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ORIGINAL ARTICLE

Ghanaian Herbal Medicines for Malaria: An Evaluation of the Clinical Safety and Effectiveness of "*Time Herbal Mixture*" in Uncomplicated Malaria

Andrews W. Tetteh, Kwesi P. Thomford[1], Merlin L. Mensah[1], Kwame O. Boadu[2], Ama K. Thomford[3], Isaac K. Amposah[4], Godfred Amofa, Benard K. Turkson[5], Michael O. Agyemang[6], Emmanuel D. J. Owusu-Ansah[7]

Herbal Medicine Unit, Kumasi South Hospital, Ghana Health Service, Ghana, [1]Department of Herbal Medicine, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, [2]Department of Maternal and Child Health, Kumasi South Hospital, [3]Department of Biomedical Sciences, University of Cape Coast, Cape Coast, [4]Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, [5]Herbal Medicine Unit, Tafo Government Hospital, Ghana Health Service, [6]Department of Pharmacy, Kumasi South Hospital, Ghana Health Service, [7]Department of Mathematics, Faculty of Physical and Computational Sciences, College of Science Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

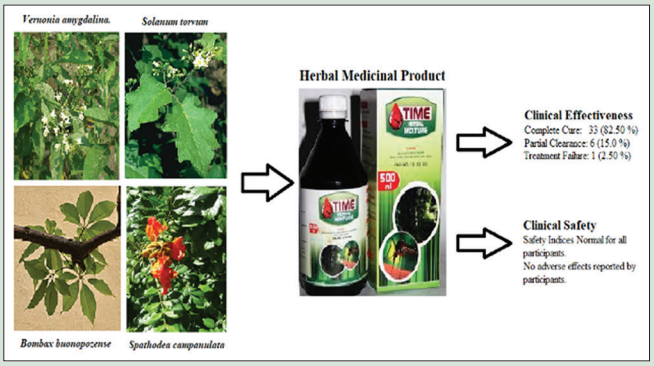
ABSTRACT

Background: Herbal antimalarials have become a popular source of treatment for most Ghanaians. The significant increase in patronage is of public health concern due to the lack of quality, safety, and efficacy data. **Aim:** In this report, we evaluated the clinical safety and effectiveness of a Ghanaian commercial product named *"Time Herbal Mixture"* (THM). The product is formulated from the leaves of *Solanum torvum* and *Vernonia amygdalina* and the stem bark of *Spathodea campanulata* and *Bombax buonopozense*. **Methods:** Participants of 40 patients diagnosed with uncomplicated malaria were recruited, treated, and followed up for a period of 28 days. This population comprised 25 (62.50%) females and 15 (37.50%) males, with a mean age of 42.29 (12.35) years. Outcome of primary interest was the ability of the product to clear blood parasites by day 7 of the study, resolution of cardinal symptoms of malaria, and an absence of adverse effects from the use of the product. **Results and Discussion:** A total of 33 (82.50%) participants achieved clearance of all parasites by day 7 (complete cure). Partial clearance was attained by 6 (15.0%) and treatment failure in 1 (2.50%). Resolution of the cardinal symptoms was also observed in most participants by day 7. The product also had a good safety profile as none of the participants reported any adverse effects. Liver, kidney, and hematological profiles were also normal after the study. **Conclusion:** "THM," therefore, has the potential to be used in cases of uncomplicated malaria.

Key words: *Bombax buonopozense*, clinical studies, herbal antimalarials, *Solanum torvum*, *Spathodea campanulata*, *Vernonia amygdalina*

SUMMARY

- "*Time Herbal Mixture*" is a Ghanaian herbal remedy formulated from the medicinal plants: *Solanum torvum*, *Vernonia amygdalina*, *Spathodea campanulata*, and *Bombax buonopozense*. Clinical testing of the product in 40 patients with uncomplicated malaria indicated it was safe and effective. The product has the potential for use as a first line antimalarial.



Abbreviations Used: ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate transaminase, GGT: Gamma-glutamyl transferase, HCT: Hematocrit, HGB: Hemoglobin, PLT: Platelet, RBC: Red blood cell, SD: Standard deviation, THM: *Time Herbal Mixture,* WBC: White blood cell.

Correspondence:
Mr. Andrews W. Tetteh,
Herbal Medicine Unit, Kumasi South Hospital,
Ghana Health Service, Kumasi, Ghana.
E-mail: ebotetteh@gmail.com
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INTRODUCTION

Herbal antimalarial products are one of the most widely patronised therapies used as first line treatment for malaria in Ghana because of their availability, cost, perceived safety and effectiveness. Every herbal medicine practitioner in the country has at least a single formulation for the management of this protozoan disease possibly due to the reason that malaria is endemic in our part of the world or the attribution of every symptom of fever to a malarial infection. Such products are widely marketed and can be easily purchased from any pharmaceutical outlet around the country.[1-3] Notwithstanding their popularity and patronage, majority of these remedies are not clinically verified for this indication. However, evidence exists from *in vitro* and *in vivo* data as support for the traditional use of these plants in the management of fevers and related conditions.

An ethnopharmacological study undertaken by Asase *et al.* reported of 29 plant species from 22 different families being employed by various herbalists as antimalarial agents. The most frequently mentioned plants

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in their study were *Morinda lucida* Benth., *Indigofera* sp., and *Nauclea latifolia* Sm.[4-6] These plants and a host of others reported by this author have also been confirmed in other studies undertaken at different sites by other workers. Komlaga *et al.* documented similar plants in their study of a district in the middle belt of Ghana. Characteristically, evidence to support the usage of such medicinal plants was reliant on *in vitro* and *in vivo* reports.[7-10]

The plants used in the formulation of the herbal medicinal product, *Time Herbal Mixture* (THM), evaluated in this study have also been cited in multiple ethnopharmacological studies on traditional medicines for malaria.[2,5,6] These plants include the leaves of *Solanum torvum* and *Vernonia amygdalina* and the stem barks of *Spathodea campanulata* and *Bombax buonopozense*. *S. torvum* was found to have moderate *in vitro* activity against the blood-stage chloroquine-sensitive (3D7) and chloroquine-resistant (INDO) strains of *Plasmodium falciparum*.[11] Using similar *in vitro* testing but this time only against chloroquine-sensitive plasmodium, Tona *et al.* indicated that the ethanolic (EtOH) fraction of the *V. amygdalina* had weaker activity compared to its petroleum ether fraction.[12] An EtOH leaf extract of the plant also produced 67% suppression of parasitemia in the 4-day *in vivo* test, while root-bark extract produced 53.5% suppression.[13] The results were reported to be better when compared to a placebo. Similarly, *S. campanulata* and *B. buonopozense* after *in vivo* evaluations were found to have significant actions against chloroquine-sensitive *Plasmodium berghei*.[14,15]

The limited evidence arising out of the clinical study of herbal medicinal products heavily limits their acceptance for inclusion into the formal health-care system. Thus, THM, one of the most patronized Ghanaian herbal products for the treatment of malaria, was selected to be evaluated to establish its safety and effectiveness as a treatment for uncomplicated malaria. The product is registered with the Food and Drug Administration of Ghana for the same indication.

METHODS

Ethical considerations

Ethical approval for this clinical 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 (SMS/KATH, CHRPE/AP/016/16), and the Research Committee of the Kumasi South Hospital before the commencement of the research. 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.[16]

Study design

The study was an open-label, prospective, non-comparative trial in patients with uncomplicated malaria confirmed by a thin and thick blood film examination after selection 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. On 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 patients 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, and signs and symptoms presented.

Inclusion and exclusion criteria

Participants included in the study comprised males and females between the ages of 15–60 years with parasitemia in the range of 20–50,000 asexual parasites per µl and an axillary temperature >37.5°C but <39.5°C at the baseline. Individuals were also recruited if they had no history of ingestion of any known antimalaria product within the past 14 days, able and willing to return for follow-up, willingness of the participant/guardian to sign an informed consent to take part in the study, and ease of access to the health facility. Exclusion criteria were based on signs of 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, hemoglobin (HGB) of <8 g/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 "THM" packaged in 500 ml amber-colored bottles was dispensed according to the recommended dose of 60 ml to be taken three times daily for 6 days by the participants. THM is prepared as an aqueous decoction according to a proprietary formula and comprises the leaves of *S. torvum* and *V. amygdalina* and the stem bark of *S. campanulata* and *B. buonopozense*. THM is defined by the physicochemical properties of pH (5.7 ± 0.16) and density (0.069 ± 0.002). Chemical definition for the product comprised an ultraviolet spectrum with 10 absorptions peaks at: 226.0 nm, 3.34 A; 229.0 nm, 3.39 A; 232 nm, 3.42 A; 234 nm, 3.43 A; 237.23 nm, 3.49 A; 241.67 nm, 3.41 A; 246 nm, 3.39 A; 240 nm, 3.42 A; 254 nm, 3.37 A; and 255 nm, 3.33 A.

Participant follow-ups

A diary card for the study was provided for participants to assess drug compliance. Participants were asked to report for follow-up visits at the hospital on days 3, 7, and 28 after the commencement of therapy. On days 14 and 21, patients were called on phone to assess if the symptoms presented were improving or getting worse, to provide the relevant clinical advice, and determine possible adverse drug reactions and side effects of the herbal product. On days 3 and 7, full case history and examination were conducted. Participants were assessed for drug compliance on the diary card; laboratory investigations of blood film for malaria parasites and full blood counts were done. On day 28, patients were made to undergo clinical assessment to verify whether the participant'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, and kidney and liver function tests were repeated. Participants with residual parasite by days 7 and 28 were referred to the orthodox health-care unit for further allopathic drug treatment.

Classification of effectiveness

The primary assessment of the effectiveness of the product was defined by its ability to totally clear parasites by day 7 of the study. Participants achieving this outcome were defined as having a complete cure. Partial effectiveness was said to have occurred if parasite clearance was >50% of initial count by day 7 and treatment failure when <50% of the parasites were cleared. Participants who recorded a partial effectiveness 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 an hematological analysis. Adverse reactions were also monitored using the standardized WHO questionnaire.[17]

Statistical analysis

Data for effectiveness and safety assessments were analyzed using a paired *t*-test, and results were considered significant if $P < 0.05$. All other data were presented as mean ± standard deviation.

RESULTS

Subjects

Fifty participants clinically diagnosed and laboratory confirmed to have uncomplicated malaria were enrolled for the study. Dropout rate for the study was 20.0%: seven participants withdrew voluntarily citing personal reasons after the enrollment procedures with another 3 lost to follow-up. The mean age for the forty participants who completed the study was 42.29 (±12.35) years comprising 25 (71.43%) females and 15 (28.57%) males.

Safety of the herbal product

The herbal product was well tolerated as none of the participants reported any adverse effect during follow-up. The product did not also affect the hematological parameters assessed during the study [Table 1]. End-of-study white blood cell (WBC), HGB, platelet, hematocrit, and red blood cell determinations were not significantly different from the baseline readings. Equally, renal assessment for the safety of the product indicated the product as having no untoward effect on the kidney. Baseline creatinine (66.56 ± 10.53) and urea (4.01 ± 0.95) were comparable to the results obtained after the study and did not show any significant difference. Assessment of the effect of THM on the liver [Table 2] indicated that all the parameters measured such as proteins, albumin, globulin, alanine transaminase, gamma-glutamyl transferase, aspartate transaminase, and alkaline phosphatase 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: Effect of the herbal product "*Time Herbal Mixture*" on the hematological indices of participants before and after the study

Parameter	Baseline $\bar{x}$ ± SD	Day 28 $\bar{x}$ ± SD	*P*
WBC	5.18±1.64	4.86±1.59	0.006
RBC	5.49±5.94	4.61±0.45	0.346
HGB	16.19±17.37	13.78±1.12	0.292
HCT	41.33±5.36	41.87±2.50	0.364
PLT	280.5±69.83	286.7±69.30	0.630

WBC: White blood cell; RBC: Red blood cell; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; SD: Standard deviation

Table 2: Results of the liver and renal assessment for participants treated with *Time Herbal Mixture*

Parameter	Baseline $\bar{x}$ ± SD	Day 28 $\bar{x}$ ± SD	*P*
Protein	73.56±5.34	75.23±4.84	0.451
Globulin	31.38±5.38	30.58±6.25	0.562
ALP	153.4±33.67	154.7±33.44	0.578
ALT	29.50±4.59	29.61±4.55	0.862
AST	28.50±6.29	29.15±4.58	0.612
ALB	36.33±7.00	37.12±4.34	0.407
GGT	2753±7.82	27.70±7.42	0.976
Urea	4.01±0.95	4.17±0.96	0.002
Creatinine	66.56±10.53	67.35±10.71	0.324

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; ALB: Albumin; GGT: Gamma-glutamyl transferase; SD: Standard deviation

Effectiveness of the product

Clinical symptoms and disease indicators

The predominant symptoms reported by participants during the study were the classical signs and symptoms of malaria. These symptoms included oral bitterness, headaches, fever, and chills. Most of the participants reported improvements in their symptoms but for three participants who reported seeing no change in the oral bitterness they experienced. Two other participants also indicated their palpitations persisted despite the treatment. Summary of symptomatic responses to the treatment is reported in Table 3.

Vital signs for participants also improved during the treatment, and mean axillary temperature significantly declined compared to the baseline reading [Table 4]. Improvements were also recorded for the mean arterial blood pressure of the 40 participants. Mean systolic BP at the start of the study was 132 (±15.89) mmHg, and this declined to 128 (±12.85) mmHg at day 7. Mean diastolic pressure also declined compared to baseline, but the difference was not statistically significant. A significant decline was, however, recorded for the mean systolic BP [Table 4].

Parasitemia and primary outcomes

Mean parasitemia for participants declined significantly during the first 7 days of treatment. Parasite count for all participants at enrollment was 848.6 (±169.7)/μL which on follow-up declined to 47.95 (±19.79)/μL on day 7 [Table 5]. Classification of the response to the treatment based on the primary outcome showed 33 (82.5%) achieved complete cure by day 7. Partial efficacy was attained by 6 (15.0%) participants. Per the set criteria, one (2.50%) participant had a response that was classified as a treatment failure. This participant had a baseline parasitemia of 1196/μL which upon treatment declined to 625/μL by day 7.

In general, participants who had an outcome of partial efficacy had a higher parasite count at the baseline than the subgroup that attained the complete cure. A comparison of the parasite count recorded at baseline and day 7 of visits showed a significant improvement ($P < 0.05$) for both the partial efficacy and complete cure groups, as reported in Table 5.

DISCUSSION

Increasing patronage of finished herbal products for the different ailments peculiar to developing countries is a public health issue. This concern is founded on the number of clinically untested products and formulations being rolled out by practitioners, hence the recommendation to evaluate such products for their benefits. It is in this regard that the clinical

Table 3: Symptomatic response of participants to the herbal treatment on day 7

Symptom	Number of participants, *n* (%)	No improvement, *n* (%)	Mild improvement, *n* (%)	Moderate improvement, *n* (%)	Maximum improvement, *n* (%)
Fever	34 (85.0)	-	4 (11.42)	4 (11.42)	27 (77.14)
Chills	35 (87.5)	-	-	2 (5.71)	33 (94.28)
Dizziness	17 (42.5)	-	11 (64.70)	6 (35.29)	-
Headache	40 (100)	-	1 (2.5)	5 (12.50)	34 (85.0)
Loss of appetite	16 (40.0)	-	28 (80.0)	6 (17.14)	1 (2.86)
Bitter taste	35 (87.5)	3 (8.57)	27 (77.14)	5 (14.28)	-
Palpitation	11 (27.5)	2 (5.71)	7 (20.0)	2 (5.71)	-

Table 4: Comparison of the vital signs of participants at baseline and on day 7

Parameter	Baseline reading $\bar{x} \pm$ SD	Day 7 $\bar{x} \pm$ SD	*P*
Temperature	37.88±0.41	37.19±0.15	9.19×10^{-14}
Systolic BP	132±15.89	128±12.85	0.013
Diastolic BP	79.0±11.28	78.5±8.93	0.700

SD: Standard deviation; BP: Blood pressure

Table 5: Comparison of baseline and end-of-study parasitemia levels for all participants and the treatment outcome subgroups obtained in the study

	Number of participants, *n* (%)	Baseline $\bar{x} \pm$ SD	Day 7 $\bar{x} \pm$ SD	*P*
All participants	40 (100.0)	848.6±169.7	47.95±19.79	5.02×10^{-6}
Complete cure	33 (82.5)	448.6±596.1	-	-
Partial efficacy	6 (15.0)	2991±358.5	215±81.72	4.9×10^{-6}
Treatment failure	1 (2.50)	1196±0.00	625±0.00	-

SD: Standard deviation

evaluation of the safety and effectiveness of the Ghanaian herbal product "THM" was undertaken.

Based on the criteria set for classifying the effectiveness of the product, i.e., complete clearance of parasitemia, *THM* can be reported as being effective for the treatment of malaria. The dropout rate of 20.0% obtained for this study is the upper limit accepted during trials,[18] however given that participants were not hospitalized such a situation may not be unusual. At the recruitment phase of the study, 50 participants qualified, 7 withdrew voluntarily for personal reasons, and 3 others lost to follow-up. Dropouts were not included in the analysis.

Over the stipulated 6 days of treatment, baseline parasitemia levels (848.6 ± 169.7) for all the participants declined significantly (47.95 ± 19.79; confidence interval: 478.2–1123; $P < 0.0001$). This improvement in parasite levels also coincided with those observed clinical symptoms reported by patients [Table 3]. Classical signs of malaria, fever and chills, were absent for almost all the participants by day 7 and were equally matched with a decrease in body temperature (37.88 ± 0.41–37.19 ± 0.15; $P < 0.0001$). The parasite clearing ability of *THM* assured that the risk of malaria-related complications will be reduced for users. Equally, the antipyretic property of the product is essential for good clinical outcomes given the risk that comes with persistent pyrexia. The antimalarial activity exhibited by the product gives credence to the reports about the traditional use of the constituent plant materials and also validates the *in vitro* and *in vivo* bioassays conducted on these plants.[19,20] The specific secondary metabolites responsible for the antimalarial actions of these plants are still speculated. *V. amygdalina* has had its antiplasmodial activity linked to the sesquiterpene lactones such as vernolepin, vernolin, vernolide, vernodalin, and hydroxyvernodalin and steroid-related constituents vernonioside BI and vernoniod.[21] *B. buonopozense*'s antimalarial action has been related to the broad class of alkaloids, flavonoids, and terpenes.[22] In the case of *S. torvum,* which is an alkaloid-rich plant, glycoalkaloids such as solamargine, solanine, and solasonine found in the plant and its family may be said to contribute in part to the antimalarial activity of the plant because of their reported antiplasmodial actions.[23] The role of numerous other alkaloids in the antiplasmodial actions of medicinal plants is also well documented.[24,25]

The terpenoid groups again contribute to the antiplasmodial actions of *S. campanulata* and are explained by the presence of hydroxyursoic, ursolic, and tomentosolic acid.[26] These terpenoid compounds supposedly affect the isoprenoid biosynthetic pathway found in the parasite. This isoprenoid pathway is an important metabolic pathway in the development of the trophozoites of *P. falciparum*. In specific instances, other terpenoid compounds such as nerolidol, farnesol, and linalool have been shown to strongly inhibit the biosynthesis of the metabolites such as dolichol and the isoprene side chain of ubiquinones in the protozoan.[27,28] The phosphorylated dolichols have a role as carriers of oligosaccharides in the biosynthesis of glycoproteins and glycosylphosphatidylinositol anchors. The ubiquinones are employed as electron carriers required for the mitochondrial respiratory chain and the prenylated proteins function as signal transducers.[29-31] The crucial role these metabolites play in the survival of the plasmodium parasites makes them ideal targets for antimalarial therapies. Other targets of action reported for plant-based antimalarials include inhibition of hemozoin formation and DNA intercalation. DNA intercalation is a signature of the alkaloids.[32-34]

On the aspect of safety, none of the participants reported any adverse effect arising out of the administration of the product. Detailed assessment for each body system to elicit any new complaints after the initiation of treatment had negative responses. Assessments of other drug-related toxicities on the kidneys, liver, and blood were negative. Comparing the baseline parameters to those obtained after the study [Tables 1 and 2], it was noted that all the liver and kidney indices were normal except for urea which increased to 4.17 ± 0.96. This increase in urea levels was considered clinically and statistically insignificant. A similar observation was made for WBC count. THM was, therefore, safe in the population tested.

CONCLUSION

Considering the current developments in the practice of herbal medicine in Ghana, verification of all products to establish their clinical safety and effectiveness should be paramount. Data from this study indicate the Ghanaian herbal product "THM" is safe and effective for the management of cases of uncomplicated malaria. The product is also able to provide relief for other associated symptoms of malaria.

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Conflicts of interest

There are no conflicts of interest.

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