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RESEARCH ARTICLE

Field Study on the Assessment of Antimalarial Drug Quality Using Minilab Kit in India

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Abstract:

Background:

A lack of proper anti-malarial medication use can lead to drug resistance, failed therapy, and even death. It is unclear how widespread the use of fake anti-malarial medications is in India. Better malaria treatment and the execution of regulatory initiatives to improve anti-malarial drug quality necessitate regional research into the quality of available anti-malarial pharmaceuticals. This study aimed to look into the quality of anti-malarial drugs in regions of India where malaria is common. Conclusions about the prevalence of substandard anti-malarial medications in Indian communities can be drawn from the findings.

Methods:

Samples of anti-malarial pills were bought from stores in five different Indian areas. One hundred and fifty anti-malarial drug samples were gathered. Using a GPHF minilab lab kit, the quality of the following samples was determined: chloroquine (n=50), artemether lumefantrine (n=50), artesunate sulphadoxine-pyrimethamine (n=14), and primaquine (n=31).

Results:

This research confirmed that 98% of the tablets disintegrated properly in a minilab disintegration test. As a result, when compared to both the full set of standards and 80% of the samples, 99% of the samples passed the preliminary qualitative TLC test. Only 4% of samples (those with insufficient amounts of the active medicinal component) failed the quantitative HPLC test.

Conclusion:

Anti-malarial medicine counterfeiting has been found to be quite uncommon in India compared to other countries. However, further research is needed, such as post-marketing surveillance, to ensure that effective anti-malarials are distributed to the public.

Keywords: Counterfeit medicines, Substandard drugs, Thin-layer chromatography, Minilab kit, Anti-malarial agents, Antimalarial drug.

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1. INTRODUCTION

Mortality and morbidity associated with malaria remain serious worldwide health concerns, particularly in developing and underdeveloped nations. The World Malaria Report 2021 estimates that there were 241 million cases of malaria worldwide in 2020, compared to 227 million in 2019, with a predominance in WHO African areas. In 2020, the global malaria-related mortality rate was reported to be 6.27 million, a 12% increase from the previous year, with 80% of deaths occurring in children under the age of five. In 2020, nine malaria-endemic nations in the WHO South-East Asia region, including India, accounted for 5 million cases, or 2% of the global malaria burden. In addition, India accounted for around 83% of malaria cases and 82% of malaria-related deaths in the WHO South-East Asia region, with *Plasmodium vivax* causing more than a third of all cases [1]. In India, the National Vector Borne Disease Control Program reported a total of 0.19 million confirmed malaria cases in 2020, along with 93 deaths. The number of *Plasmodium falciparum* cases in 2020 was estimated to reach 0.12 million [2].

To combat this scenario, one of the most important measures is the administration of an anti-malarial medicine with optimal therapeutic response. In the community, however,

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there remains a persistent risk of counterfeit and/or poor anti-malarial medications. These pharmaceuticals are fraudulently mislabeled with regard to their identity and/or source. Counterfeiting is one of the oldest and most lucrative industries, and these drugs are mislabeled with regard to their identity and/or source [3]. Falsified medications may have right or incorrect components, insufficient quantities of active substances, or counterfeit packaging [4]. Substandard medications comprise substances that have failed laboratory quality tests or do not match the manufacturer's claims. WHO statistics indicate that over 25% of medicines used in poor countries are counterfeit or substandard, diminishing public confidence in treatment protocols [5]. Several nations have also reported percentages of more than 50%. Several anti-malarial medications have been reported to be counterfeited and used in therapeutic settings. A previous research study indicated that between one-third and one-half of the anti-malarial medicine artesunate accessible in Southeast Asia contained no or insufficient amounts of the active component [6]. Large quantities of inferior medications that do not meet the quality criteria are also utilised in the treatment of malaria. The amount and quality of the Active Pharmaceutical Ingredient (API) of typical medications degrades over time when they are exposed to environmental conditions, such as light, temperature, and humidity [7]. The clinical use of inferior and counterfeit anti-malarial medications, which are difficult to detect and identify, poses a significant hazard to public health. These counterfeit/substandard drugs lead to treatment failure due to a decrease in efficacy and a rise in the establishment of drug resistance, as well as significant adverse effects from improper excipients/active components, resulting in an increase in morbidity and mortality rates [4].

A few global research studies assessing the quality of anti-malarial medications are required; consequently, such studies should be promoted given the paucity of data on this crucial problem. Population density necessitates more demanding evaluation methodologies for anti-malarial drug quality in developing nations, like India. This study has assessed the quality of antimalarial medications circulating in India's malaria-endemic regions.

2. METHODOLOGY

2.1. Study Design

The research has highlighted various geographical zones in India, including Uttar Pradesh (U.P.), Mizoram, Meghalaya, Gujarat, and Madhya Pradesh, based on malaria endemicity. Antimalarial medications, including Artesunate + Sulphadoxine-pyrimethamine (AS + SP), Artesunate + Lumefantrine (AL), Chloroquine (CQ), and Primaquine (PQ), were acquired for quality assurance testing. Between July 2015 to May 2018, encompassing more than five months a year, samples were collected from each of the regions. The antimalarial medications were acquired from licensed and unauthorised marketplaces, such as private pharmacies, hospitals, street sellers, and shops. The frequency distribution of sample quantities is depicted in Fig. (**1**).

2.2. Chemicals and Reagents

All the chemicals used in the study were of analytical grade. The reagents included hydroxylamine hydrochloride, sodium hydroxide, iron (III), chloride, phosphoric acid, hydrochloric acid, phenolphthalein, bromophenol, ethanol, methylene chloride, ethyl acetate, chloroform, acetone, toluene, methanol, and acetic acid, purchased from Sigma Aldrich, St. Louis, MO, USA.

2.3. Qualitative and Quantitative Assessment of Collected Samples

A qualitative analysis of procured antimalarial drugs was conducted using the Global Pharma Health Fund Minilab test kit (GPHF- Minilab kit). GPHF-Minilab kit is an accessible technique for simple, fast, and definitive detection of fabricated and substandard drugs. The kit contains all the labware, reagents, and standards for comparison of running antimalarials

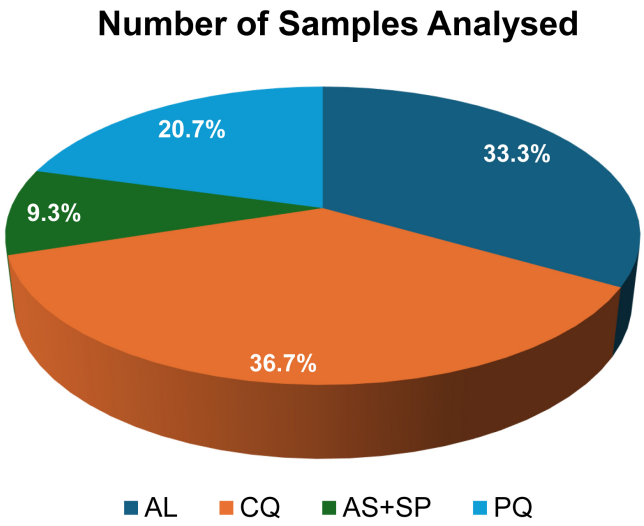

Fig. (1). Distribution of samples by quantity.

with the standards given in the kit. This qualitative test includes physical/visual inspection, disintegration test, colorimetric test, and Thin-layer Chromatography (TLC); also, High-performance Liquid Chromatography (HPLC) was performed for quantitative assessment of API.

2.4. Physical/visual Inspection

Prior to the qualitative and quantitative assessment tests, all finished medicinal products were visually screened and identified by a specific label, as required by the national legislation. The packaging was checked for legible labeling of active constituents, with international nonproprietary names and amount of all ingredients, dosage form and the number of dosage units, mass, or volume per package, batch or lot number assigned by the manufacturer, holograms, odd font, expiration date, special storage conditions or handling precautions that may be necessary, and registration number. During the visual inspection, the packaging was verified to be appropriate with no discoloration or chipping of the medicine [8].

2.5. Disintegration Test

Disintegration is defined as that state in which no residue of tablets or capsules, except fragments of undissolved coating or capsule shells, remains in the test solution. One tablet or capsule was placed in a wide-neck bottle containing 100 ml of water at 37°C. This test was repeated for five more tablets. The batch was considered to pass the test if all six tablets disintegrated. The entire test cycle was repeated if any tablet or capsule failed to disintegrate. The batch was rejected if any further tablet or capsule failed again in the second and third runs [9].

2.6. Colorimetric Test

The colorimetric technique is one of the methods for quickly identifying poor-quality medicines on the basis of the absence of the API. Colorimetric testing is based on chemicals undergoing color change when reacting with certain compounds to provide qualitative data about drug quality. Fast Red TR dye test was used to detect the active ingredient in some antimalarials; it turned yellow, indicating the presence of artesunate [10]. Similarly, AL and CQ provided a reddish-brown color with FTR. The samples were tested for the presence of API using the FTR Red TR dye test [11].

2.7. Thin-layer Chromatography

Thin-layer Chromatography (TLC) is a reliable and effective method for the validation of the identity and assessment of the API content in the pharmaceutical product/drug. After checking the presence of compounds in the corresponding drug by FTR, each sample was analyzed by TLC. Minilab kit simplifies the analysis by providing reference tablets that can be used to prepare 100% and 80% dosage strengths for comparison. In this study, TLC was performed on a sheet of glass/plastic/aluminum foil and a thin layer of adsorbent, usually silica gel, and aluminium oxide or cellulose coated on it acted as the stationary phase. After this, standards of 100% and 80% were applied to the plate at a distance of 1.5" from the bottom of the TLC plate. 100% standard was applied on the left edge and 80% on the right edge of the plate, and in between these, two samples were applied. The development chamber having a solvent mixture in it acted as the mobile phase. When the plate was kept in the chamber, the solvent mixture was drawn up to the plate *via* capillary action. It was allowed to run up to three-fourth part of the plate. Following this, the plate was removed from the chamber and then allowed to dry, and observations were taken and recorded for the movement of the sample (drug to be analyzed) in the stationary phase [12].

2.8. High-performance Liquid Chromatography

A rapid, low-cost, precise HPLC method was used for the quantitative assessment of CQ, AL, AS + SP, and PQ. HPLC procedure has been reported to be suitable for the estimation of API in each anti-malarial sample adopted from the pharmacopoeias. The samples that failed the qualitative tests were subjected to HPLC analysis at Shri Ram Institute for Industrial Research, New Delhi. For analysis, a calibration curve was prepared using varying concentrations of the reference standards provided in the kit. The Area Under the Curve (AUC) for each concentration was determined from six replicates and an average AUC was estimated [13]. The quantified API was analyzed and results were obtained using report generated method [14 - 16].

The analysis of such combinations should ideally refer to established pharmacopeial standards. Unfortunately, there is no direct mention of a specific pharmacopeia volume that details HPLC methods for artesunate and sulfadoxine-pyrimethamine directly in the sources. However, the United States Pharmacopeia (USP) and the International Pharmacopoeia are commonly referenced for methods and standards related to antimalarial drugs.

2.8.1. HPLC Method and Validation

A typical HPLC method for analyzing these compounds might involve the following parameters based on the requirements:

Column: C18 column, 250 x 4.6 mm, 5 µm particle size

Mobile phase: A mixture of buffer (pH 3 ±0.5) and acetonitrile in a 40:60 v/v ratio

Flow rate: 1.5 mL/min

Detection: UV detector at dual wavelengths of 210 nm and 303 nm

This setup allows for precise identification and quantification of the APIs in the tablets.

The validation of this HPLC method should adhere to the International Council for Harmonisation (ICH) guidelines, specifically ICH Q2(R1), which outlines the following validation parameters:

Specificity: This demonstrates that the method can unequivocally assess the analyte in the presence of components, such as impurities, degradants, and matrix.

Linearity: It establishes the method's ability to obtain test results proportional to the concentration of analyte within a given range.

Accuracy: It confirms the closeness of the test results to the true value.

Precision: This parameter evaluates repeatability and intermediate precision by performing multiple measurements under varied conditions.

Detection limit and quantitation limit: It determines the lowest amount of analyte that can be detected and quantified with acceptable precision and accuracy.

Robustness: It assesses the method's reliability under a variety of conditions, including changes in pH, mobile phase composition, and column temperature.

3. RESULTS

3.1. Distribution of Samples

The drugs procured in this study were readily available over the counter without a prescription in Gujarat, Madhya Pradesh, Uttar Pradesh, Meghalaya, and Mizoram pharmacies and other sources. For the period of 2015-2018, data were compiled on 150 medicines collected and tested across 5 states of India, as shown in Table **1**. Out of 150 medicines procured from all sites, the majority were CQ (36.7%), AL (33.3%), PQ (20.7%), and AS+ SP (9.3%).

3.2. Physical Parameters: Weights and Dimensions

The physical attributes of the drugs tested, including weight and dimensions, were the same as those of the authentic tablets. This study found a good correlation between both physical attributes and packaging material on one hand, and qualitative testing (basic tests) of API on the other because the labeled contents on the packaging material were found to be correct.

Samples collected from five states were tested in triplicate. Most of the drugs tested passed the disintegration test; however, a few CQ (3.64%) and AL (2%) tablets showed breakdown failure. Additionally, CQ (1.82%), AL (4%), and PQ (9.7%) failed in the HPLC test. Also, AL (2%) failed in the TLC test.

This study is the first report on the field survey of anti-malarial drug quality in malaria-endemic regions in India. In this study, about 98% of the drugs tested passed the Minilab disintegration test and 99% passed the preliminary qualitative TLC test in comparison to 100% and 80% of the reference standards (Fig. **2**). About 96% of samples passed the quantitative HPLC test and 4% of samples with low API did not pass. The variable disintegration and retention factor might be due to substandard quality or other factors, including storage, due to high temperature and moisture. However, HPLC analysis confirmed standard API in the tablets. C18 column, 250 x 4.6mm, 5µm particle size in isocratic mode was used. The mobile phase comprised the buffer (pH 3 ±0.5) and acetonitrile (40:60 v/v). The flow rate was adjusted to 1.5ml/min and detection was performed with a dual UV detector, *i.e*., 210 and 303nm. The precision of the proposed HPLC methodology was measured in terms of retention time (Fig. **3**). HPLC chromatograms have been shown for the formulations of chloroquine phosphate (Fig. **4**) and primaquine phosphate (Fig. **5**), the marketed formulation of artesunate + sulphadoxine-pyrimethamine (Fig. **6**), and the marketed formulation of artemether-lumefantrine (Fig. **7**).

HPLC results are presented with accompanying statistical analysis to ensure the validity and reliability of the data. Statistical analysis provides a clear understanding of the variability and precision of the measurements, enabling better interpretation of the results.

Table 1. TLC methods for different antimalarials.

Sample Tablet/Refs	Dissolution Material	Development	Colour of Spot	Detection	Observation of Spot After Staining
Chloroquine [28]	Water	Ethyl acetate (5ml): methanol (20ml): conc. ammonia (0.5ml)	Strong blue	Iodine	Reddish-brown
Artemether [29]	Acetone	Ethyl acetate (4ml): glacial acetic acid (2ml): toluene (18ml)	--------	Methanol (85ml): sulfuric acid (5ml)	Grey
Lumefantrine [30]	Acetone	Ethyl acetate (4ml): glacial acetic acid (2ml): toluene (18ml)	Strong blue-violet	Iodine	Orange-brown
Artesunate [31]	Methanol	Ethyl acetate (18ml): acetone (4ml): glacial acetic acid (0.1ml)	---------	Methanol (85ml): sulphuric acid (5ml)	Grayish brown
Sulfadoxine-pyrimethamine [32]	Methanol	Ethyl acetate (15ml): methanol (5ml):	Blue-violet	Iodine	Yellowish-brown
Primaquine [33]	Water	Ethyl acetate (5ml): methanol (20ml): conc. ammonia (0.5ml)	Blue-violet	UV light (254nm)	Yellowish-orange

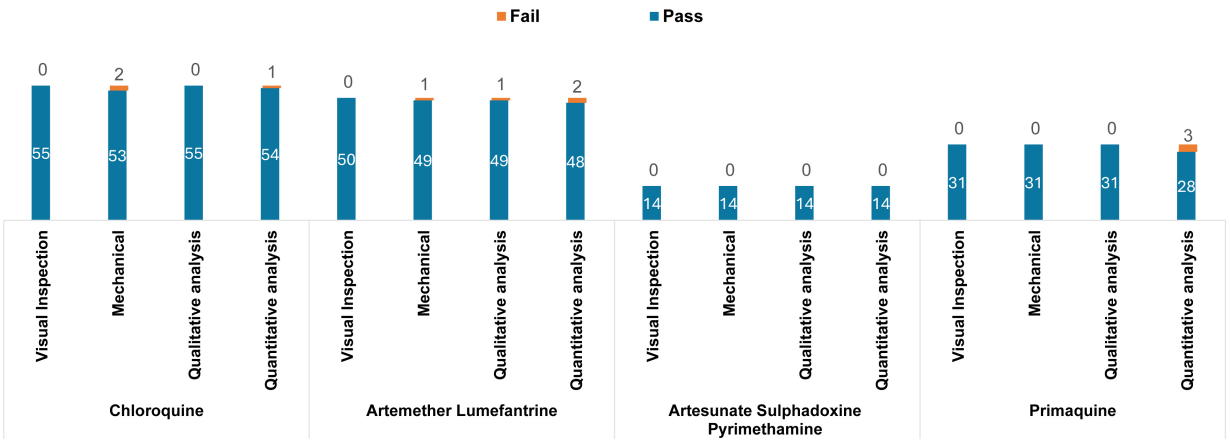

Fig. (2). Testing results of different anti-malarial medicines by qualitative and quantitative assessment (GPHF Minilab kit).

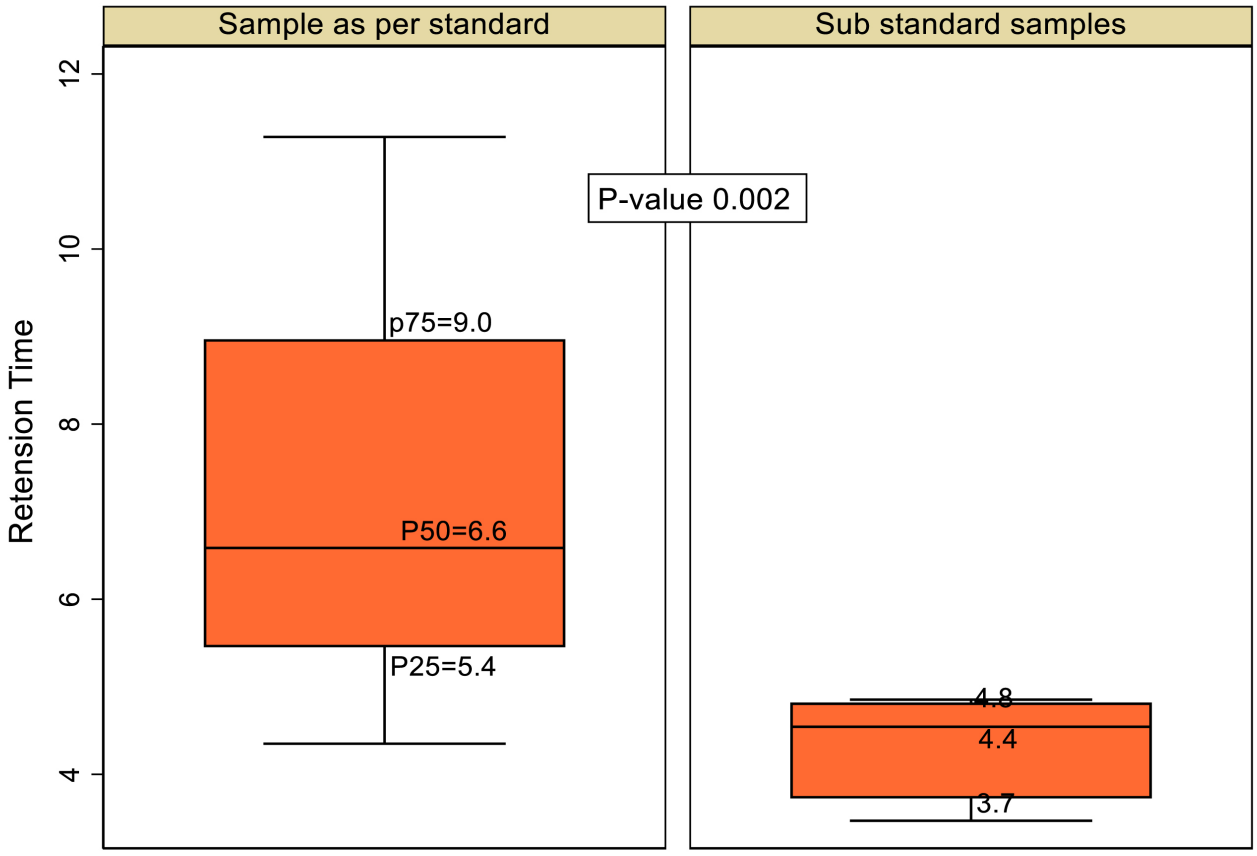

Fig. (3). Retention time indication between substandard and standard anti-malarial drugs.

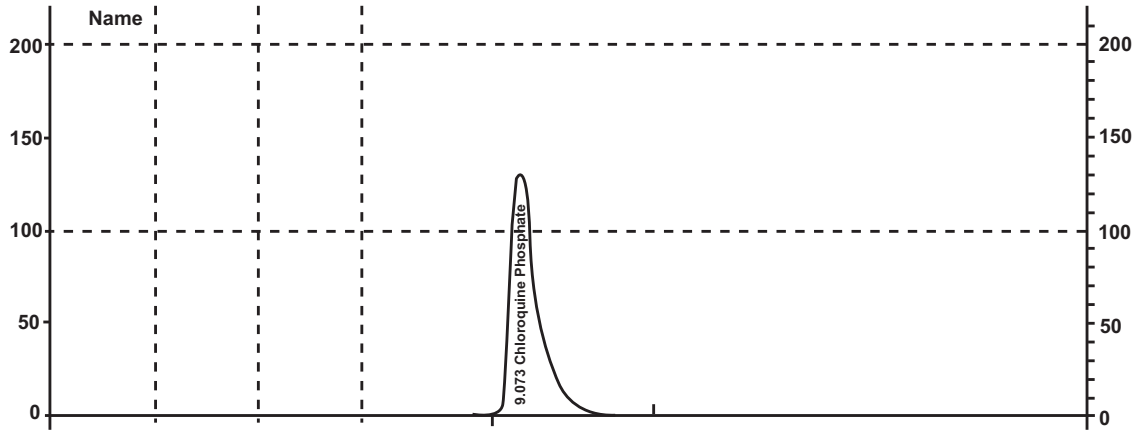

Fig. (4). Chromatogram obtained by HPLC for analysis of marketed formulation of chloroquine phosphate.

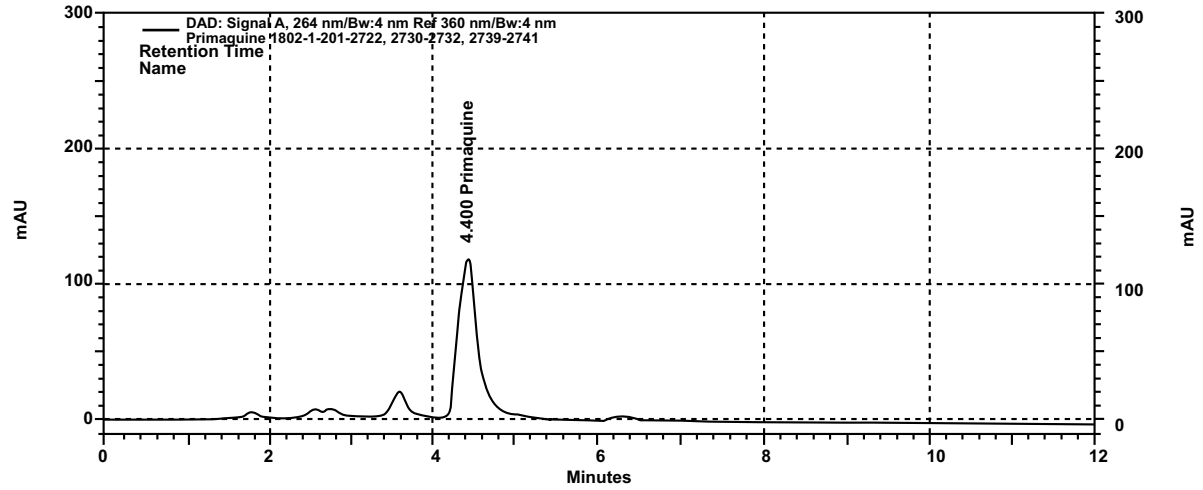

Fig. (5). Chromatogram obtained by HPLC for analysis of marketed formulation of primaquine phosphate.

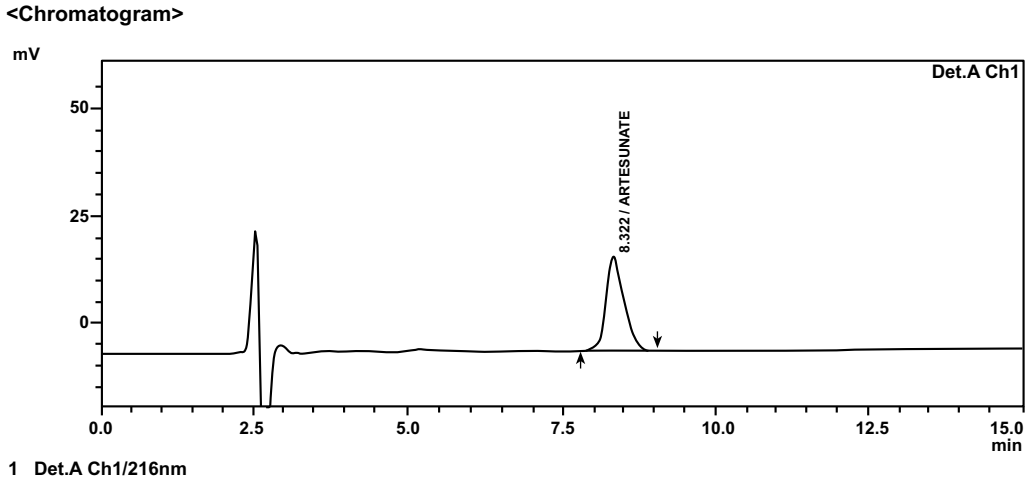

Fig. 6 contd.....

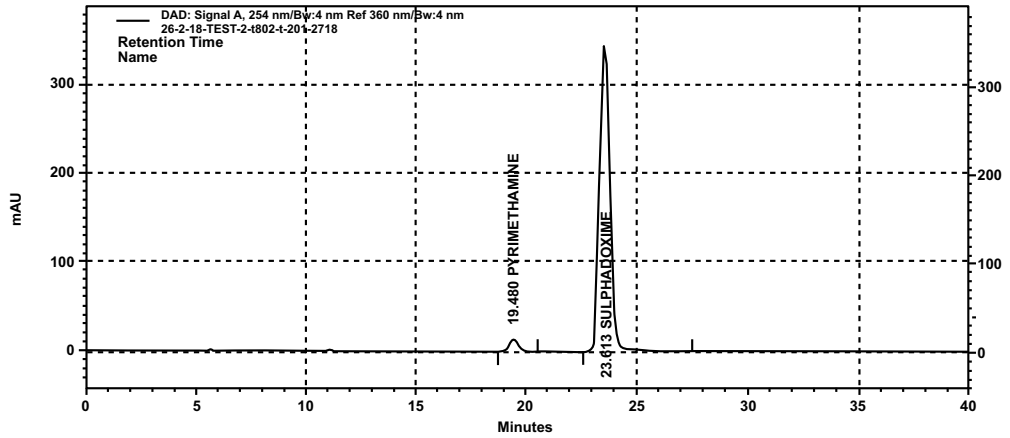

Fig. (6). Chromatogram obtained by HPLC for analysis of marketed formulation of artesunate + sulphadoxine-pyrimethamine.

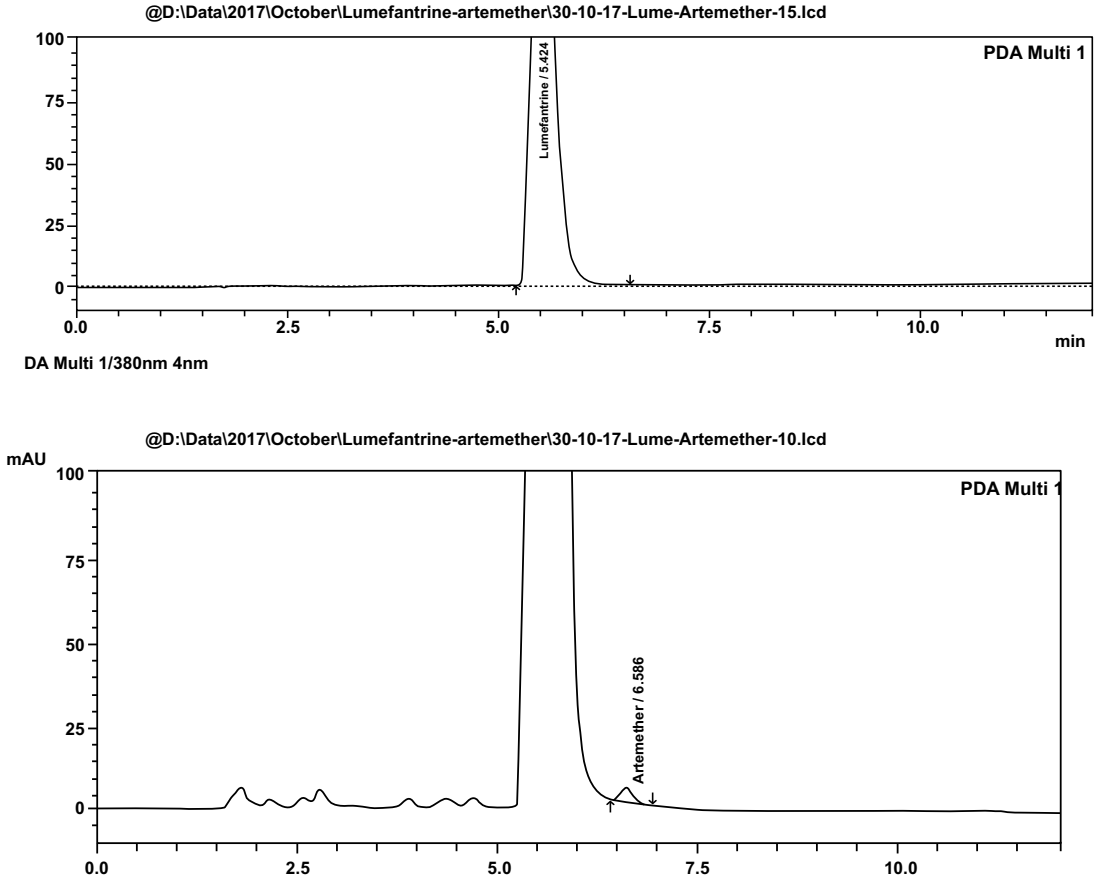

Fig. (7). Chromatogram obtained by HPLC for analysis of marketed formulation of artemether lumefantrine.

4. DISCUSSION

Treatment with an effective standard anti-malarial medicine is one of the key traditional treatments for combating mortality and morbidity caused by malaria. However, poor medicines that fail quality evaluation result in economic loss, loss of faith in the healthcare system, and the development of drug resistance. In order to protect the quality of medications, stringent regulatory measures concerning the testing and evaluation of anti-malarial drugs should be considered. In the South Asian region, 53% of anti-malarial medications have been determined to be of inadequate quality. ACT is the first-line treatment for *P. falciparum* infection [17]. According to national drug policy, *P. vivax* cases should be treated with CQ (25 mg/kg b.w.), followed by primaquine (0.25 mg/kg b.w), for 14 days to avert reversion. According to national drug policy, the current recommended ACT constitutes the fixed-dose combination of artemether and lumefantrine for the NE region (NVBDCP, 2015). The quality of CQ and PQ in pharmacies of five Indian states has been found to be better, with only 1.82% (CQ) and 9.7% (PQ) failure rate.

An increased incidence of substandard/counterfeit antimalarials in India is of utmost relevance given the regularity with which they are used to treat fever/malaria. This study has performed the nationwide field inspection of anti-malarial drug quality in India's malaria-endemic regions between 2015 and 2018 using the Minilab kit. Poor-quality anti-malarial medications have been found to be uncommon, which is comforting. Among the medicines examined, just 1% failed TLC and 4% failed HPLC. In certain Indian states, AS+SP and AL have revealed failure rates of 0% and 4%, respectively; however, other research studies suggest that these rates may be lower [18]. The quality of artesunate and amodiaquine tablets has been found to be substandard in the Ghana region [19]. 35% of artemisinin-based combination therapies were found to be substandard in the Ghana market [20]. Another study in India on counterfeit drugs has found a significant number of artesunate samples to be below (*i.e*., 71-89.2%) the normal manufacturing range (90-110% stated content) when analyzed using liquid chromatography-mass spectrometry [18].

In addition, substandard antimalarials, such as CQ (50%), pyrimethamine-sulphadoxine (13%), quinine (12%), amodia-quine (8%), artesunate (12%), and artemether-lumefantrine (5%), were observed in Burkina Faso [21]. However, antimalarials, such as CQ, quinine, and antifolates failed to meet the pharmacopeial specifications in 38%, 74%, and 12% of the collected samples, respectively, in Cameroon [22].

Previous studies have revealed several antimalarial drugs, such as artemether, artesunate, CQ, mefloquine, quinine, sulfadoxine-pyrimethamine, and tetracycline, to be fake with sub-therapeutic doses of correct ingredient, or in fake packaging, or with substandard ingredients [23]. The Dondorp survey indicated 53% of 118 tablets of artesunate and 9% of 44 tablets of mefloquine to be counterfeit because of less active ingredients [24]. Here, AS+SP indicated 0% failure rate and AL 4%. In addition, substandard anti-malarial medicines were also found to exist in Cameroon (7.1%), the Democratic Republic of Congo (2.7%), and Nigeria (1.1%) [25].

Therefore, the circulation of counterfeit drugs in India is comparatively less as compared to other states. In our study, a comparison of failure rates of different states in India has been given. A greater number of substandard samples was found in NE (Mizoram, Meghalaya) as compared to other states of India. A total of six samples contained low-active pharmaceutical ingredients. This report will be sent to The Central Drugs Standard Control Organisation (CDSCO) for necessary action. The variability in disintegration and retention factors might be due to inadequate storage, humidity, and insufficient amount of API added during formulation.

The sample size of antimalarial drugs used in this study was appropriate to make preliminary conclusions regarding the extent of counterfeit drugs. The study also targeted important malaria-endemic regions and collected drugs from licensed and unlicensed sources. Moreover, in this study, 10% of the samples were found to be expired during purchasing. Thus, the government should enforce checks and regulations for drug supply to ensure treatment efficacy and prevent the development of resistance to these substandard anti-malarials [26]. The high prevalence of substandard anti-malarials in India may be majorly due to poor regulatory measures [27] (Table **1**).

CONCLUSION

This study has aimed to precisely determine the level of substandard/counterfeit drug use utilizing a straightforward and cost-effective method. Except for six samples, all samples obtained from various places have passed the test. The circulation of substandard pharmaceuticals in the market can lead to drug resistance, treatment failure, economic loss, and death. In light of these findings, it is vital that future research be conducted in malaria-endemic regions. To ensure the safety and efficacy of anti-malarial medications reaching the Indian public, there is an urgent need to strengthen regulatory requirements from pharmaceutical management systems, including post-marketing surveillance.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to itssubmission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

API	=	Active Pharmaceutical Ingredient
AL	=	Artesunate + Lumefantrine
CQ	=	Chloroquine
PQ	=	Primaquine
TLC	=	Thin-layer Chromatography
HPLC	=	High-performance Liquid Chromatography
AUC	=	Area Under the Curve

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article. All available raw data will be shared upon reasonable request to the corresponding author [T.A].

FUNDING

None.

CONFLICT OF INTEREST

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

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