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Evaluation of the interaction between the ethanol pulp extract of *Chrysophyllum albidum* and Artemether/ Lumefantrine

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Abstract

Objective: Though *Chrysophyllum albidum* has antimalarial and antioxidant property, it is commonly consumed as a fruit in the South East Nigeria. There could be possible pharmacodynamics and pharmacokinetics interaction if the fruit is consumed while on malaria treatment with artemether-lumefantrine.

The study was designed to investigate the possible enhancement of the antimalarial potency as well as possible herb-drug interaction resulting from concurrent administration of artemeter-lumefantrine and *Chrysophyllum albidum*.

Materials and methods: Combinations of artemeter-lumefantrine and *Chrysophyllum albidum* were investigated in Antiplasmodial activity using curative test procedure. Forty mice were infected with *P. berghei*-infected red blood cells by intraperitoneal injection. The animals (23-27g, 5-6 weeks old) were divided into 8 groups (n=5). There were treated with 250 mg/kg, 500 mg/kg and 1000 mg/kg of the extract in combination with 20 mg/120 mg of artemether-lumefantrine. The parasitemia level was determined by counting the number of parasitized erythrocytes in random fields of the microscope. The effect of *Chrysophyllum albidum* on the pharmacokinetics of Artemether-lumefantrine (A/L) in mice was studied in three phases. Each phase was done utilizing a total of 30 rats assigned to 5 groups of 6 animals to which was administered A/L and/or the plant extract orally, after an overnight fast, with feeding and access to water resuming 2 h after drug administration. Concentration of artemether-lumefantine was determined using modified validated liquid chromatography assay.

Results: The combination of the pulp extract and Artemether-lumefantrine at tested doses of 250, 500 and 1000 mg/kg produced significant ($p< 0.05$, 0.01 and 0.001), dose dependent parasitaemia suppression (88.81, 94.58 and 100%) compared to the negative control group. The plasma concentration of *Chrysophyllum albidum* +Artemether-lumefantrine had a concentration of (56 ng/mg) at 30 minutes. The overall systemic exposure of AL, represented by the AUC, increased by 56.05% when CAL was concurrently administered and by 296.97% when the mice were pre-treated with the decoction.

Conclusion: *Chrysophyllum albidum* extract has a potential to increase the antimalaria property of Artemether-lumefantrine due to probable inhibitory effect on Artemether-lumefantrine metabolism by *Chrysophylum albidum*. The

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pharmacokinetics of Artemether-lumefantrine like systemic exposure and half-life were also affected by *Chrysophylum albidum.*

Keywords: Herb–drug interaction; Plasmodium berghei; Malaria chemosuppression; *Chrysophylum albidum*; Malaria parasite clearance

1. Introduction

Malaria continues to pose a greater threat to humankind and presents a significant public health setback. It is also regarded to be among the most frequent contagious diseases in the world today. The World Health Organization (WHO) African Region with an estimated 233 million malaria cases, accounted for 94% of the 249 million cases globally in 2022 [13]. The burden of malaria on households and the economies of endemic zones in Africa remain significant [12]. This is somewhat the effects of low productivity due to loss of productive workdays in a single episode of malaria infection. Malaria is caused by five plasmodia species such as *Plasmodium ovale, Plasmodium vivax, Plasmodium falciparum, Plasmodium malaria* and *Plasmodium knowlesi.* The deadliest strain causing about 99% of the deaths in Africa. The growth and replication of Plasmodium parasites begins when the vector sucks up the mature-stage (V) gametocytes during blood meal of infected human, in the mosquito's mid-gut is where the gametocytes replete its sporogonic life-cycle making the vector infectious to uninfected humans as the mosquito harbours numerous sporozoites within their salivary glands [4].

The pathophysiology of human malaria has been suggested to be as a consequence of the blood-stage Plasmodium parasite cycle inside of the human host. Generally, about 80% of people in Africa and by extension, 70% to 75% of Nigerians heavily depend on plant-source medicine to treat various diseases including malaria [2]. This suggests an intense desire and preference for the use of plant or herb-based medicine in the maintenance of the health of the majority of Nigerians, despite the availability of orthodox medication in Nigeria. Some herbal remedies have been known to alter drug dispositions as shown by significant changes in parameters like, area under the time-plasma-concentration curve (AUC), peak concentration (Cmax), and elimination half-life (T1/2) [10]. Drug-herbal interactions can either be pharmacokinetic or pharmacodynamics in nature. Pharmacokinetic interaction results from alteration in a drug's absorption, distribution, metabolism and elimination characteristics. Pharmacodynamics interaction is a result of the influence of the combined treatment at a site of biological activity. Artemether-lumefantrine (A/L) is a standard ACT antimalarial recommended by WHO for the treatment of malaria. A/L is metabolized by the liver through oxidation by CYP450 enzymes followed by glucoronidation to produce soluble compounds that are excreted.

Chrysophyllum albidium belongs to the family sapotaceae. It is commonly called Agbalumo in Yoruba, Udala in Igbo and Agbaluba in Hausa languages. This plant is also referred to as "The white star apple" [3]. This plant is highly rich in flavonoids, steroids, glycosides and saponins and thus serves as a source of anti-inflammatory, anti-spasmodic, as well as possesses diuretic properties, [3]. It has been found to possess chemosuppressive, prophylactic and curative antimalarial properties [7] hence the need to check for the interaction between the pulp of *Chrysophyllum albidum* and standard antimalarial agents like artemether-lumenfantrine.

2. Material and methods

Spectrophotometer (B. Bran Scientific &Instrument Company, England), Analytical Weighing Balance (Metler H30, Switzerland), Glass column, flasks, beakers, test tubes, measuring cylinders, rotary evaporator, Electric Oven (Gallenkamp, England), Water Bath (Techmel and Techmel, Texas, USA), National Blender (Japan), Micropippete (Finnipipette® Labsystems, Finland), syringes and needles, medical hand gloves and disserting kits. artemether-lumefantrine (coartem), Giemser stain and *P.bergei*.

2.1. Plant Extraction

Fresh *Chrysophyllum albidum* pulp was collected by carefully removing the epicarp and seed. The pulp was blended using an electric blending machine. Then, about 400g of the blended sample was macerated in 1 litre of ethanol for 72hrs. It was sieved with muslin cloth, filtered with No.1 whatman filter paper. The extract was concentrated using rotary evaporator at reduced temperature and pressure. It was further dried using water bath at 400C. The extract was stored in the refrigerator.

2.2. Acute toxicity test

2.2.1. Phase 1

This phase requires nine animals. The nine animals were divided into three groups of three animals each. Each group of animals was administered different doses (10, 100 and 1000 mg/kg) of the crude extract. The animals were placed under observation for 24 hours to monitor their behavior as well as if mortality will occur.

2.2.2. Phase 2

This phase involves the use of four animals which were distributed into four groups of one animal each. The animals were administered higher doses (2000, 3000, 4000 and 5000 mg/kg) of plant extract if all the animals in phase 1 survive. Animals were observed for 24 hours for behavior as well mortality.

Then the LD50 is calculated by the formula:

$LD50 = \sqrt{(D0 \times D100)}$

D0 = Highest dose that gave no mortality.

D100 = Lowest dose that produced mortality

2.3. Detection of analytical wavelength for pure drug sample and plant extract

HPLC was carried out using a ThermoFinningan LCQ-Deca mass spectrometry connected to a UV detector. The samples to be used for the HPLC analysis were injected to the HPLC/ESI-MS set up. A solution of the sample was sprayed at the atmospheric pressure through a 2-5kV potential. HPLC was run on a Eurospher C-18(6* 2 mm, i.d) reverse phase column. The mobile phase was H20 0.1% Formic acid (A) to which MeOH (B) or ACN (C) was added by a linear gradient: initial,0% of B ; 45min, 80% of B ;55 min, 100% of B. The flow rate was at 400ul/min and the absorbence was detected at 254nm. Electron ionization was performed at a capillary temperature of 200oc and drift voltage of 20cv.

2.4. Antiplasmodial activity

Rane curative test procedure was used. Forty mice were infected with *P. berghei*-infected red blood cells by intraperitoneal injection on the first day. At 72 h post-infection when the level of parasitemia would have been >4%, the animals (23-27g, 5-6 weeks old) was divided into 8 groups (n=5). There were 6 test groups: 3 of the test groups received orally, 250mg/kg, 500mg/kg and 1000mg/kg of the extract. While the other 3 received orally 250mg/kg, 500mg/kg and 1000mg/kg of the extract in combination with 20mg/120mg of artemether/lumefantrine (commercial drug). Two control groups were used, negative control (infected and treated with 0.09ml distilled water) and positive control (infected and treated with 8mg/kg artemether/lumefantrine). Blood samples were collected from the animals on day 4 and day 7 post treatments.

2.5. Parasitemia monitoring

Parasitemia was monitored using a previously described method. Blood samples were collected from the tip of the tails of the animals. Thin blood films will be dried and fixed for 15 mins using methanol was stained subsequently using 10 % Glemsa for 25 mins. The stained films were washed off using phosphate buffer, pH 7.2 and was dried. The films were then be immersed in oil and viewed at 100x magnification. The parasitemia level was determined by counting the number of parasitized erythrocytes in random fields of the microscope.

2.6. Cage side observation.

Changes in feeding and body weight was monitored on daily bases.

2.7. Drug Interaction Study

The method described by Adepiti [1] on the interaction of herbal decoction and an antimalarial was adopted and modified to fit the present study. The effect of *Chrysophyllum albidum* on the pharmacokinetics of Artemether-lumefantrine (A/L) in mice was studied in three phases. Each phase was done utilizing a total of 30 rats assigned to 5 groups of 6 animals to which was administered A/L and/or the plant extract orally, after an overnight fast, with feeding and access to water resuming 2 h after drug administration. In the first phase, single oral doses of Artemether-lumefantrine (pure drug) (20 mg/kg) prepared in distilled water at a final volume of 200 µL was administered.

Thereafter, each animal was anesthetized for 3–5 min and blood (0.6–1.0 ml drawn by retro-orbital venous plexus at 0, 0.25, 0.5, 1, 2, 4, 6, 25, 30, 48, 54, 72, 96, 168and 246 h. After the last dose from all animals (n=6) for each time point. All blood samples were immediately transferred into heparinized tubes and centrifuged at about 3000×g for 10 min for plasma collection.

For the second phase, all study animals were administered single, concurrent, oral doses of Artemether-lumefantrine and plant extract. Blood was collected and processed as earlier described for the first phase. In the final phase, all study mice were pre-treated orally with the plant extract, once daily, for 3 days. This was followed by the administration of single oral doses of Artemether-lumefantrine along with the last dose of the plant extract on day 3. Blood samples was similarly collected and processed as described for the earlier phases. All biological samples were used for analysis immediately they are collected.

2.8. Plasma analysis

Concentration of artemether-lumefantrine was determined using validated liquid chromatography assay as described earlier with some modification.

2.9. Pharmacokinetic Data Analysis

The sampling period of 0–246 h in the present study was based on an earlier human study as described by (FDA, 2002). Concentration–time data across the three phases of the study was fitted by a non-compartmental model, using WinNonlin (version 5.3, Pharsight Corp, Mountain View, CA, USA), for the determination of pharmacokinetic end points. Mean ratios alongside their 90% confidence intervals was computed for the maximum concentrations of A/L to assess the significance of the plant interactions. Quantification of A/L was done through a validated high-performance liquid chromatography (HPLC) method.

2.10. Statistical analysis

Results gathered from the study was analyzed using statistical package for social sciences (SPSS-25). Results was presented as mean ± Standard error of mean (SEM) of sample replicates. Raw data was subjected to one-way analyses of variance (ANOVA) followed by post hoc turkey's test. $P<0.05$ was considered to be statistically significant.

3. Results

Table 1 Results of Phytochemical Analysis of ethanol extract of Chrysophyllum albidum pulp

	Phytochemical	**Crude extract**
1	Tannins	+ + +
2	Alkaloids	+++
3	Phenol	++
4	Flavonoids	+++
5	Cardiac glycosides	+++
7	Saponins	+++
8	Fats and oils	++
9	Steroids	+++
10	Terpenoids	++
11	Proteins	---

(-) => Not Present; (+) => Present in small concentration; (++) => Present in moderately high concentration; (+++) => Present in high concentration

3.1. Acute toxicity

No deaths were recorded after 24 hours of administration of the various doses (10, 100, and 1000 mg/kg body weight) of the *Chrysophyllum albidum* pulp. In the second stage, four dose ranges were also used 2000, 3000, 4000, and 5000 mg/kg body weight and there was no death after 24 hours. The LD50 was determined as 5000mg/kg.

Table 2 Curative Effect of ethanol pulp Extract of *Chrysophyllum albidum* in Plasmodium bhergei Infected Mice

Treatment	Parasitaemia suppression (Mean ± SEM)		Parasite Clearance (%)	Mean Survival Time (Days)
	Day 4	Day 7		
Neg. Control	23.4 ± 0.17	29.5 ± 0.43	-	7.2± 2.52
AL (8mg/kg)	15.7 ± 1.01	3.9 ± 0.18***	86.79***	28.0 ± 0.21***
CAL 250 mg/kg	19.9± 0.63	15.9 ± 0.30*	46.10	17.3 ± 1.46*
CAL 500 mg/kg	17.7 ± 0.80	12.8 ± 0.44**	56.61**	19.9 ± 0.50**
CAL 1000 mg/kg	15.3 ± 0.43	7.9 ± 1.09***	73.22***	23.0± 0.31***
CAL+AL 250 mg/kg	11.4 ± 0.23	3.3 ± 0.30*	88.81***	20.9 ± 1.22***
CAL+AL 500 mg/kg	7.8 ± 0.80	1.6 ± 0.44**	94.58***	25.3 ± 0.33***
CAL+AL 1000 mg/kg	3.1 ± 0.43	0.0 ± 0.00***	100***	28.0± 0.31***

Values presented as Mean ± SEM, n = 5, * and **, *** significantly different from Neg. control group at p< 0.05, 0.01 and 0.001 using one way ANOVA and Dunnett's post hoc test. ; Where: Neg. control = Negative control, CAL= Chrysophyllum albidum, AL= Artemether-lumefantrine

Table 3 Weight monitoring in Curative effect of ethanol pulp Extract of *Chrysophyllum albidum* in *Plasmodium bhergei* Infected Mice

Treatment	Weight before induction (WBI)	Weight after induction (WAI)	Weight after 28 days
Neg. Control	35.1 ± 0.20	28.7 ± 0.15	-
AL (8mg/kg)	29.8 ± 0.38	26.8 ± 1.29	31.2 ± 0.17***
CAL 250 mg/kg	33.7± 0.11	30.5 ± 0.21	30.5 ± 1.33
CAL 500 mg/kg	35.3 ± 1.45	28.4 ± 0.69	34.6 ± 0.78**
CAL 1000 mg/kg	31.8 ± 0.19	27.6 ± 1.27	31.4 ± 1.51***
CAL+AL 250 mg/kg	30.9 ± 0.48	25.9 ± 0.53	30.6 ± 0.73***
CAL+AL 500 mg/kg	30.6 ± 0.60	28.2± 0.46	31.2 ± 1.35***
CAL+AL 1000 mg/kg	32.6 ± 0.52	28.8 ± 0.39	34.1 ± 1.20***

Values presented as Mean ± SEM, n = 5, * and **, *** significantly different from Neg. control group at p< 0.05, 0.01 and 0.001 using one way ANOVA and Dunnett's post hoc test. ; Where: Neg. control = Negative control, CAL= *Chrysophyllum albidum,* AL= *Artemether-lumefantrine*

Table 4 Parasitemia monitoring on *Plasmodium berghei* Infected Mice

Treatment	Parasitaemia suppression (Mean ± SEM)	Chemosuppression (%)
Neg. Control	34.2 ± 0.45	-
AL (8mg/kg)	4.1 ± 0.10***	88.02***
CAL 250 mg/kg	20.5 ± 0.88*	48.97*
CAL 500 mg/kg	13.3 ± 0.90**	61.11**
CAL 1000 mg/kg	11.7 ± 0.18**	65.7**
CAL+AL 250 mg/kg	4.3 ± 0.56***	87.43***
CAL+AL 500 mg/kg	1.1 ± 0.70***	96.78***
CAL+AL 1000 mg/kg	0.0 ± 0.00***	100.00***

Values presented as Mean ± SEM, n = 5, * and **, *** significantly different from Neg. control group at p< 0.05, 0.01 and 0.001 using one way ANOVA and Dunnett's post hoc test. ; Where: Neg. control = Negative control, CAL= *Chrysophyllum albidum,* AL= *Artemether-lumefantrine*

Table 5 Weight monitoring Parasitemia monitoring on Plasmodium berghei- berghei Infected Mice

Treatment	Weight before induction (WBI)	Weight after induction (WAI)	Weight after 28 days
Neg. Control	29.7 ± 1.29	25.5 ± 0.27	-
AL (8mg/kg)	30.5 ± 0.49	28.4 ± 0.33	29.9 ± 0.55**
CAL 250 mg/kg	28.3± 0.28	23.6 ± 1.39	27.7 ± 0.22*
CAL 500 mg/kg	33.9 ± 0.89	27.3 ± 2.11	33.6 ± 0.78**
CAL 1000 mg/kg	30.7 ± 1.55	28.2 ± 0.88	30.1 ± 0.33**
CAL+AL 250 mg/kg	32.5 ± 0.31	30.0± 0.19	31.2± 0.12***
CAL+AL 500 mg/kg	35.4 ± 1.81	26.9± 0.85	34.5 ± 0.99***
CAL+AL 1000 mg/kg	30.9 ± 0.15	26.8 ± 0.72	31.1 ± 0.36***

Values presented as Mean ± SEM, n = 5, * and **, *** significantly different from Neg. control group at p< 0.05, 0.01 and 0.001 using one way ANOVA and Dunnett's post hoc test. ; Where: Neg. control = Negative control, CAL= *Chrysophyllum albidum,* AL= *Artemether-lumefantrine*

Table 6 Drug Interaction Study (Pharmacokinetic study)

Pharmacokinetic parameters	Dosing schedule		
	AL alone	Concurrent AL + CAL	Pre-treatment with CAL+ AL
Cmax (ng/mL)	42.34±0.56	47.49±0.29 (12.16%)	82.82±1.47 (95.61%)
t½ (h)	3.10	6.09 (96.45%)	7.88 (154.19%)
AUC_{∞} (ng·h/mL)	100.66	157.08 (56.05%)	399.59 (296.97%)
MRT_{∞} (h)	2.99	6.78 (126.76%)	10.30 (244.48%)
Cl/F (mL/h)	2945.17	1933.24 (52.34%)	709.88 (314.88%)
V_d/F (mL)	4654.19	8559.63 (83.91%)	4907.13 (5.43%)

Values of C_{max} are shown as mean ± standard deviation, Mice per group, n=5. AL alone single oral dose administration of *Artemether-lumefantrine* (8 mg/kg), AL+AC concurrent dosing of AL (8 mg/kg) with AC (1000 mg/kg), pre-treatment with AC+AL single oral administration of *Artemether-lumefantrine* (8 mg/kg) to mice after pre-treating with AC (1000 mg/kg/day) for 3 days C_{max} maximum concentration, MRT Mean residence time, t½ half-life, Cl/F Clearance, AUC area under the time-concentration curve, V_d/F volume of distribution.

4. Discussion

The secondary metabolites found in the plant are responsible for a variety of pharmacological effects, and their existence in the extract has been demonstrated by the presence of alkaloids, saponins, flavonoids, phenol, cardiac glycosides, steroids, terpenoids, and tannins. According to Biamonte, quinine is the earliest antimalarial medication and is an alkaloid that was extracted from the bark of the Cinchona tree. Artemisinin, which is currently used, is a terpenoid that was derived from Artemisia annua and is classified as sesquitrepine lactone [5]. This indicates that the antiplasmodial effect that has been found is caused by the secondary metabolites in CAL. Flavonoids are found in the CAL; [11] have reported that flavonoids have an antiplasmodial impact by preventing the production of fatty acids by parasites, which disrupts their metabolism and ultimately leads to the death of the parasites. Additionally, it was noted that flavonoids work against plasmodesmata by specifically targeting functional biomolecules of the parasite, including proteins, DNA, and enzymes [8]. The alkaloid conessine, which was extracted by Dua and his associates from the bark of Holarrhena antidysenterica, was discovered to have a strong antiplasmodial action on mice [6]. It was discovered that the CAL included alkaloids and flavonoids, which may have contributed to the antiplasmodial action that was seen. The observed antimalarial impact may be explained by the individual or combined actions of these secondary metabolites. This study showed that in mice, CAL changed the pharmacokinetics of AL. The half-life of AL was extended by the herb-drug combination.

Moreso, derived pharmacokinetic data indicate that CAL accelerated AL's absorption rate, as seen by a noteworthy increase in the Cmax of roughly 12.16%. In humans, AL is rapidly and thoroughly biotransformed, and even a small amount of AL enhances effectiveness, particularly in the initial days following treatment. AL's success in the present malaria treatment is a result of this feature. The higher Plasmodium parasite clearance and longer survival of the experimental mice previously described may therefore be explained by the prolonged systemic presence of both AL following the co-administration of CAL and AL. The use of composite blood sampling, which permits one blood collection by heart puncture, may be considered a study constraint. As a result, blood was combined from a number of animals at each time point, potentially eliminating individual variance. The purpose of the current study's mouse selection was to exclude species-related bias from the interpretation and comparison of the pharmacokinetic data produced here with the pharmacodynamic result that was previously documented when AL and CAL were delivered together. However, it is important to note that although the current study employed healthy mice, the earlier work that showed how effective AL was when CAL was present used animals that had malaria. Interestingly, a second peak in AL concentration was seen at 2 hours, which coincided with the Cmax at ½ hours. The rat's fecal excretion of AL and earlier observations in people are consistent with this occurrence. Previous research has examined the interactions between some plant components of CAL and drug transport and metabolic pathways. In a concentration-dependent manner, the extract of *Mangifera indica* suppressed CYP1A2, 2A6, 2C9, 2D6, and 3A4 Furthermore, according to Showande, CAL dramatically suppressed CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, which are CYP enzymes that are primarily in charge of the metabolism of a number of medications in humans.

Furthermore, mild inhibition of p-glycoprotein, a key class of transport proteins for xenobiotics, has also been found with mangiferin (chemical ingredient of CAL) and the ethanol extract of *Azadirachta indica* roderio)Furthermore, a previous study showed that when rabbits were given chloroquine and an aqueous leaf extract of *A. indica*, one of the plant components of MD, orally at the same time, the effects were as follows: the volume of distribution, AUC, and Cmax of the drug were reduced, but the Tmax remained unchanged and the half-life increased from 26.7 to 60.2 hours [10].

When compared to concurrent herb-drug administration, a longer half-life for AL after pre-treatment with CAL may result from a gradual build-up of the herbal preparation's inhibitory component or components. This would be consistent with findings from a previous study that observed *M. indica* to inhibit CYP enzymes in a concentration-dependent manner, resulting in a 50% decrease in enzyme activity at 250 µg/mL of extract. The complicated interaction between herbs and conventional medications can be exemplified by the enhanced absorption of AL by CAL, as evidenced by an increased Cmax despite an unaltered Tmax.

Coadministered xenobiotic absorption is predicted to be affected by the inhibitory effects of CAL components on p-glycoproteins [9]. P-glycoproteins are active efflux transporters that facilitate the hepatobiliary, direct intestinal, and urinary excretion of drugs and their metabolites [9]. Therefore, the reduced intestinal efflux activity of p-glycoproteins with CAL interventions or the competition between AL and CAL components for p-glycoprotein binding sites may have contributed to the higher Cmax of AL.

5. Conclusion

The antimalaria property of AL was affected by CAL. There was an increased pharmacological effect due to probable inhibitory effect on AL metabolism by CAL. The pharmacokinetics of AL were also affected by CAL. The systemic exposure and half-life of AL were both extended by concurrent administration and pre-treatment with CAL, indicating an inhibitory effect on AL metabolism that is more prominent with pre-treatment with CAL. The improved pharmacological effect of the combination in a previous study in mice infected with Plasmodium may have its origins in the current findings. It might be necessary to confirm this advantageous interaction between CAL and AL in human volunteers.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest, financial or otherwise.

References

[1] Adepiti, A. O., Adeagbo, B. A., Adehin, A., Bolaji, O. O., & Elujoba, A. A. (2020). Influence of MAMA decoction, an Herbal Antimalarial, on the Pharmacokinetics of Amodiaquine in Mice. European Journal of Drug Metabolism and Pharmacokinetics, 45(1), 81–88. https://doi.org/10.1007/s13318-019-00583-7

[2] Adjei, B. (2013). Utilization of Traditional Herbal Medicine and its role in health care delivery in Ghana: The case of Wassa Amenfi West district (Doctoral dissertation), Kwame Nkrumah University of Science and Technology

[3] Akinpelu, D. A., Odewade, J. O., Aiyegoro, O. A., Ashafa, A. O. T., Akinpelu, O. F., & Agunbiade, M. O. (2016). Biocidal effects of stem bark extract of Chrysophyllum albidium G. Don on vancomycin-resistant Staphylococcus aureus. BMC Complementary and Alternative Medicine, 16(1), 1–9. https://doi.org/10.1186/s12906-016-1080-6

[4] Amoah LE, Kakaney C, Kwansa-Bentum B.,Kusi KA (2015). Activity of Herbal Medicines on Plasmodium falciparum Gametocytes: Implications for Malaria Transimission in Ghana. PLOS ONE 10(11): e0142587. https://doi.org/10.1371/journal.pone.0142587.

[5] Bray F., Laversanne M., Weiderpass E., Soerjomataram I.,(2021). The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer.127(16):3029-3030.doi:10.1002/cncr.33587.Epub2021 Jun 4.PMID: 34086348.

[6] Dua N., Seshadri A., Badrinarayanan A. (2022). DarT-mediated mtDNA damage induces dynamic reorganization and selective segregation of mitochondria. J Cell Biol.221(10):e202205104.doi:10.1083/jcb.202205104. Epub 2022 Sep 8. PMID: 36074064; PMCID:PMC9463037.

[7] Ihekwereme, Chibueze, Melidem, C., Maduka, I., & Okoyeh, J. (2018). In Vivo Antiplasmodial and Toxicological Effects of Extracts of Fruit Pulp of Chrysophyllum albidium G. Don (Sapotaceae). Tropical Journal of Natural Product Research, 2(3), 126–131. https://doi.org/10.26538/tjnpr/v2i3.5

[8] Kaur K., Meenakshi J., Kaur T., Jain R., (2009). Antimalarials from nature. Bioorg. Med. Chem.doi:10.1016/j.bmc.2009.02.050

[9] Kawakami N., Namkoong H., Ohata T., Sakaguchi S., Saito F., (2018). Clinical features of Mycoplasma pneumonia in older adults. https://doi.org/10.1111/ggi.13278

[10] Onyeji Cyprian O. (2022). Prospects of Integration of Nanotechnology to Antimalarial Herbal Remedies for Improved Therapeutic efficacy. Afr J Tradit Complement Altern Med., (20) 18 (1): 27-35.https://doi.org/10.21010/Ajtcamv18i1.3

[11] Okokon J.E., Mobley R., Edem U.A., (2022). In vivo and In vitro antimalarial activity and chemical profiling of sugarcane leaves. Sci Rep 12, 10250.https//doi.org/10.1038/s41598-022-14391-8

[12] Rouhani S., Clarke S.E., Diarra S.(2017). Impact of a malaria intervention package in schools on Plasmodium infection, anaemia and cognitive function in school children in Mali: a pragmatic cluster-randomised trial. BMJ Glob Health2:e000182.doi:10.1136/bmjgh-2016-000182

[13] WHO. World malaria report 2023. Geneva:World Health Organization;2023