Evaluation of Efficacy and Safety of Mama Antimalarial Herbal Tablets in adults with Uncomplicated Plasmodium Falciparum Malaria: A Pilot Randomised Controlled Trial

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Abstract **DOI: https://doi.org/10.64052/httwb879**

Background: Malaria, caused by Plasmodium falciparum in humans, is a major cause of morbidity and mortality, especially in sub-Saharan Africa. Herbal preparations for the management of malaria are available in different cultures. MAMA Antimalarial Herbal Tablets (MAHT) were prepared by direct compression from MAMA Powder, which is an herbal antimalarial product already patented and listed for the treatment of malaria in Nigeria. The study evaluated the efficacy and safety of the tablets and compared them with those of Artemether-Lumefantrine tablets in uncomplicated Plasmodium falciparum-infected adults.

Methods: This was a pilot, open-label, randomised controlled Phase II clinical trial. Ten patients with uncomplicated malaria were randomised into each of the two arms of the study using computer-generated random numbers. Ten received MAMA Antimalarial Herbal Tablets (MAHT) and 10 received artemether-lumefantrine (AL). Patients' biodata and clinical information were collected using a proforma. Malaria parasite density was assessed on Days 0, 3, 5, and 7. Safety assessment was done on Days 0, 3 and 28 by measuring haematological, liver and renal function parameters. The data were analysed using SPSS version 25.

Results: Twenty participants were enrolled. Parasite clearance was progressive in both groups, with parasite positivity in the MAHT group declining from 100% at baseline to 80% on Day 3, 20% on Day 5 and 0% on Day 7. In the AL group, parasite positivity declined from 100% at baseline to 80% on Day 3 and 0% on Days 5 and 7. There was no statistically significant difference in parasite clearance between the two groups ($p>0.05$). There was a significant increase in albumin and conjugated bilirubin in the MAHT group on Day 3 and a decrease in haemoglobin in both groups on Day 28, but there was no consistent pattern of laboratory deterioration suggestive of clinically important toxicity in either of the treatment groups.

Conclusion: This pilot study provides a signal of antimalarial activity of MAHT, with progressive parasite clearance observed through Day 7. The serial haematological, hepatic and renal assessments showed tolerability of the antimalarial herbs, but the small sample size precludes firm conclusions regarding efficacy and safety. These preliminary findings require a larger multicentre study to affirm and ratify our experimental outcomes.

Keywords: : Malaria, Antimalarial, Herbal Tablets, Alstonia Boonei, Picralima Nitida, Safety Profile

Introduction

Malaria, caused by *Plasmodium*, is a major cause of morbidity and mortality, especially among under-five children, pregnant women, and non-immune migrants in malaria endemic regions.[1] An estimated 95% of the global malaria cases and 94% of malaria deaths occur in the World Health Organisation (WHO) African Region.[2] Traditional medicine remains an important modality of health care around the world, although reliable estimates of its population-level use remain difficult to establish. In the WHO Global Report on Traditional, Complementary and Integrative Medicine, among the 52 Member States that provided estimates of use, 12 reported that 80–99% of their populations used such medicine, while 14 reported use among 60–79% of their populations.[3] The combination of the powders of *Alstonia boonei* stem bark and *Picralima nitida* seed in a particular ratio has been used in antimalarial therapy in Nigeria. Following the ethnomedical claims and animal experiments as well as through the observational experiences of voluntary users, the formulation has been reported to possess considerable efficacy on chloroquine-sensitive *Plasmodium* in mice.[4,5]

The stem bark of *Alstonia boonei* De Wild.[6,7] and the seed of *Picralima nitida* (Stapf.) Th. & H. Dur. (Apocynaceae) have been ethnomedically documented among the commonly used antimalarial plants in Nigeria and West Africa. Preclinical investigation into the activity of the combination of the plants in the ratio 1:1 revealed safety and significant activity against *Plasmodium* in rodent models. *A. boonei* stem bark and *P. nitida* were combined in the ratio of 1:2, gave the best antimalarial chemosuppressive activity (64.4 %) at a very low dose of 12.5mg/kg, which was not significantly different from chloroquine (70.3 %, 5mg/kg).[4] The safety profile was also determined using acute and sub-chronic toxicity, neuro-behavioural properties and the histopathology of

vital organs of mice. No acute or sub-chronic toxicity was observed, while the histopathology analysis revealed essentially normal organs.[4] Further evaluation of *MAMA* powder at a particle-size range of 120–250 µm and suspended in polyethylene glycol revealed higher antimalarial activity (82%, 6.25mg/Kg).[8]

MAMA Powder®, the component of MAHT, was patented and officially listed by the National Agency for Food and Drug Administration and Control, with the NAFDAC registration number A7-2352L. Before this time, *MAMA Powder®* had been in use without any observed or reported adverse effects. In recent times, the tablet dosage form, MAMA Antimalarial Herbal Tablet (MAHT), has been introduced without reported adverse effects. However, there is no clinical data to support the safety profile and claimed efficacy of the herbal product in humans with malaria.

Artemether-lumefantrine (AL) is a first-line antimalarial drug which has been recommended by the WHO and has proven efficacy in the treatment of uncomplicated *Plasmodium falciparum* malaria.[9] This study investigated MAHT, obtained by direct compression of *MAMA Powder®* to generate preliminary clinical evidence for its use as an alternative treatment. The study aimed to evaluate the safety profile of MAHT and compare its efficacy with AL in adults with uncomplicated *Plasmodium falciparum* malaria. We hypothesised that there was no statistical difference in parasite clearance and clinical treatment outcome between MAHT and AL.

Material and Methods

Study Design: It was a pilot, open-label, randomised controlled Phase IIa clinical trial. It was conducted to provide preliminary evidence on the antimalarial activity and tolerability of MAHT compared to AL in adults with uncomplicated *Plasmodium falciparum* malaria. In this study, AL was the standard against which the preliminary antimalarial activity and tolerability of the investigational MAHT preparation was assessed. With respect to treatment allocation, participants and treating clinicians were aware of the treatment administered. The malaria microscopists and data analyst, during the initial analysis, were blinded with respect to treatment allocation to minimise observer bias in the assessment of parasitaemia and tolerability respectively.

Study Site and Study Population

This study was conducted between May 2022 and June 2022 at Iyiola Hospital, Ile-Ife, Osun State in South-Western Nigeria. The study participants were adults between the ages of 18 and 65 years with uncomplicated malaria. A diagnosis of uncomplicated malaria was made when the participants had a history of fever with or without an axillary temperature of ≥37.5 ºC; parasite density count of between 2 000 and 200 000 parasites⁄µl on Giemsa-stained thick film; and ability to swallow oral medication. Patients with sickle cell anaemia, severe malnutrition and a history of hypersensitivity to any of the study drugs were excluded from the study.

Sample Size, Sampling Technique and Randomisation of Study Participants

Ten participants on each arm of the trial, giving a total sample size of 20 participants, were enrolled pragmatically in this external pilot to assess recruitment, randomisation, supervised treatment administration, follow-up and completeness of serial parasitological and safety assessments, while getting initial information on outcome variability to inform a subsequent adequately powered trial and not to demonstrate comparative efficacy, equivalence or non-inferiority. Written informed consent was obtained from each of them. They were randomised into the treatment groups in a ratio of 1:1. The allocation sequence was generated by the principal investigator using computer-generated random numbers. The allocation sequence was concealed in 20 sealed, similar, tamper-proof, opaque brown envelopes (10 MAHT/10 AL), each placed in a box. After enrolment, each participant picked an envelope from the box at random. The envelope was opened by a research assistant who administered the treatment. The test group was MAHT while the control group was AL.

Data Collection

Clinical and laboratory data were recorded on each of the follow-up days by the study physicians on the case report forms developed in line with the World Health Organisation proforma for antimalarial therapeutic efficacy trials. They include weight, axillary temperature (measured with a mercury thermometer (U-MECR) to the nearest 0.1°C), history of fever in the previous 24 hours, and laboratory parameters.

Laboratory Procedures

For screening for eligibility on Day 0, malaria infection was confirmed with a histidine-rich protein-2-based malaria rapid diagnostic test kit. For each eligible participant, 8 mL of venous blood was collected and used as follows: 2.5 mL for FBC, 5 mL for LFT and E/U/Cr. One drop was collected in the centre of the slide for the thin film and two more drops on another slide for a thick film. Random blood glucose was measured with a drop of capillary blood. Additionally, two drops of blood for thick film for malaria parasite density were taken on Day 3, 5, and 7 while 8 mL of blood was collected for FBC (3 mL), LFT and E/U/Cr (5 mL) on Day 3 and 28. Each participant's study identification number and study follow-up day number were written on the frosted edge of each grease-free slide and specimen bottle.

The study microscopists prepared, fixed, and stained thin and thick films for malaria parasites.10 Two microscopists independently examined each slide using a light microscope set at ×1000 magnification. The number of asexual parasites that were observed was divided by the number of white blood cells (WBCs), and then multiplied by an assumed normal WBC level of 8,000/ µL of blood, to calculate the malaria parasite density.10 If no parasite was found after examining 200 microscope fields, a slide was considered parasite-negative.10 The average of the two counts was taken as the parasite density. A malaria parasitologist re-examined the slide if the parasite density showed a discordance of more than 25%. The average of the two most reliable counts is taken.

Preparation of MAMA Antimalarial Herbal Tablets

MAMA Herbal Antimalarial Tablet was prepared by compressing a uniform volume of MAMA Powder (750mg) by direct compression in the Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife.

Drug Administration

The participants randomised into the MAHT group received MAMA Antimalarial Herbal Tablets®, an investigational two-herb preparation containing *Alstonia boonei* and *Picralima nitida* in a 1:2 ratio. MAHT was administered at the protocol-specified dose of 3.13 mg/kg/day in two divided doses. The dosing schedule for most adults comprised four tablets twice daily for three days. Those randomised to the artemether-lumefantrine group received Coartem® manufactured by Novartis Pharmaceuticals, given as a co-formulated tablet of 80/480 mg given at the time of initial diagnosis, after eight hours and then twice daily on each of the following two days.9 Each study participant was given a slip bearing his/her study identification number and the days of follow-up. The first doses of both treatments on Day 0, were administered under supervision while the participants were still in the hospital. They were later seen in the hospital on the morning of Days 1 and 2 for direct supervision of the morning doses and monitoring of treatment response. A designated clinician called each of them on the phone at the time when the evening dose was due to monitor their treatment response and adherence.

Follow-up

Besides the follow-up on Day 1 and 2 mentioned above for participants randomised to the MAHT group, all participants were followed up on days 3, 5, 7, and 28. On each of the days, each participant's temperature was measured during the visits and they were asked if there were any adverse events since the last visit. An adverse event was regarded as any sign or symptom that did not exist before the commencement of treatment but occurred during treatment or follow-up.[10,11] Blood samples were collected for scheduled investigations.

Safety Protocol

All 20 participants were assessed for adverse events throughout the treatment period and follow-up through Day 28. For those randomised into the MAHT group, participants' safety measurements were prespecified in the study protocol. These included clinical monitoring, predefined criteria for treatment discontinuation and rescue therapy, giving free Coartem® to participants who had been treated with MAHT in the event of persistent parasitaemia or clinical deterioration, and appropriate management and reporting of adverse events. We assessed the safety of the trial drug clinically and through serial haematological, hepatic and renal investigations. Adverse events were assessed for severity and causality. In case of any serious adverse event, the protocol specified that such events would be managed and reported in accordance with ethical requirements. No adverse events or serious adverse events were reported in either treatment group. There were no treatment discontinuations due to adverse events, and no participant developed clinical deterioration, persistent parasitaemia, or required rescue antimalarial treatment.

Study endpoints

The primary endpoints of treatment of uncomplicated malaria were complete parasite clearance and incomplete parasite clearance. Complete parasite clearance was defined as the ability of the treatment to totally clear parasites by Day 7 of the study, while incomplete parasite clearance was defined as the presence of parasites on Day 7.12 The secondary endpoints are the safety profile and tolerability of the two treatment regimens. The safety profile was assessed by measuring haematological, liver function, and renal indices on Day 0, 3, and 28, while tolerability was assessed by the participants' reports of adverse events.

Data analysis

Data were analysed using the Statistical Product and Service Solutions software version 25 (SPSS, Chicago, IL, USA). The distribution of continuous variables was assessed using visual inspection of histograms and Q–Q plots and the Shapiro–Wilk test. As this was a small pilot study with limited sample size, inferential analyses were considered exploratory. Continuous and normally distributed variables such as the mean age, weight, baseline temperature, and malarial parasite density of the participants were summarised using mean and standard deviation, and the safety profile of the treatments was analysed by conducting paired t- tests of changes in laboratory parameters over follow-up. A p-value of < 0.05 was taken as statistically significant. Statistical findings were interpreted cautiously, with emphasis on the magnitude and direction of observed changes rather than statistical significance alone. The independent variables are the two treatment groups, while the dependent variables are malaria parasite density, malaria parasite clearance, cure rate, drug safety, and adverse effects.

Ethical Considerations

The study protocol was approved by the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife (ERC/2019/08/02). The study was further registered with the Pan African Clinical Trials Registry, Cochrane South Africa (PACTR202202608761158). Signed written informed consent was obtained from each participant before their recruitment into the study. The data were collected anonymously. Each participant was given a token equivalent to $2 on every follow-up day to cover the costs of transportation to the hospital.

Results

Of the 32 patients that were screened, 20 were found eligible for the study; all 20 were randomised, with 10 participants allocated to receive MAHT and 10 to receive AL. All randomised participants commenced their assigned treatment and were included in the analysis. There were no withdrawals, losses to follow-up, or major protocol deviations during the study period; consequently, the analysis population comprised 10 participants in each treatment arm. Table 1 below shows the baseline characteristics and treatment groups of the study participants. The participants in the AL and MAHT groups were generally comparable at baseline. The mean age was 31.5 ± 9.7 years in the AL group and 38.9 ± 13.2 years in the MAHT group, with no statistically significant difference between the groups (p=0.170). Similarly, there were no significant differences in age categories (p=0.118), sex distribution (p=0.656), mean weight (60.26 ± 13.06 kg vs 70.40 ± 15.78 kg; p=0.135), or mean baseline temperature (37.90 ± 0.28°C vs 37.65 ± 0.57°C; p=0.228) between the AL and MAHT groups, respectively. Baseline malaria parasite density was also comparable between the AL and MAHT groups (7,778.0 ± 852.84 vs 7,731.0 ± 1,722.73 parasites/µL; p=0.939). Overall, there was no statistically significant difference in the measured baseline characteristics between the two treatment groups.

Table 1: Baseline Characteristics of Study Participants by Treatment Groups

Characteristics	AL n (%)	MAHT n (%)	statistic	p-value
Age (years)				
18–23	2 (20.0)	2 (20.0)	4.267⁺	0.118
24–44	7 (70.0)	3 (30.0)		
45–65	1 (10.0)	5 (50.0)		
Mean ± SD	31.5 ± 9.7	38.9 ± 13.2	−1.428ᵗ	0.170
Sex				
Male	6 (60.0)	4 (40.0)	0.653⁺	0.656
Female	4 (40.0)	6 (60.0)		
Weight (kg)				
55.0–64.9	4 (40.0)	6 (60.0)	2.019⁺	0.364
65.0–74.9	1 (10.0)	2 (20.0)		
75.0–84.9	5 (50.0)	2 (20.0)		
Mean ± SD	60.26 ± 13.06	70.40 ± 15.78	−1.565ᵗ	0.135
Temperature (°C)				
36.4–37.4	7 (70.0)	0 (0.0)	0.395⁺	0.537
37.5–38.4	2 (20.0)	8 (80.0)		
38.5–39.4	1 (10.0)	2 (20.0)		
Mean ± SD	37.90 ± 0.28	37.65 ± 0.57	1.249ᵗ	0.228
Malaria parasite density (parasites/µL)				
Mean ± SD	7,778.0 ± 852.84	7,731.0 ± 1,722.7	0.077ᵗ	0.939

Note: ⁺ Fisher's exact test; ᵗ independent-samples t-test. AL = artemether-lumefantrine; MAHT = MAMA Antimalarial Herbal Tablets

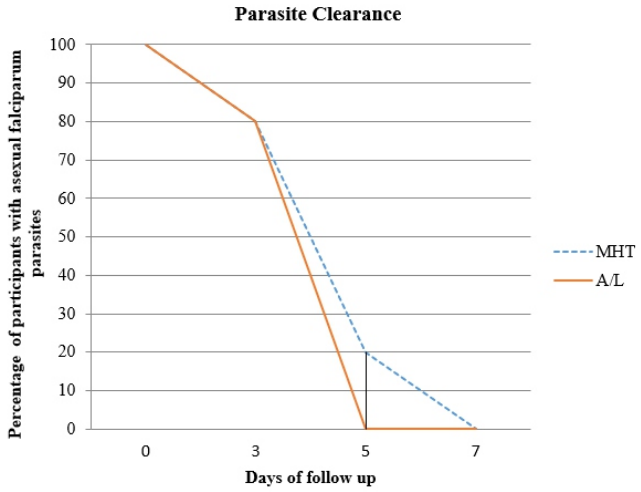

Figure 1. Parasite clearance of AL and MAHT

Figure 1 shows a progressive decline in parasite positivity following treatment with both artemether-lumefantrine (AL) and MAMA antimalarial herbal tablets (MAHT). In the MAHT group, parasite positivity declined from 100% at baseline to 80% on Day 3, 20% on Day 5 and 0% on Day 7. In the AL group, parasite positivity declined from 100% at baseline to 80% on Day 3 and 0% on Days 5 and 7. Although the pattern suggests more rapid parasite clearance with AL, both treatments achieved complete parasite clearance by Day 7.

Table 2: Changes in haematological parameters from baseline through Follow-up among Participants Treated with MAHT and AL

Investigations	MAHT			AL		
	Day 0 Mean ± SD n=10	Day 3 Mean ± SD n=10	p-value	Day 0 Mean ± SD n=10	Day 3 Mean ± SD n= 10	p-value
Full Blood Counts						
Haemoglobin (g/dl)	13.00 ± 0.81	12.99 ± 0.81	0.935	12.12 ± 1.41	12.04 ± 1.39	0.609
Total WBC (x10³cells/µL)	6.64 ± 1.66	6.70 ± 1.65	0.592	8.14 ± 2.09	6.94 ± 2.49	0.008*
Neutrophil (%)	50.40 ± 10.41	48.00 ± 11.92	0.035*	50.20 ± 21.35	50.60 ± 21.05	0.443
Platelet (x10³ cells/µL)	243.10 ± 40.86	243.80 ± 40.25	0.905	175.00 ± 44.52	198.80 ± 30.01	0.236

Investigations	Day 0 Mean ± SD n=10	Day 28 Mean ± SD n=10	p-value	Day 0 Mean ± SD n=10	Day 28 Mean ± SD n= 10	p-value
Full Blood Counts						
Haemoglobin (g/dl)	13.00 ± 0.81	12.52 ± 0.96	0.021*	12.12 ± 1.41	11.60 ± 1.24	0.008*
Total WBC (x10³ cells/µL)	6.64 ± 1.66	6.81 ± 1.27	0.268	8.14 ± 2.09	5.88 ± 2.02	0.056
Neutrophil (%)	50.40 ± 10.41	48.70 ± 15.46	0.548	50.20 ± 21.35	39.00 ± 12.54	0.051
Platelet (x10³ cells/µL)	243.10 ± 40.86	243.10 ± 40.86	---	175.00 ± 44.52	216.60 ± 35.44	0.036*

P-values are from paired t-tests comparing Day 0 with the respective follow-up day within each treatment group. *Statistically significant at $p < 0.05$. SD: standard deviation; WBC: white blood cell count.

Table 2 shows the changes in haematological parameters following treatment. In the MAHT group, neutrophil percentage changed significantly between Day 0 and Day 3 ($p = 0.035$), while haemoglobin concentration, total WBC, and platelets did not. By Day 28, the MAHT group showed significant reductions in haemoglobin concentration ($p = 0.021$). In the AL group, total WBC reduced significantly between Day 0 and Day 3 ($p = 0.008$), while by Day 28 haemoglobin concentration reduced significantly ($p = 0.008$) and platelet count showed a statistically significant increase ($p = 0.036$). Overall, no consistent pattern of clinically concerning haematological deterioration was observed with either treatment during follow-up.

Table 3: Changes in Liver Function Parameters from Baseline through Follow-up among Participants Treated with MAHT and AL

Investigations	MAHT			AL		
	Day 0 Mean ± SD n=10	Day 3 Mean ± SD n=10	p-value	Day 0 Mean ± SD n=10	Day 3 Mean ± SD n=10	p-value
LFT						
Protein (g/L)	73.30 ± 3.92	73.00 ± 4.74	0.726	75.00 ± 6.67	75.20 ± 7.25	0.937
Albumin (g/L)	33.50 ± 2.22	34.50 ± 2.42	0.015*	42.40 ± 4.65	41.00 ± 4.81	0.072
Total Bilirubin (µmol/L)	9.20 ± 2.90	9.40 ± 3.98	0.790	9.40 ± 3.98	12.60 ± 6.24	0.241
Conjugated Bilirubin (µmol/L)	2.90 ± 1.20	5.20 ± 2.25	0.004*	5.20 ± 2.25	6.60 ± 4.14	0.465
ALP (U/L)	104.00 ± 26.33	102.00 ± 25.71	0.112	153.40 ± 125.47	154.00 ± 157.72	0.961
ALT (U/L)	12.20 ± 2.82	12.30 ± 2.83	0.832	6.40 ± 2.55	4.80 ± 2.94	0.016*
AST (U/L)	14.20 ± 3.43	14.30 ± 4.16	0.904	13.60 ± 6.17	11.20 ± 3.36	0.171
GGT (U/L)	27.40 ± 9.28	26.20 ± 8.26	0.313	38.00 ± 17.10	36.00 ± 12.72	0.377

Investigations	Day 0 Mean±SD n=10	Day 28 Mean±SD n=10	p-value	Day 0 Mean±SD n=10	Day 28 Mean±SD n= 10	p-value
LFT						
Protein (g/L)	73.30 ± 3.92	73.30 ± 5.72	1.000	75.00 ± 6.67	78.60 ± 5.23	0.289
Albumin (g/L)	33.50 ± 2.22	34.70 ± 4.00	0.126	42.40 ± 4.65	40.60 ± 4.14	0.439
Total Bilirubin (µmol/L)	9.20 ± 2.90	9.40 ± 3.57	0.801	9.40 ± 3.98	9.40 ± 3.37	1.000
Conjugated Bilirubin (µmol/L)	2.90 ± 1.20	3.40 ± 1.07	0.177	5.20 ± 2.25	4.20 ± 1.40	0.186
ALP (U/L)	104.00 ± 26.33	108.80 ± 34.10	0.435	153.40 ± 125.47	159.20 ± 152.01	0.564
ALT (U/L)	12.20 ± 2.82	11.60 ± 2.76	0.394	6.40 ± 2.55	6.40 ± 1.96	1.000
AST (U/L)	14.20 ± 3.43	13.70 ± 4.24	0.381	13.60 ± 6.17	12.20 ± 3.36	0.508
GGT (U/L)	27.40 ± 9.28	26.70 ± 9.17	0.257	38.00 ± 17.10	38.80 ± 17.03	0.869

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

p-values are from paired t-tests comparing Day 0 with the respective follow-up day within each treatment group.

Table 3 shows the changes in liver function parameters at baseline and during follow-up among participants treated with MAHT and AL. In the MAHT group, albumin ($p = 0.015$) and conjugated bilirubin ($p = 0.004$) increased significantly by Day 3, while ALT, AST and GGT remained essentially unchanged. In the AL group, ALT decreased significantly on Day 3 ($p = 0.016$). There were no significant changes in any liver function parameters in either treatment group between Day 0 and 28. Overall, the findings suggest

no consistent evidence of clinically important hepatic toxicity with either treatment during follow-up.

Table 4 shows that there were no statistically significant changes in serum urea or creatinine from baseline to Day 3 or Day 28 in either treatment group (all p>0.05). In the MAHT group, urea remained relatively stable from 3.67 ± 0.59 mmol/L at baseline to 3.62 ± 0.61 mmol/L on Day 3 and 3.83 ± 0.65 mmol/L on Day 28. Similarly, creatinine changed minimally from 79.40 ± 9.59 µmol/L at baseline to 79.70 ± 10.11 µmol/L on Day 3 and 78.30 ± 5.56 µmol/L on Day 28. In the AL group, urea decreased slightly from 3.08 ± 0.94 mmol/L at baseline to 2.96 ± 0.32 mmol/L on Day 3 and increased to 3.14 ± 0.43 mmol/L by Day 28, while creatinine decreased from 105.00 ± 18.05 µmol/L at baseline to 98.80 ± 21.19 µmol/L on Day 3 and 100.60 ± 16.51 µmol/L on Day 28. None of these changes was statistically significant. Overall, the findings indicate that neither MAHT nor AL was associated with significant changes in the measured renal function parameters during the follow-up period.

Table 4: Changes in Renal Indices from Baseline through Follow-up among Participants Treated with MAHT and AL

Investigations	MAHT			AL		
	Day 0 Mean ± SD n=10	Day 3 Mean ± SD n=10	p-value	Day 0 Mean ± SD n=10	Day 3 Mean ± SD n= 10	p-value
Renal Indices						
Urea (mmol/L)	3.67 ± 0.59	3.62 ± 0.61	0.644	3.08 ± 0.94	2.96 ± 0.32	0.631
Creatinine (µmol/L)	79.40 ± 9.59	79.70 ± 10.11	0.878	105.00 ± 18.05	98.80 ± 21.19	0.425
	Day 0 Mean ± SD n=10	**Day 28 Mean ± SD n=10**	**p-value**	**Day 0 Mean ± SD n=10**	**Day 28 Mean ± SD n= 10**	**p-value**
Renal Indices						
Urea (mmol/L)	3.67 ± 0.59	3.83 ± 0.65	0.129	3.08 ± 0.94	3.14 ± 0.43	0.772
Creatinine (µmol/L)	79.40 ± 9.59	78.30±5.56	0.513	105.0 ± 18.05	100.60 ± 16.51	0.316

p-values are from paired t-tests comparing Day 0 with the respective follow-up day within each treatment group.

Discussion

This pilot trial provides preliminary clinical evidence on the efficacy and tolerability of MAHT in adults with uncomplicated Plasmodium falciparum malaria using AL as an active comparator. Parasite clearance and laboratory safety indices suggest MAHT possesses antimalarial activity without causing overt acute organ toxicity. These human clinical findings represent an important translational step from traditional use and preclinical antiplasmodial evidence toward formal evaluation of this standardised formulation.

The apparent antimalarial activity of MAHT aligns with earlier experimental studies on its constituent plants, *A. boonei* and *P. nitida*.[5-7,13] Preclinical work demonstrated significant chemosuppressive and curative activity for *A. boonei* stem bark and *P. nitida* seed combinations, particularly at a 1:2 ratio. AL was chosen as a comparator per current WHO recommendations for uncomplicated malaria. Contemporary Nigerian data confirm AL's high therapeutic efficacy (94.7% PCR-uncorrected; 100% PCR-corrected Adequate Clinical and Parasitological Response in Ile-Ife).14 While outcomes in our AL arm align with these regional data, the lack of a statistically significant difference between MAHT and AL in this pilot study showed a promising result which requires further evaluation in a larger multicentre trial.

Some laboratory parameters changed significantly during follow-up, including conjugated bilirubin in the MAHT group on Day 3 and haemoglobin in both groups on Day 28. These changes were not associated with clinical deterioration, adverse events, or predefined toxicity thresholds requiring treatment discontinuation or rescue therapy. All laboratory results were all within the normal reference range. However, given the small sample size, these findings provide only preliminary evidence of short-term MAHT tolerability and cannot exclude uncommon or delayed adverse effects. Although parasite clearance by Day 7 confirms initial activity, this reflects short-term parasitological clearance rather than definitive cure, which requires standard WHO 28-day follow-up. Furthermore, while the absence of reported adverse events and stable hepatic/renal indices align with preclinical safety profiles of the *A. boonei–P. nitida* combination, exposing only 10 participants to MAHT cannot exclude uncommon or idiosyncratic reactions.

The key limitations of this pilot study include the small single-centre sample size, lack of Day 28 PCR-corrected endpoints, and limited serial parasite-density measurements. Nevertheless, these findings demonstrate that standardised traditional formulations can undergo conventional clinical evaluation—a crucial step for identifying novel antimalarial candidates amid rising drug resistance without replacing established ACTs.

Conclusion

This pilot randomised controlled trial provides preliminary evidence that MAHT possesses antimalarial activity and an encouraging short-term tolerability profile in adults with uncomplicated *P. falciparum* malaria. The findings call for further clinical development of the formulation but are not sufficient to establish therapeutic equivalence to artemether–lumefantrine or to confirm safety in a broader population. A larger, multicentre randomised controlled trial with adequate power using standardised WHO therapeutic-efficacy endpoints, appropriate molecular correction of recurrent parasitaemia and comprehensive safety monitoring is recommended.

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Conflicts of interest

AA Elujoba, AO Adepiti, BA Adeagbo, and GE Adetogun are the developers of MAHT. The remaining authors declare no competing financial or non-financial interests related to this work.

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