the safety of the product. General health and disease indices such as body weight and blood pressure were normal on Day 1 and did not show any clinically significant change at the end of the study. General body temperature which was however marginally high at baseline showed a significant decline after treatment.

Treatment outcomes were assessed according to WHO guidelines, as adequate clinical and parasitological response. The mean parasitaemia of participants declined significantly after the 7<sup>th</sup> day of treatment with 35 (83.34%) of subjects attaining the primary outcome of Complete cure. Partial efficacy was recorded in 7 (16.66%) of the participants. These participants after referral to receive the conventional treatment recorded a negative parasitaemia. Comparatively, the baseline parasite density for 7 participants who recorded the partial efficacy was higher compared to those who were successfully treated. Baseline parasite levels were 2730.50 ( $\pm 21.79$ ) and 302.76 ( $\pm 17.91$ ) for the Partial efficacy and Complete cure groups respectively.

This finding may be interpreted as defining the level of parasitaemia within which the product can be used, thus stipulating the clinical limits under which the product may be effective. Again, the fixed dose administered for the product could have affected the outcome as an increase in dose could have improved the therapeutic effect of the product. Clinical response of the test medicine *Adutwumwaa malamix*, produced a rapid fever clearance; 28 (80.0%) and 31 (96.43%) of the study subjects became reporting of marked improvement in the symptoms of fever and chills respectively after 7 days of treatment. Other non-characteristic symptoms such as headache, dizziness and fatigue resolved with minimal intervention. Overall the Ghanaian herbal medicinal product *Adutwumwaa malamix* was well tolerated by subjects. The results therefore indicate that the treatment was very safe, and effective for the treatment of uncomplicated malaria. The

antimalarial activity of the product can be linked to the constituent plants in the product. The active principles responsible for the antimalarial activity of the formulation cannot be specified. Phytochemical screening of the herbal product indicated the presence of the tannins, triterpenoids, saponins, alkaloids and flavonoids. Several of these metabolites have been previously reported as having anti-plasmodial activity. *Anthocleista nobilis* has been reported as having moderate anti-plasmodial effect *in vivo*, this activity has been attributed to the alkaloids in the plant (Sanon *et al.*, 2013). Similarly, the antimalarial actions of *Phyllanthus fraternus* has been widely reported (Komlaga *et al.*, 2016; Sittie *et al.*, 1998; Malau *et al.*, 2009). These findings are very significant as *Adutwumwaa malamix*, could serve as a potential alternative for the treatment of uncomplicated malaria in Ghana.

## CONCLUSION

The outcome of the study indicated that *Adutwumwaa malamix*, a FDA Ghana registered antimalarial product is an effective herbal product for the management of uncomplicated malaria in humans. Its ability to clear plasmodium parasites makes it a potential useful antimalarial agent with no observed adverse effects.

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**Conflict of Interest:** Authors declare that there are no ethical conflicts

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