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Research article

Evaluation of packaging, labels, and some physicochemical properties of herbal antimalarial products on the Ghanaian market

Hilda Amekyeh [a], Doris Kumadoh [b,c], Donatus Wewura Adongo [d], Emmanuel Orman [e], Sadique Abubakar [a], Audrey Dwamena [a], Mike Okweesi Aggrey [f,*]

[a] Department of Pharmaceutics, School of Pharmacy, University of Health and Allied Sciences, PMB 31, Ho, Ghana
[b] Department of Pharmaceutics, Centre for Plant Medicine Research, Mampong-Akuapem, Ghana
[c] Department of Production, Centre for Plant Medicine Research, Mampong-Akuapem, Ghana
[d] Department of Pharmacology and Toxicology, School of Pharmacy, University of Health and Allied Sciences, PMB 31, Ho, Ghana
[e] Department of Pharmaceutical Chemistry, School of Pharmacy, University of Health and Allied Sciences, PMB 31, Ho, Ghana
[f] Department of Pharmacognosy and Herbal Medicine, School of Pharmacy, University of Health and Allied Sciences, PMB 31, Ho, Ghana

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ABSTRACT

Introduction: Malaria is a parasitic disease that is endemic in tropical areas and can be life-threatening. There has been a decrease in the prevalence of malaria in Ghana but the burden of the disease is still high in the country. Many Ghanaians depend on herbal products for malaria treatment. This study aimed to survey and evaluate commercial herbal antimalarials in the Volta Region of Ghana.

Methods: A survey of finished herbal antimalarials was done at herbal shops, pharmacies, and over-the-counter medicine seller shops. Products available on shelves were purchased and their details were recorded, after which they were examined using a visual inspection tool. The density, pH, and extract weight per dose of each sample were also determined.

Results: Thirty-four liquid formulations (A-1–34) containing 1–9 different herbs were found. The majority of the product labels had errors in consumer age classifications. Unconventional ways of stating doses were found on two products (A-13, "tot"; A-19, cupful). Six products did not have dosing devices. No duration of treatment was indicated on 24 products. Dose errors were found on A-14 and A-22. Samples A-17 and A-28 did not have registration or batch numbers. Product A-28 did not have its herbs listed on it and was indicated for persons aged 3–8 years at a dose of 45 mL. The relative density range for the products was 0.997–1.015. From the pH investigation, no product was extremely erosive; however, 10 samples were deemed erosive (pH, 3.0–3.99), whereas 24 were minimally erosive (pH, $\geq$4.0). The extract weight per dose volume (20–90 mL) was 0.048–1.766 g, indicating that unit dose capsules or tablets could be formulated from the products.

Conclusion: The findings clearly show that Ghanaian authorities responsible for regulating herbal products must enforce guidelines for the formulation, label details, and sale of antimalarial products. Additionally, the unpleasant taste of liquid herbal mixtures can affect patient compliance and dosing convenience; therefore, it is recommended that oral solid dosage forms of herbal antimalarials are produced as alternatives to the liquid mixtures.

* Corresponding author.
E-mail address: maggrey@uhas.edu.gh (M.O. Aggrey).

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1. Introduction

Malaria is a mosquito-borne parasitic disease that is endemic in tropical areas and can be life-threatening. The initial symptoms of malaria include fever, chills, headache, and flu-like illness. Although treatments for malaria are available, the increased prevalence of the condition due to drug resistance can result in a high incidence of mortality [1,2]. According to the 2022 World Malaria Report, the number of cases of malaria increased from 245 million in 2020 to 247 million in 2021, although the estimated number of deaths from the disease decreased from 625,000 in 2020 to 619,000 in 2021. Notwithstanding the decrease in mortality rate, the high numbers still indicate that malaria is a global public health concern [3]. Ghana is one of the countries in the world that has a high burden of malaria.

As a result of the socio-cultural practices of Ghanaians, a high percentage of the population depends on local herbal medicines for the treatment of malaria and other conditions [4,5]. According to the World Health Organization (WHO), "herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations thereof" [6].

Herbs and the extracts prepared from them usually have a complex composition and are regulated differently in various regions, which results in major classification, standardisation, and quality issues. These concerns are further worsened by the presence of adulterants and contaminants in some herbal products. However, the clinical, economic, health, and pharmaceutical value of these products has been increasing with steady market growth [7], which means that these products must be well monitored for their safety. The WHO has recommended that herbal medicines should be included in existing national pharmacovigilance systems and that in countries that do not have such systems, comprehensive national pharmacovigilance systems that include coverage of herbal medicines must be established. This is very important to ensure the safety of these products because of the misconception among consumers that herbal products are safe [8].

Generally, there is limited data on the quality, safety, and efficacy of some plants, their extracts and preparations, as well as the active compounds they contain. Consequently, the requirements and procedures for the quality control of finished herbal products, especially those that contain a mixture of herbs, are more complex than those for other pharmaceuticals. This is because the quality of such products is affected by the quality of the raw material used [8]. In Ghana, there is progress in the plant medicine industry with respect to the manufacture, packaging, and licensing of herbal products. This has resulted in the production of herbal formulations with improved efficacy and reduced toxicity [9].

This study aimed to survey and evaluate herbal antimalarials for sale in herbal shops, pharmacies, and over-the-counter medicine seller (OTCMS) shops in Ho, which is the capital city of the Volta Region of Ghana.

2. Materials and methods

2.1. Sample collection

A survey of all commercial herbal antimalarial products was done at herbal shops, pharmacies, and OTCMS shops in the Ho Municipality of the Volta Region of Ghana until no new product was found from November 2022 to January 2023. Thirty-four products were purchased and subsequently analysed.

2.2. Collection of details and visual inspection of samples

The basic details of each product, including manufacturing and expiry dates, price per bottle, registration number from the Food and Drugs Authority of Ghana (FDA), listed indications, constituent plants, and dosage were recorded. The products were then visually inspected using a checklist based on previously developed and modified inspection tools [10–12].

Briefly, the visual inspection tool (Supplementary Table 1) had five sections containing several indicators for assessment. The first section focused on product packaging, accompanying items (package insert and dosing device), product name registration, and label legibility and indelibility. The second section contained assessment items on the name(s) and amount(s) of herbs used and product expiration. The third section was on dosage information. The fourth and fifth sections contained parameters to assess product traceability and physical appearance, respectively.

2.3. Assessment of pH and density

The pH of each product was determined using a calibrated digital pH meter (model ST3100-F; OHAUS Corporation, Parsippany, NJ, USA). Each formulation was well shaken, after which 10 mL was transferred into a 25 mL beaker for pH determination. The relative density of each herbal mixture was determined using a pycnometer. The weight of the pycnometer and its stopper was taken, after which the weights of equal volumes of water and the samples were taken individually. Relative density was then estimated as the ratio of the weight of each sample to the weight of water only. All pH and density measurements were performed at room temperature (approximately 30 °C). Triplicate determinations were made for each product.

2.4. Determination of dry extract weight per product dose

The weights of dry glass Petri dishes were recorded. Next, 50 mL of the various products were poured into separate labelled dishes.

The samples were then placed in a hot-air oven and allowed to dry for 72 h at 60 °C. The dishes were reweighed, after which the weights of the dried extracts were estimated. The amount of extract contained in a dose volume was then calculated for each product [13]. The procedure was performed in triplicate for each sample.

2.5. Data handling and statistical analysis

Data collected using the visual inspection checklist as well as those obtained from the laboratory assessment of physicochemical parameters were transferred into Microsoft Excel, checked for accuracy, and imported into IBM SPSS Statistics software (version 26; IBM Corp., Armonk, NY, USA). The data were analysed using descriptive statistics, such as frequencies and percentages, as well as contingency analysis. Multivariate data analysis was also performed using principal component analysis (PCA) and clustered heatmap analysis. P values < 0.05 were considered statistically significant.

3. Results

3.1. General survey findings

The survey yielded 37 different locally produced herbal antimalarial products after visiting 14 pharmacies, 6 OTCMSs, and 4 herbal shops; however, three products were a few days near expiration and were therefore excluded as no new batches were available during the study period. The remaining samples were coded A-1 to A-34. All the samples were liquid dosage forms for oral use.

3.2. Results of the visual inspection of samples

The results of the visual inspection are shown in Supplementary Table 1 and Table 1. Out of the 34 samples, 24 (70.59%) had secondary packaging and each was intact. All the samples had intact primary packaging. The closures of only A-14, A-23, and A-31 were not intact or airtight. Additionally, only A-12, A-17, and A-21 did not have clear storage information on their bottles.

Table 1
Results of visual inspection of the samples.

Parameter	Yes n (%)	No n (%)	Not applicable n (%)
Packaging			
Is there an external packaging?	24 (70.59)	10 (29.41)	0 (0.00)
Is the external packaging intact?	24 (70.59)	0 (0.00)	10 (29.41)
Is the bottle intact?	34 (100.00)	0 (0.00)	0 (0.00)
Is the closure of the bottle intact and airtight?	31 (91.18)	3 (8.82)	0 (0.00)
Does the primary packaging provide clear information on the storage conditions of the medicine?	31 (91.18)	3 (8.82)	0 (0.00)
Does the product come with a package insert?	6 (17.65)	28 (82.35)	0 (0.00)
Dosing device provided with the product	6 (17.65)	28 (82.35)	0 (0.00)
Does the label on the carton match the label on the bottle?	24 (70.59)	0 (0.00)	10 (29.41)
Are all the details on the labels legible and indelible?	33 (97.06)	1 (2.94)	0 (0.00)
Symbol ® follows the trade name	8 (23.53)	26 (76.47)	0 (0.00)
Side effects stated	0 (0.00)	34 (100.00)	0 (0.00)
Identification			
Secondary packaging has the following information on the outer side			
Active ingredient(s) name(s)	24 (70.59)	0 (0.00)	10 (29.41)
Amount(s) of active ingredient(s) per packaging	0 (0.00)	24 (70.59)	10 (29.41)
Expiry date in uncoded form	23 (67.65)	0 (0.00)	11 (32.35)
Primary packaging carries the following information on the outer side			
Active ingredient(s) name(s)	33 (97.06)	1 (2.94)	0 (0.00)
Amount(s) of active ingredient(s) per packaging	0 (0.00)	33 (97.06)	1 (2.94)
Expiry date in uncoded form	34 (100.00)	0 (0.00)	0 (0.00)
Dosage			
Dosage clearly indicated on primary packaging	34 (100.00)	0 (0.00)	0 (0.00)
Dosage clearly indicated on secondary packaging	24 (70.59)	0 (0.00)	10 (29.41)
Traceability			
Secondary packaging carries the following information on the outer side			
Name and address of manufacturer OR company/person responsible for placing the product on the market	23 (67.65)	1 (2.94)	10 (29.41)
Batch number	23 (67.65)	1 (2.94)	10 (29.41)
Primary packaging carries the following information on the outer side			
Name and address of manufacturer OR company/person responsible for placing the product on the market	34 (100.00)	0 (0.00)	0 (0.00)
Batch number	32 (94.12)	2 (5.88)	0 (0.00)
Approval/registration number	32 (94.12)	2 (5.88)	0 (0.00)
Physical Appearance			
Colour of product is homogeneous	34 (100.00)	0 (0.00)	0 (0.00)
Product texture is homogeneous, free from lumps/clots, foreign particles	27 (79.41)	7 (20.59)	0 (0.00)

Unfortunately, a substantial proportion of the products (n = 28/34, 82.35%) did not have package inserts, and this included all products without secondary packaging. A similar proportion of the products (n = 28/34, 82.35%) did not have accompanying dosing devices, and this likewise included all products without secondary packaging and a significant proportion of those without package inserts ($\chi 2 = 5.247$, $p = 0.022$). Primary and secondary packaging labels matched in each instance.

The label details on all the samples except A-15 were legible and indelible. Only a few products (n = 8/34, 23.53%) had the symbol ® following their product names, indicating that their tradenames are registered with the Registrar-General's Department of Ghana. It was also noted that none of the products had any information on side effects on their packaging. Constituent plants were listed on all secondary packaging and most (n = 33/34, 97.06%) of the primary packaging. Only A-28 did not have its component plant(s) listed on its bottle. None of the products had the amounts of herbs used in preparation indicated on either their primary or secondary packaging. Only A-31 did not have an expiry date on its secondary packaging. Aside from this, the expiry dates on all the primary (n = 34) and secondary (n = 23) packaging of the samples were in uncoded form. Additionally, all primary and secondary packaging had dosages written on them (Supplementary Table 1, Table 1).

It is important that the label of every medicinal product contains information that can be used to trace the market authorisation holder. Among the products, it was found that only A-25 and A-31 did not have manufacturer's details and batch number, respectively, on their secondary packaging. All primary packaging had product manufacturers' details; however, only products A-17 and A-28 had neither FDA registration numbers nor batch numbers on their bottles. Furthermore, only seven products (A-3, A-6, A-12, A-15, A-20, A-29, A-31) had valid approval at the time of our search on the FDA website (http://196.61.32.245:98/publicsearch; May 4, 2023). The remaining products were either not registered or their registration validity periods had expired as of the search time. Lastly, each product had a homogenous colour. However, the texture of a few samples (n = 7/34, 20.59%) was not homogenous as those products contained some particles (Supplementary Table 1, Table 1).

3.3. Specific product details

Specific details of the individual products are shown in Table 2. All the samples were contained in amber-coloured plastic bottles, and the material used for secondary packaging for those that had it (n = 24) was paper. The shelf lives indicated on the products were in the range of 1–3 years. The volume and price ranges of the products were 300–1000 mL and GHS 12–45, respectively (Table 2). Fig. 1 shows the cost effectiveness of the various products via the relationship between pack volume, number of daily doses per bottle,

Table 2
Specific packaging details of the samples.

Product code	Production date	Expiry date	Primary packaging	Secondary packaging	Volume (mL)	Bottle cost (GHS)
A-1	09/21	09/23	Amber plastic	Paper	500	15.00
A-2	07/22	07/24	Amber plastic	Paper	500	17.00
A-3	01/21	01/24	Amber plastic	Paper	330	23.00
A-4	05/22	05/25	Amber plastic	Paper	500	15.00
A-5	10/21	10/23	Amber plastic	Paper	500	15.00
A-6	12/21	12/23	Amber plastic	N/A	1000	19.00
A-7	03/21	03/23	Amber plastic	N/A	750	23.00
A-8	01/22	01/24	Amber plastic	Paper	350	22.00
A-9	06/22	06/23	Amber plastic	Paper	500	33.00
A-10	12/21	12/22	Amber plastic	N/A	750	25.00
A-11	05/21	05/23	Amber plastic	Paper	750	15.00
A-12	10/22	10/24	Amber plastic	N/A	460	21.00
A-13	01/22	01/24	Amber plastic	N/A	500	17.00
A-14	10/21	10/23	Amber plastic	Paper	750	18.00
A-15	01/22	01/24	Amber plastic	Paper	500	20.00
A-16	08/22	08/23	Amber plastic	Paper	300	21.00
A-17	09/21	12/23	Amber plastic	N/A	750	13.00
A-18	07/21	07/23	Amber plastic	Paper	350	15.00
A-19	07/21	07/23	Amber plastic	Paper	330	18.00
A-20	10/21	10/23	Amber plastic	Paper	330	28.00
A-21	01/22	01/24	Amber plastic	Paper	330	20.00
A-22	09/21	09/24	Amber plastic	Paper	750	18.00
A-23	06/22	06/24	Amber plastic	N/A	330	15.00
A-24	09/22	09/24	Amber plastic	Paper	500	28.00
A-25	09/21	09/24	Amber plastic	Paper	500	18.00
A-26	07/22	07/23	Amber plastic	N/A	1000	45.00
A-27	06/22	06/24	Amber plastic	Paper	330	15.00
A-28	06/21	06/23	Amber plastic	N/A	500	12.00
A-29	03/22	03/24	Amber plastic	Paper	750	23.00
A-30	05/22	05/24	Amber plastic	Paper	500	25.00
A-31	07/22	01/24	Amber plastic	Paper	500	23.00
A-32	06/21	06/23	Amber plastic	Paper	500	28.00
A-33	06/22	06/24	Amber plastic	Paper	330	17.00
A-34	10/22	10/23	Amber plastic	N/A	500	18.00

and cost of daily treatment.

3.4. Indications of the products

It can be seen in Table 3 that twelve of the products were indicated for only malaria. Product A-5 had five co-indications, which was the highest among the samples. Fig. 2 shows that the indications other than malaria that were listed on the products were fever (38.2%), body pains (23.5%), appetite loss (17.6%), typhoid (17.6%), jaundice (11.8%), menstrual disorders (5.9%), arthritis, immune booster, stomach pains, and ulcer (2.9% each). Interestingly, the first three items, which form the majority of the co-indications, are classic symptoms of malaria [3,14].

3.5. Dosages of the products

The doses and dosing frequencies of the samples are shown in Table 3. All the bottles had daily dosages indicated on them; however, 70.6% (n = 24) of their labels had no treatment duration specified on them.

The duration of treatment for the 10 products that had the information on them was as follows: A-34, 3 days; A-7, 5 days; A-1, A-3, A-12, A-25, A-29, A-30, and A-33, 7 days; and A-11, 14 days. The doses of A-13 and A-19 were stated unconventionally in "tot" and "cupful" units, respectively. The label of A-14 showed an adult dose of 500 mL and an age category for children as "112–18 years". A-15 did not state an age category for children. One tablespoon was considered equal to 10 mL on sample A-22. The label of product A-8 indicated adult age as >12 years, whereas the majority of the product labels indicated children's age range as 12–18 years. It was disturbing that for product A-28, the only age range for children was indicated as 3–8 years, and the dose for this group was 45 mL.

3.6. Herbs used in the products

Individual products contained a minimum of one herb (A-19, A-21, A-23) and a maximum of nine different herbs (A-24) (Table 3). Overall, 53 different plants were collectively used in the 34 products. *Cryptolepis sanguinolenta* was the plant used in all the monoherbal products. The most common herbs were *Azadirachta indica* (n = 10), *Cryptolepis sanguinolenta* (n = 8), *Alstonia boonei* (n = 7), *Xylopia aethiopica* (n = 6), *Khaya senegalensis* (n = 5), *Citrus aurantifolia*, *Morinda lucida*, *Paullinia pinnata*, and *Tetrapleura tetraptera* (n = 4 in each instance). The remaining plants were used in less than four products each (Tables 3 and 4). None of the products had the exact plant part used indicated on their label.

References found from a literature search online for the antimalarial use of the various plants in the products are shown in Table 4. The reports were based on in vitro test results, in vivo experiment findings, and/or folkloric use of the plants in various countries across the globe. No reference for direct antimalarial use was found for 18.9% (n = 10) of the plants. However, among those ten plants, the following were found to be indicated for other conditions listed on their product labels: *Aframomum melegueta* for pain [15], *Musa sapientum* for ulcer [16], *Swietenia macrophylla* for pain [17], and *Urena lobata* for stomach pain [18].

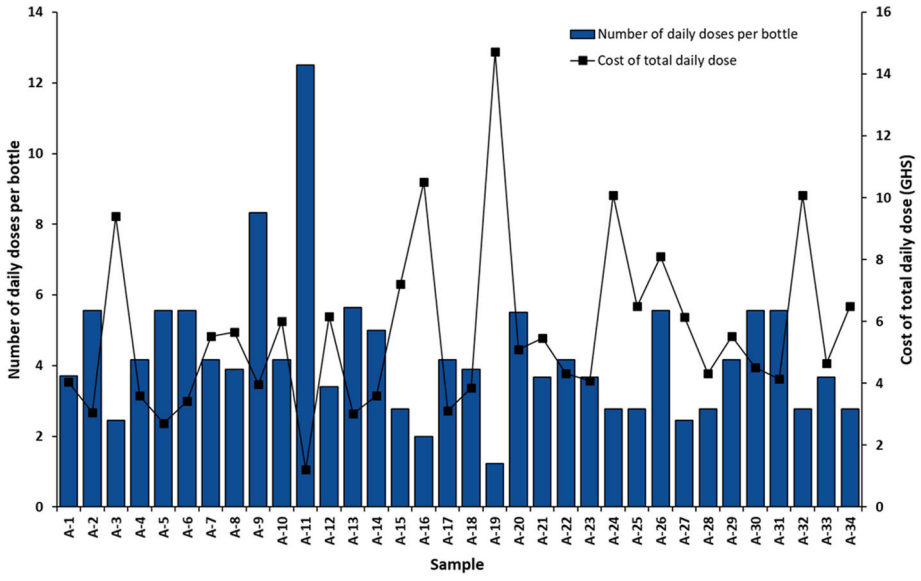

Fig. 1. Number of doses per bottle and cost of total daily dose.

Table 3
Indications, compositions, and dosages of the products.

Product code	Indication(s) listed	Constituent plant(s)	Dosage for adults	Dosage for children
A-1	Malaria Typhoid Arthritis Menstrual disorder	*Clausena anisata* *Cryptolepis sanguinolenta* *Thonningia sanguinea*	≥18 years 45 mL three times daily after food for 7 days	12–17 years 30 mL three times daily after food
A-2	Malaria	*Anthocleista nobilis* *Phyllanthus fraternus* *Vitex grandifolia*	≥18 years 30 mL three times daily	12–17 years 30 mL two times daily Repeat for three weeks
A-3	Malaria Fever	*Bidens pilosa* *Citrus aurantifolia* *Paullinia pinnata* *Psidium guajava* *Xylopia aethiopica*	≥18 years 45 mL three times daily for 7 days	12–18 years 30 mL three times daily for 7 days
A-4	Malaria Fever Typhoid Jaundice	*Azadirachta indica* *Nauclea latifolia* *Phyllanthus niruri*	≥18 years 30 mL four times daily	12–17 years 15 mL four times daily
A-5	Malaria Jaundice Fever Body pains Menstrual pains Loss of appetite	*Bombax buonopozense* *Cola gigantea* *Solanum torvum* *Spathodea campanulata* *Vernonia amygdalina*	≥18 years 30 mL three times daily before food	9–12 years 15 mL three times daily
A-6	Malaria Typhoid Fever	*Alstonia boonei* *Lannea kerstingii* *Mangifera indica*	≥18 years 60 mL three times daily after food	12–18 years 30 mL three times daily after meal
A-7	Malaria	*Azadirachta indica* *Morinda lucida* *Phyllanthus fraternus* *Tridax procumbens*	≥18 years 60 mL three times daily for 5 days	12–16 years 30 mL three times daily after meals for 5 days
A-8	Malaria Fever Stomach pains	*Anthocleista nobilis* *Khaya senegalensis* *Rauwolfia vomitoria* *Urena lobata*	>12 years 30 mL three times daily after meals	6–12 years 15 mL two times daily after meals
A-9	Malaria	*Alstonia boonei* *Kigelia africana* *Nauclea latifolia*	≥18 years 30 mL two times daily after meals	12–18 years 10 mL twice daily after meals
A-10	Malaria Body pains Loss of appetite	*Azadirachta indica* *Citrus aurantifolia* *Moringa oleifera*	≥18 years 60 mL three times daily after meals	12–17 years 40 mL three times daily
A-11	Malaria	*Alchornea cordifolia* *Alstonia boonei* *Khaya senegalensis* *Monodora myristica* *Trichilia heudelotii* *Xylopia aethiopica*	>18 years 20 mL three times daily after food for 14 days	12–18 years 15 mL three daily after meals for 14 days
A-12	Malaria Fever	*Momordica charantia* *Morinda lucida*	No age indicated 45 mL three times daily before food for 7 days	N/I
A-13	Malaria Loss of appetite	*Alstonia boonei* *Carica papaya* *Tetrapleura tetraptera*	≥18 years One “tot” two times daily before meals	12–17 years 15 mL two times daily before meals
A-14	Malaria Fever Body pains	*Alchornea cordifolia* *Morinda lucida* *Xylopia aethiopica*	≥18 years 500 mL three times daily after meals	“112”–18 years 20 mL three times daily after meals
A-15	Malaria Typhoid Loss of appetite	*Azadirachta indica* *Khaya senegalensis*	≥18 years 60 mL three times daily	Age range N/I 30 mL three times daily after meals
A-16	Malaria	*Alstonia boonei* *Azadirachta indica* *Cryptolepis sanguinolenta* *Monodora myristica* *Xylopia aethiopica*	≥18 years 75 mL two times daily after food	N/I

(*continued on next page*)

Table 3 (*continued*)

Product code	Indication(s) listed	Constituent plant(s)	Dosage for adults	Dosage for children
A-17	Malaria Fever Body pains	*Alchornea cordifolia* *Swietenia macrophylla*	No age indicated 60 mL three times daily	N/I
A-18	Malaria Body pains	*Alstonia boonei* *Khaya senegalensis* *Paullinia pinnata* *Pycnanthus angolensis* *Rauwolfia vomitoria*	≥18 years 30 mL three times daily after meals	12–17 years 15 mL three times daily after meals
A-19	Malaria	*Cryptolepis sanguinolenta*	≥18 years Day 1: Three (3) cupfuls (90 mL) three (3) times daily after meals (cup on bottle) Day 2 onwards: 60 mL three times in the day after meals	12–17 years Day 1: Two (2) cupfuls (60 mL) three times in the day Day 2 onwards: 30 mL three times in the day after meals
A-20	Malaria	*Adenia cissampeloides* *Enantia polycarpa* *Moringa oleifera* *Plumbago capensis* *Tetrapleura tetraptera*	≥18 years 20 mL three times daily after food	≥12 years 10 mL three daily before or after meals
A-21	Malaria	*Cryptolepis sanguinolenta*	≥18 years 30 mL three times daily	12 years 15 mL three times daily after meals
A-22	Malaria	*Azadirachta indica* *Citrus aurantifolia* *Cryptolepis sanguinolenta*	≥18 years 4 tablespoonfuls (40 mL) three times daily after meals	≥12 years 2 tablespoonfuls (20 mL) three (3) times daily
A-23	Malaria	*Cryptolepis sanguinolenta*	≥18 years 30 mL three times daily after meals	N/I
A-24	Malaria Ulcer Body pains	*Aframomum melegueta* *Carica papaya* *Monodora myristica* *Morinda lucida* *Musa sapientum* *Tetrapleura tetraptera* *Vernonia amygdalina* *Xylopia aethiopica* *Zingiber officinale*	No age indicated 60 mL three times daily	N/I
A-25	Malaria Immune booster General body pains	*Paullinia pinnata* *Xylopia aethiopica*	≥18 years 60 mL three times daily before meals for 7 days	13–17 years 60 mL three times daily before meals for 7 days
A-26	Malaria Fever Typhoid Jaundice	*Carica papaya* *Cassia alata*	≥18 years 60 mL three times daily after meals	≥12 years 30 mL two times daily after meals
A-27	Malaria	*Azadirachta indica* *Cryptolepis sanguinolenta*	≥18 years 45 mL three times daily after meals	12–17 years 30 mL three times daily after meals
A-28	Malaria Fever Jaundice Typhoid	N/I	≥18 years 60 mL three times daily before food	3–8 years 45 mL three times daily before meals
A-29	Malaria Fever	*Aloe schweinfurthii* *Cassia siamea* *Khaya senegalensis* *Piliostigma thonningii*	≥18 years 60 mL three times daily for 7 days	13–17 years 60 mL three times daily for 7 days
A-30	Malaria Loss of appetite Body pains	*Azadirachta indica* *Cymbopogon citratus* *Moringa oleifera* *Ocimum viride* *Paullinia pinnata* *Tetrapleura*	≥18 years 30 mL three times daily 5 min before meals for 7 days	12–17 years 15 mL three times daily 5 min before meals for 7 days

(*continued on next page*)

Table 3 (*continued*)

Product code	Indication(s) listed	Constituent plant(s)	Dosage for adults	Dosage for children
		tetraptera		
		Theobroma cacao		
A-31	Malaria	*Bombax*	≥18 years	12–17 years
	Loss of appetite	*buonopozense*	30 mL three times daily after meals	15 mL three times daily after meals
		Cola gigantea		
		Solanum torvum		
		Spathodea campanulata		
		Vernonia amygdalina		
A-32	Malaria	*Carapa procera*	≥18 years	N/I
	Fever	*Cryptolepis sanguinolenta*	60 mL (2 of the 30 mL cup on bottle) three times daily	
A-33	Malaria	*Alstonia boonei*	≥18 years	12–17 years
	Fever	*Azadirachta indica*	30 mL three times daily after meals for 7 days	15 mL three times daily after meals
A-34	Malaria	*Azadirachta indica*	≥18 years	N/I
		Citrus aurantifolia	60 mL three times daily after meals for 3 days	
		Hoslundia opposita		
		Phyllanthus fraternus		
		Securinega virosa		

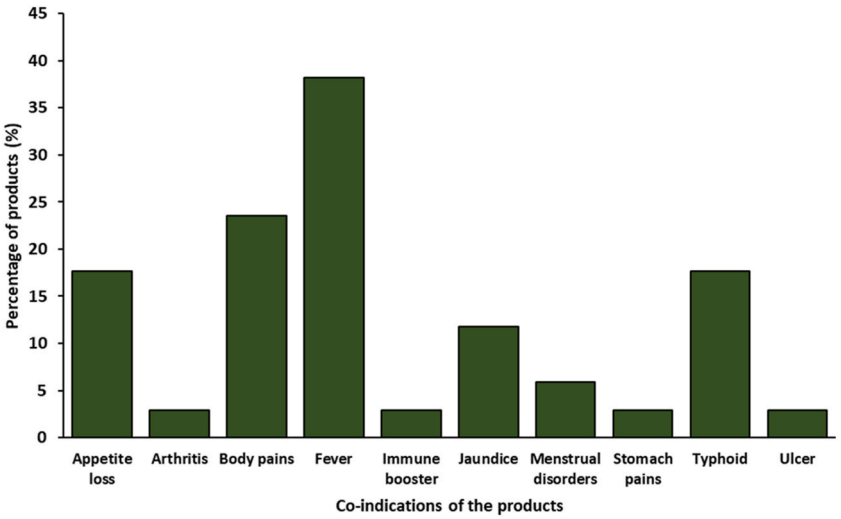

Fig. 2. Indications other than malaria on the product labels.

3.7. pH, relative density, and extract weights after drying

The pHs and relative densities of the herbal mixtures are shown in Fig. 3. The pH range was 3.22–6.43, indicating that the samples were acidic or slightly acidic. The percentages of the products with pH values of <3.0, 3.0–3.99, and ≥4.0 were 0%, 29.4%, and 70.6%, respectively. The relative densities of the products were in the range of 0.997–1.015. The weights of the extracts per product dose ranged from 0.048 ± 0.04 g for 30 mL of A-4 to 1.766 ± 0.003 g for 30 mL of A-18 (Fig. 4).

3.8. Comparison of the physicochemical parameters of the products

Analysis of the physicochemical characteristics of the products revealed that the samples could be grouped into four classes. One class was a group of products with relatively high pH values (range, 5.17–6.43). The second group was comprised of those with a high number of doses per bottle. As per the recommended dosages for the products, it is possible to achieve several doses per product purchased for these samples. This means that products in this group are possibly cost-effective and could be the preferred choice if economic factors are considered during the purchase of a herbal antimalarial product. The number of doses per product in this group was 5.55–12.50, with A-11 having the highest number. The third group of products was characterised by high relative density (1.003–1.015) and high extract weight per dose (0.904–1.766); these products present as options with relatively higher extract concentrations per dose administered for the management of malaria. The fourth group of products is composed of those that have high costs for their daily dose (GHS 9.41–14.73) as well as high dose volumes (45–90 mL). In effect, this group of products could be

Table 4
Plants used to formulate the herbal products.

Plant	Literature reference(s) for antimalarial effect	No. of samples containing plant	Plant	Literature reference(s) for antimalarial effect	No. of samples containing plant
Adenia cissampeloides	[19]	1	*Moringa oleifera*	[20]	3
Aframomum melegueta	None found	1	*Musa sapientum*	None found	1
Alchornea cordifolia	[21]	3	*Nauclea latifolia*	[21]	2
Aloe schweinfurthii	None found	1	*Ocimum viride*	None found	1
Alstonia boonei	[21]	7	*Paullinia pinnata*	[22,23]	4
Anthocleista nobilis	[24]	2	*Phyllanthus fraternus*	[25]	3
Azadirachta indica	[26]	10	*Phyllanthus niruri*	[27]	1
Bidens pilosa	[28]	1	*Piliostigma thonningii*	[28]	1
Bombax buonopozense	[29]	2	*Plumbago capensis*	None found	1
Carapa procera	[30]	1	*Psidium guajava*	[23]	1
Carica papaya	[22,31]	3	*Pycnanthus angolensis*	[21]	1
Cassia alata	[21]	1	*Rauwolfia vomitoria*	[21]	2
Cassia siamea	[25]	1	*Securinega virosa*	[24]	1
Citrus aurantifolia	[32]	4	*Solanum torvum*	[26]	2
Clausena anisata	[33]	1	*Spathodea campanulata*	None found	2
Cola gigantea	[34]	2	*Swietenia macrophylla*	None found	1
Cryptolepis sanguinolenta	[35]	8	*Tetrapleura tetraptera*	[36]	4
Cymbopogon citratus	[31]	1	*Theobroma cacao*	[37]	1
Enantia polycarpa	[38]	1	*Thonningia sanguinea*	None found	1
Hoslundia opposita	[23,31]	1	*Trichilia heudelotii*	[38]	1
Khaya senegalensis	[22]	5	*Tridax procumbens*	[28]	1
Kigelia africana	[28]	1	*Urena lobata*	None found	1
Lannea kerstingii	[39]	1	*Vernonia amygdalina*	[22,31]	3
Mangifera indica	[21,22]	1	*Vitex grandifolia*	None found	1
Momordica charantia	[40]	1	*Xylopia aethiopica*	[41]	6
Monodora myristica	[41]	3	*Zingiber officinale*	[42]	1
Morinda lucida	[40]	4			

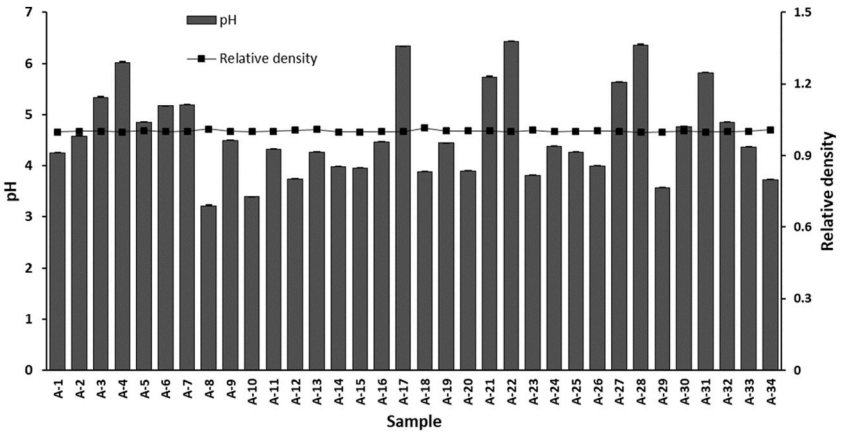

Fig. 3. pH and relative densities of the products.

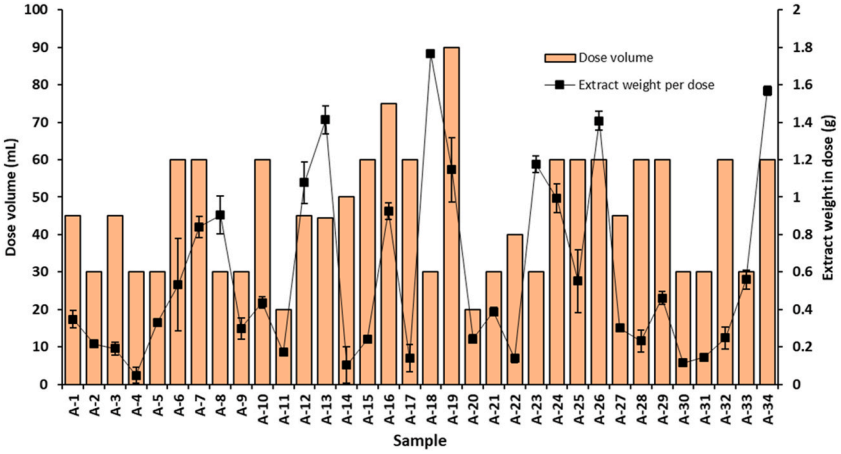

Fig. 4. Residue weights in unit doses of the products after drying.

considered the most expensive in terms of cost per dose. The breakdown of the products in the respective groups is shown in Fig. 5.

4. Discussion

The proper use of herbal medicines of assured quality is essential to reduce risks associated with such products. Unfortunately, the regulation and registration of herbal medicines are not properly developed in most countries. Additionally, available standards for regulating the labelling and publicity of herbal medicines are few, and many of these products are sold as over-the-counter

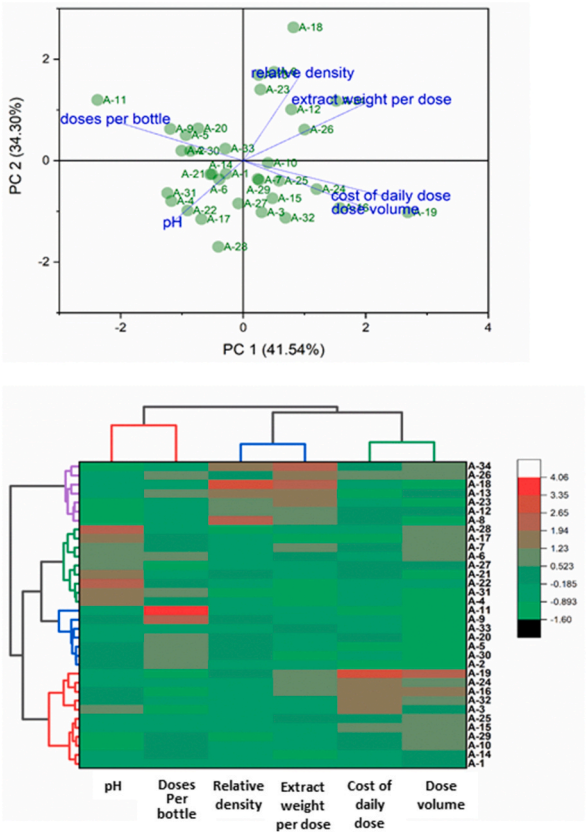

Fig. 5. Multivariate data analysis of the properties of the herbal antimalarial products. [Top] Biplot from principal component analysis of the parameters. [Bottom] Clustered heatmap analysis showing the relationship among the products and the parameters investigated. PC, principal component.

preparations or dietary supplements. As a result, consumers may be unaware of the potential side effects of herbal medicines and how to use the products safely [6]. Usually, the package and label details of such products are the main source of information for consumers; therefore, these details need to be suitable and useful.

4.1. Lack of package inserts and other packaging and labelling issues

It is troubling that only six products had package inserts. A package insert contains detailed information provided by a drug manufacturer on a drug product that is reviewed and approved by the relevant drug regulatory authority. Its use is to provide complete and unbiased prescribing directions to health professionals as well as information to ensure patient safety [43]. A study conducted in Brazil revealed that although a high percentage of the population usually read package inserts, people with low educational backgrounds have difficulty reading and understanding them [44], which may be the same for other populations with similar demographics. Nevertheless, a package insert is an essential component of the packaging of a drug product that drug regulatory authorities in Ghana must ensure that manufacturers provide. The closures of three products were not intact or airtight, indicating that they may be contaminated or deteriorate easily. Moreover, the liquid formulations can leak out of their bottles, which may be undesirable to the consumer. The information on the labels of most products was legible and indelible, which are important qualities to ensure that consumers easily read label information and that the information cannot be easily cleaned or altered, respectively. The uncoded expiry dates on the product labels are very important to allow for easy reading and interpretation by consumers.

4.2. Absence of dosing devices, unstandardised dosing devices, and dose errors

The absence of dosing devices with some of the sampled products may leave consumers to use household devices, which may be inaccurate, to measure doses [45].

The “tot” used to state the dose for A-13 is the local term for a shot glass. Although a standard shot glass has a volume of approximately 44.36 mL, there are different types of shot glasses with different volumes, which makes it a non-standard measurement tool for the antimalarial mixture. The dose of A-14 was stated as “500 mL”, which we believe is an error, considering that the total pack volume of the product is 750 mL and the dose for non-adults is 20 mL. This mistake is highly unacceptable and very concerning, as it gives doubt as to the authenticity of the product’s FDA approval. The dose for sample A-19 was stated in “cupfuls”, which was in reference to the dosing cup accompanying the product. We believe that it is unacceptable to state a dose as such, as any other cup may be used to measure the product when the accompanying device is misplaced or destroyed. This can lead to underdosing or overdosing because the full measure of some other dosing cup, irrespective of the actual volume, may be used by a consumer. It is therefore important for regulatory authorities to ensure that all doses stated on the labels of herbal antimalarials are indicated in the usual “mL” metric standard. Another concern may be that a “cup” is a cooking measurement that corresponds to about 250 mL, which further indicates the unsuitability of the term. It was also observed that the dosing information stated on product A-22 suggested “4 tablespoons” and “2 tablespoons” as being equal to “40 mL” and “20 mL”, respectively, which are wrong. This possibly indicates a misconception by the manufacturer of that product that one tablespoonful is 10 mL instead of 15 mL.

4.3. No information on side effects of products

Unfortunately, the labels of all the samples had no information on side effects; however, it cannot be overemphasised that herbal antimalarials, and herbal medicines in general, must be used carefully as being natural does not necessarily mean that they are always safe to consume. Moreover, some plants with medicinal value may be inherently toxic [8]. Therefore, since there is a lack of data on the safety of several herbs, it is important to encourage healthcare professionals as well as consumers and manufacturers of herbal products to report the side effects of herbal preparations to the relevant authorities. In Ghana, these would include the FDA and the Traditional Medicine Practice Council under the Ministry of Health.

4.4. Concerns with doses for different age categories

An error detected on product A-14 was that “112–18 years” was stated as the age range for children. Although a typographical error, it is unacceptable for a commercial product bearing a registration number to have such a mistake. Product A-15 also had a dosage for children but there was no age range indicated, which may leave room for inappropriate use in young children. The age groups on most of the product labels indicate that some manufacturers are not abreast with the various age classifications. Usually, the age groupings of non-adults are region-specific; however, the differences are not substantial. According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the age ranges for newborns, infants and toddlers, children, and adolescents are 0–27 days, 28 days–23 months, 2–11 years, and 12–16 to 18 years, respectively [46], which clearly show that the designations indicated on most of the products are incorrect.

With respect to A-28 being indicated for persons aged 3–8 years at 45 mL, there may be concerns about the appropriateness of the product and its high dose volume for this group of children. It is logical that liquid formulations are the most appropriate dosage form for younger paediatric patients as they cannot swallow solid oral dosage forms; however, the dose volume of a liquid medicine for them must be considered. It is suggested that target dose volumes of medicines for this population should be < 5 mL for those aged <5 years and <10 mL for those aged ≥ 5 years. This is because these volumes are convenient for both a child and their caregiver during drug administration [47]. Notwithstanding these concerns, A-28 may have all these issues because it may not be FDA-approved.

4.5. Treatment durations and associated cost of treatment

The estimates of treatment costs were made based on the adult dosage for each sample. Ideally, the total cost of treatment should be considered; however, this was not possible as only 10 of the products had their duration of treatment indicated on their packaging. The Ghana FDA and other relevant authorities must ensure that treatment duration, which is very essential information, is indicated on herbal antimalarial products to ensure effective treatment when these products are consumed. Without this information, these antimalarials may be consumed as though they are supplements and various risks may be associated with their long-term use.

For all the 10 formulations that had treatment durations specified on them, it was noted that the total volume of preparation needed to cover the indicated treatment duration was more than the respective product volume. Notwithstanding these shortfalls, with the available data, A-11 appears to be the best product with respect to cost effectiveness per treatment day, as it has the lowest cost per daily dose and yet contains the highest number of doses. In contrast, A-19 contained the smallest number of daily doses but was the most expensive with respect to daily treatment costs. With its pack volume of 330 mL and a required daily volume of 270 mL, almost one bottle of product A-19 would be required for each day of treatment. By the end of treatment, the patient would have been exposed to extremely high volumes of the product, which may raise a concern of sub-acute toxicity.

4.6. Traceability of the products

The Ghana FDA registers food items, drugs, herbal preparations, supplements, and medical devices, among others, to protect public health and safety [48]. A batch number (also known as a lot number) is a "unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined" [49]. The batch numbers of the samples investigated in the present study are excluded from the presented data to ensure product anonymity. The lack of FDA approvals and batch numbers on A-17 and A-28 brings to question the authenticity of the preparations. Moreover, these products cannot be tracked during a recall.

4.7. Medicinal plant space for antimalarial products

A herbal antimalarial mixture can contain several herbs; however, it is reported that in Africa, causes of acute kidney injury include herbal toxins and infections such as malaria [50–52]. This means that the management of malaria with a mixture of herbs must be done carefully. For instance, the condition of the raw herbal materials used and precautions taken during product manufacture must be highly considered to ensure that contamination is minimised to fall within acceptable limits.

In the present study, individual herbal products contained up to seven antimalarial plants with A-24 containing the highest number. Currently in Ghana, the herbs approved by the Ministry of Health for treating malaria caused by *Plasmodium falciparum* are *Azadirachta indica*, *Cassia occidentalis*, *Cryptolepis sanguinolenta*, *Khaya senegalensis*, and *Morinda lucida*, either alone or in combination [53]. From the results obtained, *Azadirachta indica*, *Cryptolepis sanguinolenta*, *Alstonia boonei*, *Xylopia aethiopica*, and *Khaya senegalensis* were the main plants used to formulate the herbal products surveyed. Our findings support those of a previous study in which these plants were common components of herbal antimalarials surveyed in the Ashanti and Greater-Accra Regions of Ghana [54]. The preference for these plants by herbal product manufacturers calls for the need to establish standards to regulate their quality, as the same plants collected from different parts of the country may have different levels of quality [55]. Furthermore, the use of the plants in the samples raises the issue of plant utilisation and its associated concerns with biodiversity conservation [56]. The over-reliance on a few plants by manufacturers may be concerning, especially when the plant parts used are stems, roots, or whole parts. Therefore, while it is recommended that appropriate quality standards for these plants used to treat malaria are established because of their popularity, it may be beneficial if equal attention is given to less explored plants, such as those that were used in less than three products in the current study (Tables 3 and 4).

The successful treatment of malaria with drugs isolated from plants, such as quinine from *Cinchona* and artemisinin from *Artemisia annua* L., clearly shows that comprehensive studies on plants that are folklorically used to treat malaria can yield valuable compounds that can be developed into beneficial pharmaceutical antimalarial dosage forms [57]. Additionally, the examples of cryptolepine and its analogues from *Cryptolepis sanguinolenta* [35], xylopic acid from *Xylopia aethiopica* [58], and gedunin, azadirone, and neemfruitin from *Azadirachta indica* [59] present potential cases of hits that could be explored to develop new antimalarial drug candidates. This can potentially curb the use of a cocktail of plants and plant parts possibly containing several phytochemicals and their associated effects.

4.8. Concerns with the characteristics of the formulations

4.8.1. Physical appearance

The particles in the seven preparations that were not homogeneous could be contaminants, filtered portions of the marc from plants used in their preparation, or precipitates that formed following the cooling of hot decoctions during production. It may not be concerning if the particles are not contaminants, as it has been found that particle aggregates in decoctions may increase the absorption of active ingredients through various mechanisms [60].

4.8.2. pH and relative density

A liquid for oral consumption that is too acidic can cause dental erosion, which can be defined as the irreversible acidic dissolution

of the surface structure of the tooth chemically in the absence of microorganisms [61]. Relative erosivity zones established from previous studies on the solubility of apatite in acid indicate that beverages with pH values of <3.0, 3.0–3.99, and ≥4.0 are considered extremely erosive, erosive, and minimally erosive, respectively [62]. This indicates that 29.41% (n = 10) and 70.59% (n = 24) of the samples may be considered erosive and minimally erosive, respectively. The suitable products in terms of pH were those that formed one of the clusters in the PCA with pH of 5.17–6.43 (Fig. 5). The acidity of the antimalarial herbal mixtures is most likely due to the types and amounts of acidic phytochemicals they contain. In addition to the fact that erosion of the tooth surface can occur as pH in the oral cavity decreases to less than 4.0, every unit decrease in pH corresponds to a 10-fold increase in enamel solubility, which can further cause a 100-fold increase in enamel demineralisation as pH drops from 4.0 to 2.0 [63]. However, the erosive potential of a liquid is influenced by how the liquid is consumed. For instance, the contact time of the acidic substance with the teeth, swallowing rate, frequency and duration of exposure to acidic beverage, the viscosity of the liquid, and drinking habits (e.g., sipping, swishing) can affect teeth erosion [64]. Therefore, a simple solution to control the erosive effect of the antimalarials is to put caution on the labels that following dose intake, the mouth should be rinsed with a neutral liquid such as water.

The relative densities of the products were in the range of 0.997–1.015, which is a very narrow range to indicate that the samples were almost as dense as water. Each product was easily pourable from its bottle.

4.8.3. Extract weight per dose

From the survey, all the herbal antimalarials were liquids and several of them had high dose volumes of up to 90 mL. We believe that manufacturers could consider formulating more concentrated mixtures to achieve low dose volumes for convenience of product intake. In addition, we recommend that solid dosage forms of these liquid products are formulated as substitutes. To achieve this, dry powder extracts could be produced from the mixtures by evaporating the solvents used for extraction. Alternatively, the mixtures could be spray-dried or freeze-dried with or without the use of adsorbents, or they could be dried and milled [65]. A powder thus obtained can then be compressed into tablets, filled directly into hard shell capsules, or processed into granules for tableting or filling into capsules after adding the relevant excipients. In this way, the tablets or capsules could be useful alternatives that are also convenient to carry compared to bulky liquid mixtures. Additionally, the capsules can mask the bitter taste of some herbs. Thus, we determined how much dry extract was contained in a dose of each product. All the samples except A-23 dried completely within 72 h in the oven to leave a solid residue. The weights of the extracts were found to be small enough for formulation into unit-dose tablets or capsules. Sample A-23, which remained a very concentrated semisolid extract, could be processed into a powder by adding absorbents such as starch, lactose, microcrystalline cellulose, and/or light magnesium carbonate [13].

4.9. Limitation of the study

Only herbal antimalarials for sale in pharmacies, OTCMS facilities, and herbal shops were analysed in this study. Therefore, it is possible that other herbal antimalarial products available to consumers were missed because they are available in other types of facilities.

5. Conclusion

Our findings from this study revealed a lack of dosing devices in some herbal antimalarial packages as well as errors in stated doses, age ranges, and tablespoon volume. Additionally, unconventional ways of stating doses were found on two products. The high usage of herbal medicines by Ghanaians makes it imperative for regulatory authorities to ensure that herbal antimalarial products have all the needed details on their labels to correctly guide consumers and prescribers and that the products are safe for consumption. Important details required include correct doses in "mL", duration of treatment, known side effects, the names of all component herbs, and batch numbers. Safety monitoring of commercial herbal antimalarials by the relevant divisions of the Ghana FDA may also reveal unregistered products that the public can be warned about. Additionally, the formulation of solid dosage forms of herbal antimalarials must be encouraged for consumers who may prefer them.

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Data availability

Research data is available upon request. Data can be obtained from the corresponding author via email.

CRediT authorship contribution statement

Hilda Amekyeh: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Doris Kumadoh:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Donatus Wewura Adongo:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Emmanuel Orman:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Sadique Abubakar:** Methodology, Investigation. **Audrey Dwamena:** Methodology, Investigation. **Mike Okweesi Aggrey:** Writing – review & editing, Writing – original draft, Methodology,

Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27032.

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