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RESEARCH ARTICLE

Detection of Poor Quality Artemisinin-based Combination Therapy (ACT) Medicines Marketed in Benin Using Simple and Advanced Analytical Techniques

Achille Yemoa[1*,#], Védaste Habyalimana[2,3,#], Jérémie K. Mbinze[4], Victoria Crickboom[5], Benjamin Muhigirwa[6], Agnès Ngoya[4], Pierre-Yves Sacré[2], Fernand Gbaguidi[7], Joëlle Quetin-Leclercq[8], Philippe Hubert[2] and Roland D. Marini[2]

[1]*Laboratoire de Chimie Analytique et Analyse des Médicaments (LCAM), Faculté des Sciences de la Santé, Ecole de Pharmacie, Université d'Abomey Calavi, Cotonou, Bénin;* [2]*Department of Pharmacy, CIRM, Laboratory of Analytical Chemistry, University of Liege (ULg), Liège, Belgium;* [3]*Rwanda Biomedical Center/Medical Procurement and Production Division, Kigali, Rwanda;* [4]*Laboratory of Drug Analysis, Faculty of Pharmaceutical Sciences, University of Kinshasa, Kinshasa, Democratic Republic of Congo;* [5]*Faculté de pharmacie et des sciences biomédicales de l'UCL, Université Catholique de Louvain (UCL) Bruxelles, Belgium;* [6]*Medical Services Department, Rwanda Social Security Board (RSSB), Pharmacies Division, Kigali, Rwanda;* [7]*Laboratoire de Chimie Pharmaceutique Organique, Faculté des Sciences de la Santé, Ecole de Pharmacie, Université d'Abomey-Calavi, Cotonou, Bénin;* [8]*Louvain Drug Research Institute (LDRI), Pharmacognosy Research Group, Université Catholique de Louvain (UCL), Bruxelles, Belgium*

Abstract: ***Background*:** Poor quality antimalarial medicines still represent a threat to the public health, especially in Sub-Saharan Africa which bears a disproportionate share of the global burden of malaria. It is essential and urgent to strengthen mechanisms against counterfeit medicines. One of the approaches is regular market surveillance through quality controls.

***Methods*:** 12 samples of artemether/lumefantrine were collected from formal and informal drug sellers in Cotonou (Benin) as well as additional other similar samples from Rwanda (13 samples) and from D.R. Congo (9 samples). Thin Layer Chromatography (TLC) as classical and simple identification test was applied in Benin while an analytical chemistry laboratory in Belgium (ULg, Pharmacy Department) was asked for further analyses with HPLC and Raman spectroscopy using a developed and validated HPLC method for rapid analysis of artemether/lumefantrine.

***Results*:** The results obtained in Belgium confirmed the lack of the two active ingredients in the suspected sample of ACT medicine from Benin whereas some samples from Rwanda and D.R. Congo were found to present risk of substandard drugs either for under-dosing or over-dosing.

***Conclusions*:** Counterfeit/falsified of artemisinin-based combination therapy (ACT) medicines are really scourge that needs to be fought through strong collaboration between public health authorities and appropriate quality control laboratories.

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1. INTRODUCTION

Artemether/Lumefantrine (AL) was the first fixed-dose artemisinin-based combination therapy recommended and pre-qualified by the World Health Organization (WHO) for the treatment of uncomplicated malaria caused by *P. falciparum*. It is currently recommended as a first-line treatment for uncomplicated malaria in several countries [1].

The efficacy of AL in Africa and South America remains high, with treatment failure rates generally below 10%. Currently, 40 countries in Africa and 6 countries in South America are using this combination as first or second-line treatment. In Angola, Burkina Faso, Gambia, Ghana, Malawi, Niger, Nigeria and Zimbabwe, isolated studies conducted between 2006 and 2013 have shown treatment failure rates with AL above 10% [1].

In 2014, global financing for malaria control increased from an estimated US$ 0.96 billion in 2005 to US$ 2.5 billion. As far as spending on malaria control commodities (artemisinin-based combination therapies "ACTs", insecticide-treated bed nets "ITNs", insecticides and spraying equipment for indoor residual spraying "IRS", and rapid diagnostic tests "RDTs") are concerned, it is estimated to have increased over the past 11 years, from US$ 0.04 billion in 2004 to US$ 1.6 billion in 2014, and accounted for 82% of

*Address correspondence to this author at the Laboratoire de Chimie Analytique et Analyse des Médicaments (LCAM), Faculté des Sciences de la Santé, Ecole de Pharmacie, Université d'Abomey Calavi, Cotonou, Bénin; Tel: +229 97 078207; E-mail: achille.yemoa@fss.uac.bj

[#]These authors have contributed equally to this manuscript.

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international malaria spending in 2014. ACTs represented 25% of total commodity spending in that year [1].

The therapeutic benefits of ACTs are their high efficacy, rapid action and the reduced likelihood of resistance development. In order to make best use of this medicine combination, it is very important to address issues of quality. According to the WHO, 200,000 deaths over one million that occur from malaria annually would be avoidable if the available medicines were effective, of good quality and used correctly [2]. Unfortunately, recent studies report the circulation of higher levels of poor quality antimalarial medicines (*i.e.* counterfeit/falsified, substandard, and degraded) in most malaria endemic countries, and therefore highlighting the need of strengthening national drug regulatory authorities through quality assurance and quality control (QC) systems, as well as regular market surveillance in order to secure the public health [3].

Analytical chemistry applying separative screening methods, especially with liquid chromatography (LC), are suitable in fighting against the spread of counterfeit/falsified and other poor quality medicines in this context [4, 5].

In the framework of fighting against poor quality antimalarial medicines marketed in Benin, especially ACTs; we conducted several analyses to assess the quality of suspected samples. At first, thin layer chromatography (TLC) was applied as simple identification technique allowing to detect the presence or not of the claimed active ingredients prior to their assay. Then, further analyses including HPLC and Raman spectroscopy were carried out to gain more information on suspected samples and similar samples from Rwanda and DRC in order to aware their status. The applied HPLC method was developed and validated in-house during our previous study for rapid analysis of AL [5].

2. MATERIALS AND METHOD

2.1. Samples

Drug sampling was done in Cotonou, the economic capital of Benin. This southern city concentrates most health facilities (about 45% of medical units installed in urban areas), the big markets in the country [6] including the international market Dantokpa. The samples, herein tablets were collected from formal markets in pharmaceutical establishments (pharmacies opened to public) and informal drug sellers. Twelve samples were collected: 3 from pharmacies opened to public (formal system) and 9 from informal vendors (informal market system). They were submitted to visual inspection and instrumental analyses.

Additional samples were collected from Rwanda (13 samples) and D.R. Congo (9 samples), and analyzed at the University of Liège (ULg)/Pharmacy Department-Laboratory of analytical chemistry (Belgium).

2.2. Visual Inspection

According to the WHO guidelines for visual inspection of samples [7], we focused on the control of packaging, of labeling and of physical appearance of the pharmaceutical forms namely the specific size, the shape and the color in order to assess any abnormal presentation that can be an indice of potential counterfeiting or deterioration [8]. All samples were further submitted to instrumental analyses to check the presence or not of the active ingredients, the presence of undeclared compounds in the formulation, impurities or sub-degradation compounds when detectable as well. The Fig. (**1**) summarizes the analytical steps that were followed during this study. Additional pharmacopoeial tests were done namely uniformity of weight and disintegration tests [9, 10].

2.3. Instrumental Analysis Methods

2.3.1. Chemical and Reagents

Methanol (HPLC gradient grade), anhydrous acetic acid, toluene, ethyl acetate, concentrated sulfuric acid (96%), formic acid (98%-100%) and orthophosphoric acid European Pharmacopoeia grade (85%) were purchased from Merck (Darmstadt, Germany) and ammonium formate (99%) was from BDH Prolabo (Almere, Netherlands).

Ultrapure water was obtained from a Milli-Q Plus 185 water purification system from Millipore (Billerica, MA, USA). Antimalarial drugs containing AM (20, 40 or 80 mg) and LF (120, 240 or 480 mg) were purchased from formal and informal drug sellers.

2.3.2. Thin Layer Chromatography

We used an adapted standard operating procedures (SOP) provided with the MiniLab®. The GPHF-Minilab® is a mini-laboratory used in developing countries by medical stores and hospital managers, drug inspectors, and other authorities to detect counterfeit and substandard pharmaceuticals to provide basic quality controls. A model is available at the Benin National Quality Control Laboratory of Medicines and other Health Commodities, Ministry of Health (Cotonou). We have adapted our protocol from this model. Each sample was monitored on TLC plates as stationary phase made of silica gel 60F254S (Merck; Germany) while the mobile phase was a mixture of (toluene/ethyl acetate/anhydrous acetic acid (9: 2: 1; v/v/v). The lamp detection-UV was done at 254 nm for lumefantrine while for artemether, we used a spray reagent (methanol/sulfuric acid concentrated (19:1; v/v) followed by 5 minutes heating.

A stock solution of reference standards of artemether (AM) (2 mg/mL) and lumefantrine (LF) (12 mg/mL) was prepared in methanol acidified by anhydrous acetic acid (9:1; v/v). Dilutions were performed in methanol in order to obtain solutions at 3 different concentration levels:

Level 1 (60%): 1.2 mg/mL (for AM) - 7.2 mg/mL (for LF);

Level 2 (80%): 1.6 mg/mL (for AM) - 9.6 mg/mL (for LF);

Level 3 (100%): 2 mg/mL (for AM) - 12 mg/mL (for LF);

For the samples, powdered (n = 10 tablets) or liquid (n = 2 bottles) portions were taken and treated in the same way as reference solutions to give final expected concentrations of 2 mg/mL (for AM) and 12 mg/mL (for LF). The solutions were freshly prepared and protected from light. They were centrifuged at 3500 rpm for 5 minutes at 25°C. The super-

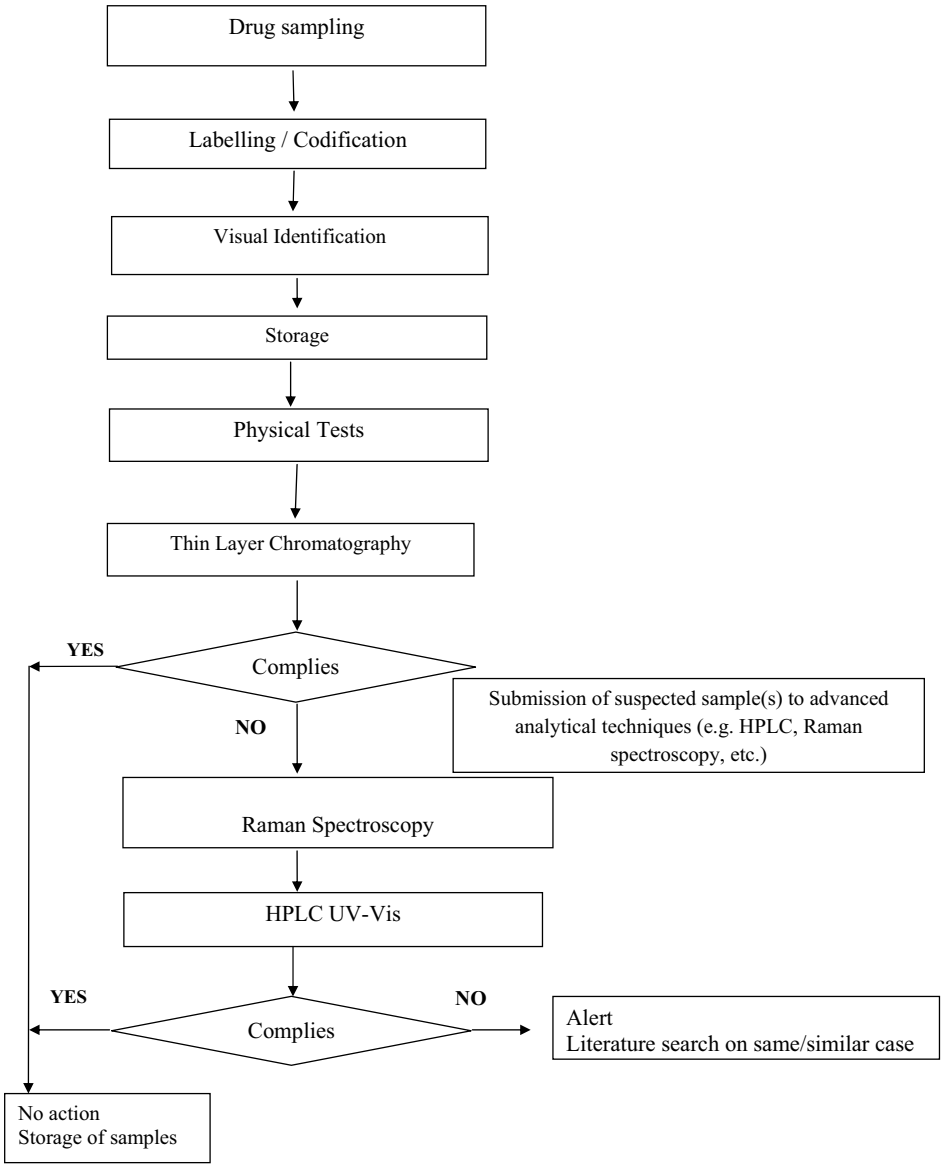

Fig. (1). Flowchart of the analytical and decisional approach.

natant was used for TLC analysis. All samples were analyzed in duplicate on the TLC plate.

For identification purposes, we compared the Rf value and the spot intensity of the standard reference against those observed with the sample solution.

2.3.3. Raman Spectroscopy Method

Intact tablet samples *vs*. intact small quantities of reference materials were used. The samples were analyzed with LabRAM HR Evolution (Horiba scientific, Kyoto, Japan) instrument equipped with two-dimensional Newton 970 front-illuminated EMCCD detector (1600 × 200 pixel sensor) (Andor Technology Ltd, Belfast, UK), Leica 50× Fluotar LWD objective and 785 nm laser with a power of 45 mW (XTRA II single frequency diode laser, Toptica Photonics AG, Munich, Germany). A 300 gr/mm grating was used to record the spectra in the spectral range of 1853-464 cm^{-1}.

The confocal slit-hole was fixed at 200 μm; each spectrum results from two acquisitions per 1 second. The spectra were collected with the LabSpec 6 (Horiba Scientific) software. Once acquired, the spectra were baseline corrected using the Asymmetric Least Squares (AsLS) algorithm with a λ value of 10^5 and a p-value of 10^{-3}. The baseline corrected spectra were the analyzed by MCR-ALS with non-negativity constraints on both concentration and spectra. Two spectra were resolved [11, 12]. The baseline corrected spectra were then scaled between 1 and 0 and compared to the spectral database. All spectrum processing and correlation coefficient computations were performed using Matlab R2013a software (The Matworks, Natick, MA, USA) and in-house routine coding.

2.3.4. HPLC Analyses

HPLC analyses were performed according to the methods described in [5] with some few adaptations. They were carried out on a Waters 2695 Alliance (Waters, Milford, MA, USA) separation module coupled to Waters 2996 photodiode array (PDA) detector (Waters). The system was controlled with Empower 2.0 software (Waters). The chromatographic

separation was done in a Zorbax SB-C18 (dp 3.5 µm) column (100 mm × 4.6 mm ID) maintained in a controlled compartment at 25°C, applying as mobile phase an isocratic mixture of methanol and 10 mM ammonium formate buffer adjusted to pH 2.8 with formic acid (85:15, v/v); the pump flow rate was 0.7 mL/min. The sample solutions were maintained in a controlled compartment at 15°C. The injection volume was 6 µL. The UV detection wavelength was fixed at 210 nm. However, the UV spectra were recorded online from 210 nm to 400 nm.

3. RESULTS AND DISCUSSIONS

Our sampling (n = 9) took place at the biggest unofficial market "Adjegounlé" (located at the international market Dantokpa) with two additional markets in Cotonou: Fifadji and Gbegamey. Three (n = 3) samples were collected from official pharmacies.

Visually, none of the samples was expired at the day of purchase; only three inserts were written in French (official language in Benin) while all others were written in English. Irregularities were observed in the physical appearance of several samples such as small brown or black spots leading to suspect contaminants. One batch presented a non-homogeneous color. Moreover, among the samples from Benin, we noticed a sample not containing the indicated quantity of blisters probably due to the bad habit of patients who buy incomplete doses for their medication and that the missing blister was already sold earlier. All samples (n = 10) met the requirements for the uniformity of weight test (when weighed singly, the deviation of the individual masses from the average mass has not exceed 5%) [10]. One sample failed the disintegration test fixed at 30 minutes for film coated tablets [9], and the tablets were not yet disintegrated after 3 hours.

The twelve samples were coded for confidentiality, and were submitted to analysis with TLC. Eleven out of twelve samples were found to contain AL. Indeed the Rf value and the spot intensity of these two active ingredients were equivalent and similar to those of the standard solutions. The remaining sample (Fig. **2**) failed to that test (*i.e.* Coartem®; Batch number F2261; Manufactured date: 01/2014; Expired date: 02/2018; collected from the market of Fifadji). It corresponds to the sample that failed the disintegration test (time over 3 hours), thus it was suspected to contain no active ingredient after two tests failures.

In Benin, a pilot study conducted in 2010 on the quality control of some antimalarial drugs sold in the same unofficial market Adjégounlè (Dantokpa market), reported that 2/3 of artemether- lumefantrine samples failed with the standards of the pharmacopoeia [13].

Thus we decided to focus on the sample having failed preliminary tests in our study, and submitted it to further analyses with advanced analytical techniques such as Raman spectroscopy and HPLC available at our partner Laboratory of Analytical Chemistry (GMP certified and WHO prequalified) based at the University of Liege (Belgium).

Raman spectroscopic analysis was done to check whether the suspected Coartem® contains a known compound, by comparing its spectral characteristic to a spectral database created for this purpose to generate candidate products that are likely to be in the composition of the suspected medicine. By comparing the sample to earlier AL recorded database, matching result are: Artemether (r = 0.3343), lumefantrine

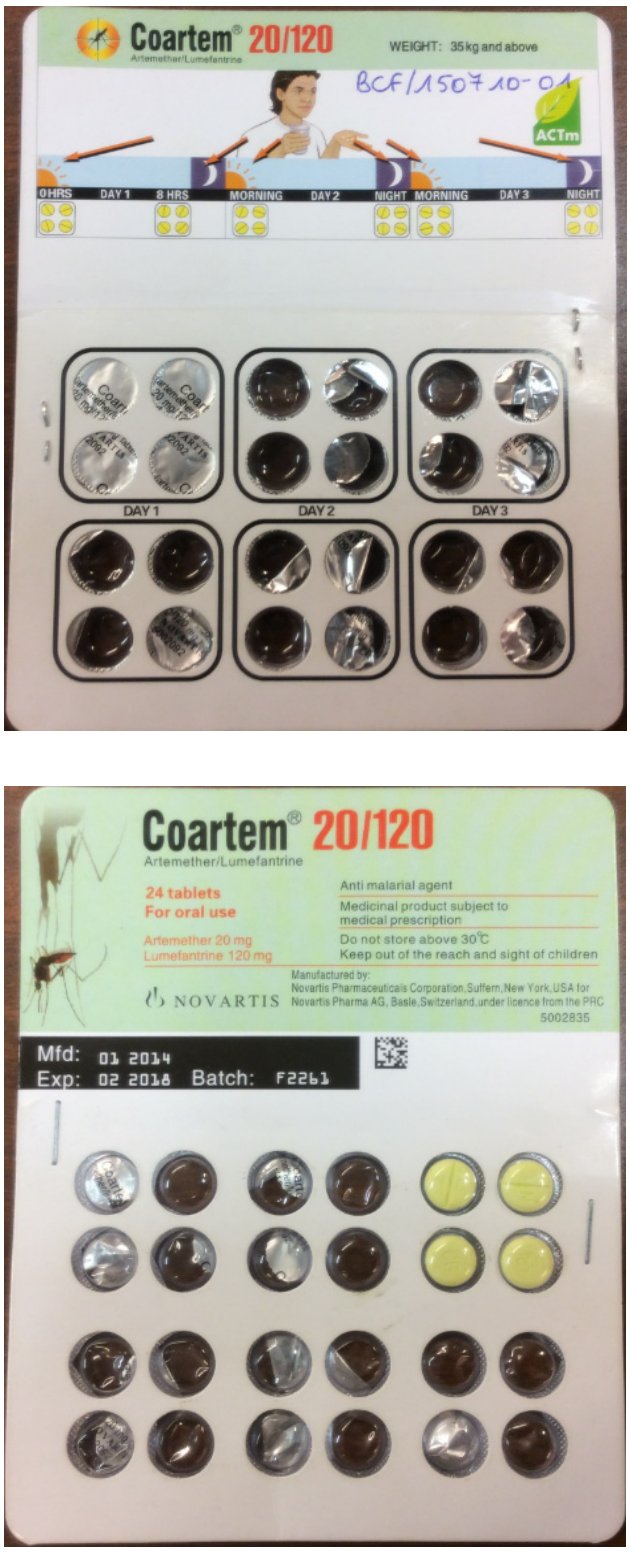

Fig. (2). Suspected Coartem® 20/120 sample (BCF/1507 10-01) having failed TLC and disintegration tests.

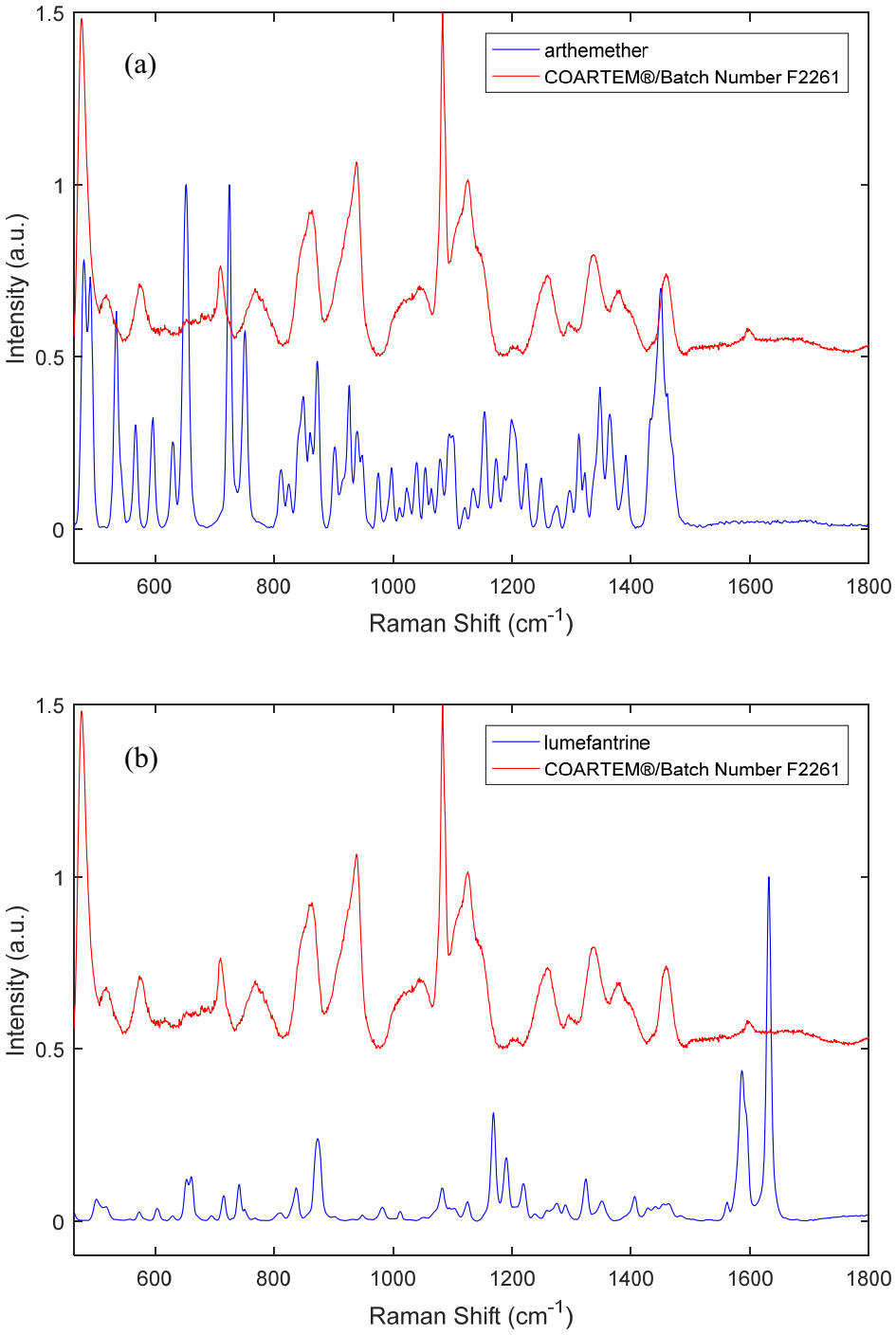

Fig. (3). Raman Spectra: (**a**) Artemether spectrum in blue *vs*. sample spectrum in red; (**b**) Lumefantrin spectrum in blue *vs*. sample spectrum in red. The spectra were offset for clarity. (*The color version of the figure is available in the electronic copy of the article*).

(r = -0.0680) (Fig. **3**). The computer system generated a list of compounds with related levels of likeliness to be in the composition of the sample (Fig. **4**). The two best matches are: calcium carbonate (r =0.9458), potato starch (r = 0.9184), which are normally known as inactive pharmaceutical excipients. Some components from Raman spectroscopy best matches suspected to be in the sample are usually used in that formulation. However, we were not able to identify the coloring agent to yellow imitating the color of lumefantrine.

On the other hand, as illustrated in Fig. (**5**), HPLC results confirmed that none of the two active ingredients was detected in the sample. Hence, by considering all previous analyses, we concluded that the Coartem® 20/120, batch number F2261, Mfd: 01 2014, Exp: 02 2018 is a counterfeit containing no active ingredient.

Furthermore, we conducted a literature search on the same batch product to see whether there is an alert issued about the same product, or a reported study. We were very

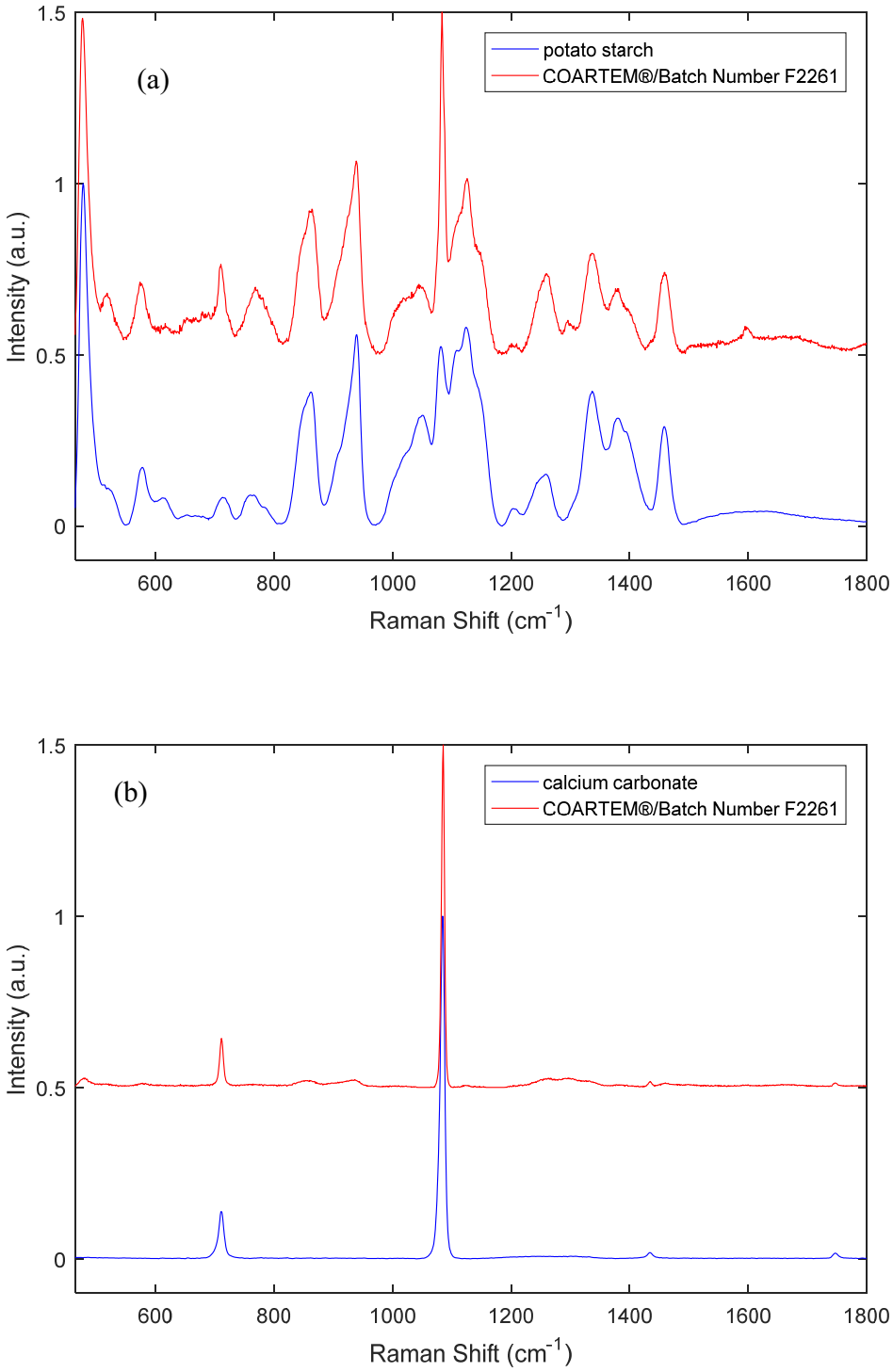

Fig. (4). Spectroscopy Raman results. Compounds with related levels of likeliness to the sample: (**a**) For potato starch (r = 0.9184) and (**b**) Calcium carbonate (r= 0.9458). The spectra were offset for clarity.

interested with an article published in Malaria Journal on "Assessing the quality of anti-malarial drugs from Gabonese pharmacies using the MiniLab®" [12]. This field study reported 2 samples that failed the test, and one of the two samples is the same fake Coartem we sampled in Cotonou (Benin). However, even if the two products have a common batch number (*i.e.* F2261), brand name (Coartem®), and manufacturer (Novartis), they have totally different manufacture and expiry dates *i.e.* Mfd: 01 2012, Exp: 02 2016 (found in Gabon) *vs*. Mfd: 01 2014, Exp: 02 2018 (found in Benin). High performance liquid chromatography was used to confirm the absence of APIs in the AL sample [14].

In early 2013 a batch of falsified Coartem® was discovered in Yaoundé (Cameroon), containing no active pharmaceutical ingredients. The product failed the screening by the minilab® and was forwarded by an NGO to a WHO pre-

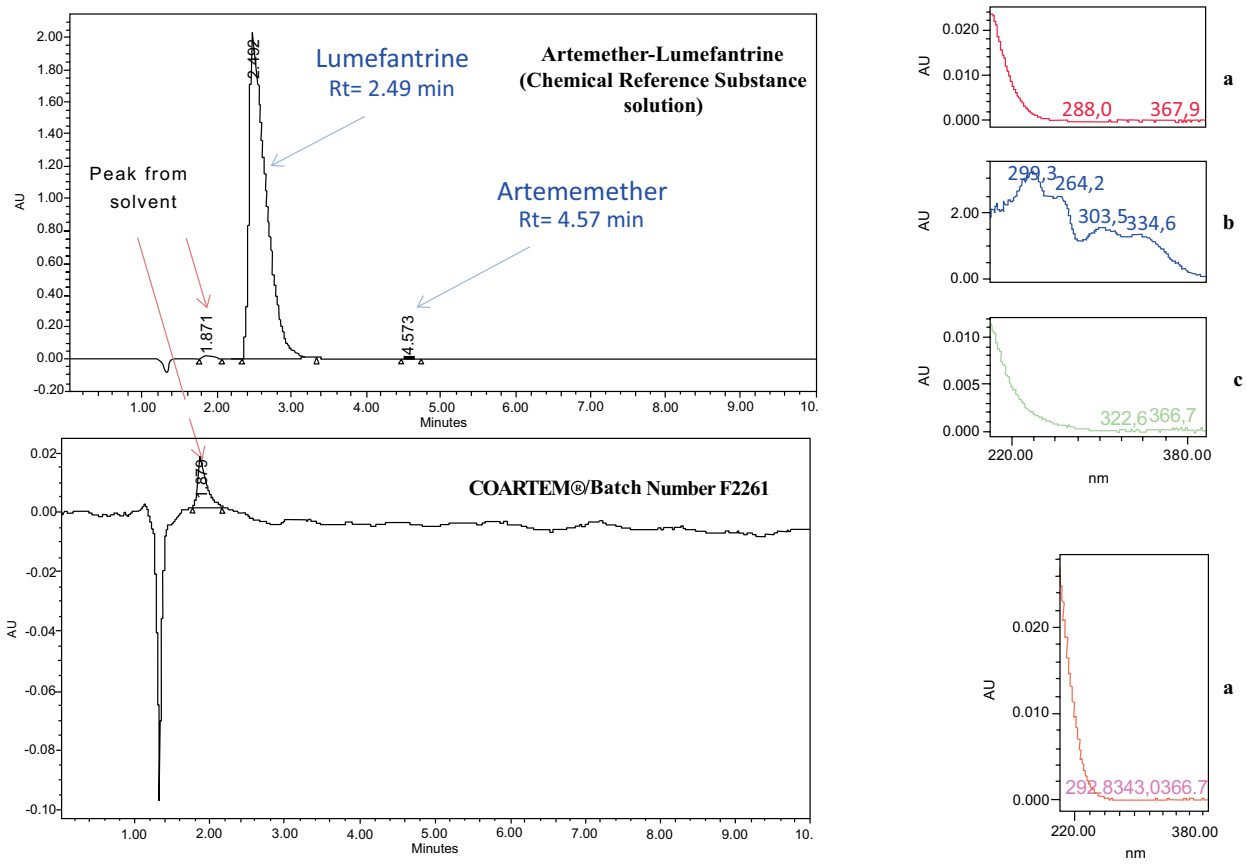

Fig. (5). Chromatograms and UV-Vis spectra of sample BCF/1507 10-01 (Coartem®; Batch number F2261; Mfd: 01.2014; Exp: 02.2018; collected from the market of Fifadji; Benin); (**a**) Methanol spectrum; (**b**) Lumefantrin spectrum; (**c**) Artemether spectrum.

qualified laboratory in Nairobi (Kenya) for more detailed analysis. Subsequent testing revealed that the product contained none of the claimed active pharmaceutical ingredients. The details of the falsified batches of Coartem® were: Batch number: F1901, Exp: 01.2014/Mfd: 01.2012; batch number: F2261, Mfd: 01.2012/Exp:01.2014. Surprisingly, this second one has the same batch number as the counterfeit samples found in Gabon and Benin, but the manufacture and expiry dates are totally different in the three cases. These are both genuine Novartis batch numbers which have passed their expiry dates. No genuine Coartem® bearing these batch numbers should now be in circulation [15]. The same batch number is also in circulation in Mali [unpublished data]. The weakness of drug regulatory authorities in controlling the pharmaceutical supply chain is partly responsible of the prevalence of illicit medicines in resource limited countries. More efforts are still needed especially in those countries in order to effectively fight against the spread of poor quality medicines (counterfeit/falsified, sub-standards, and degraded), and therefore protect the public health against the terrible dangers they can cause. Sensitization, regular seize and destroy operations, prosecution of counterfeiters, regular market surveillance through quality controls, *etc*. are some urgent recommended actions; but above all, there is a real need of strengthening national drug regulatory authorities and set up a strong collaborations at national and international levels to overcome the porosity of borders in resource limited countries that can explain the easy circulation of fake medicines in those countries. In this context, further contacts were established with other research team members who are facing the poor quality medicines situation: Rwanda (East Africa); D.R. Congo (Central Africa). Similar samples were collected, 13 from Rwanda and 9 from D.R. Congo. Those samples were analyzed by the same HPLC method [5]. As can be seen in Table **1**, all samples from these countries were compliant with the assay test specifications of 90.0% to 110.0% according to the United States and International Pharmacopoeias for both Artemether and Lumefantrine. However, 3 samples from D.R. Congo seemed to present a risk of under dose due to result (90.7%) closer to 90% limit and over dose due to results (109.4% and 108.4%) closer to 110% limits while the standard deviations were somewhat high. When we look on the survey study conducted by the WHO in six African countries [16] in which it was compared the outcomes of quality control laboratory testing and the GPHF-Minilab® screening, it was mentioned that GPHF-Minilab® can reliably detect grossly sub-standard samples, but should not be used as an independent testing resource or provide quantitative data except in conjunction with more sensitive techniques such as HPLC, *etc*. [17]. In the present study case, we supplemented our adapted TLC method (simple analytical technique, robust) by RAMAN spectroscopy and HPLC-UV Vis (advanced analytical techniques) to confirm the primary result. In this way, the results of our study support previous reports and publications on the issue of counterfeit medicines and drastic consequences they can cause to the public health. In fact, the problem is still critical, especially in resource limited countries, and there is real

Table 1. Results of Artemether (AM) and Lumefantrine (LF) assays in tablets samples from D.R. congo and rwanda.

Samples from D.R. Congo (mean in %. ± SD; n=3)				Specifications (USP and Ph. Int) 90.0 – 110 %	Conclusion or Remark for AM and LF
No.	Samples Codes	Content of LF (%)	Content of AM (%)		
1.	RC001	98.2 ± 1.8	100.2 ± 0.2	OK	Compliant
2.	RC002	104.2 ± 1.5	97.7 ± 0.6	OK	Compliant
3.	RC003	109.4 ± 1.8	100.9 ± 1.3	OK	Risk of overdose for LF
4.	RC004	104.1 ± 0.8	96.6 ± 1.2	OK	Compliant
5.	RC005	107.8 ± 0.4	96.9 ± 0.6	OK	Compliant
6.	RC006	108.4 ± 1.8	100.1 ± 0.8	OK	Risk of overdose for LF
7.	RC007	94.6 ± 0.2	94.6 ± 0.5	OK	Compliant
8.	RC008	101.9 ± 1.2	90.7 ± 1.8	OK	Risk of underdose for AM
9.	RC009	106.7 ± 0.5	95.5 ± 0.8	OK	Compliant
Rwanda Samples					
1.	K0904	94.1 ± 0.2	91.9 ± 0.7	OK	Compliant
2.	Q40093	97.1 ± 1.8	96.7 ± 0.1	OK	Compliant
3.	Q40037/ 7221596	92.7 ± 0.1	91.3 ± 1.0	OK	Compliant
4.	FA181	96.6 ± 0.8	93.5 ± 0.1	OK	Compliant
5.	Q40212	96.5 ± 1.2	98.8 ± 0.7	OK	Compliant
6.	Q40125	97.0 ± 0.3	97.7 ± 1.7	OK	Compliant
7.	X1684	97.7 ± 0.5	97.2 ± 0.5	OK	Compliant
8.	F3266	95.4 ± 1.1	94.0 ± 0.4	OK	Compliant
9.	DY11334909	95.9 ± 0.1	101.0 ± 1.4	OK	Compliant
10.	Q40353	94.1 ± 0.1	106.1 ± 1.9	OK	Compliant
11.	F3262	95.7 ± 0.6	95.8 ± 1.0	OK	Compliant
12.	Q30167	97.0 ± 0.1	97.7 ± 0.8	OK	Compliant
13.	P04013D	98.7 ± 0.8	107.7 ± 1.2	OK	Compliant

need to strengthen National Drug Regulatory Authorities of those countries in order to ensure that the distributed medicines are of the required quality, safety and efficacy.

CONCLUSION

A counterfeit artemether/lumefantrine medicine was detected thanks to simple TLC testing adapted from GPHF-Minilab®, and disintegration test. The suspected fake medicine was submitted to Raman spectroscopy and HPLC analyses confirming the absence of both active ingredients in the sample collected at Fifadji market (Cotonou, Benin). The same fake batch of Coartem® was surprisingly found in Gabon, Mali and Cameroun but under different manufacture and expiry dates in the three cases. However, even if the counterfeit ACT was found in Benin, Gabon, Mali, and Cameroon, and not found in the analyzed few samples from D.R Congo and Rwanda (Central Africa), it does not mean that the fake medicine would not be infiltrated to other countries including the Central Africa, and elsewhere where ACTs are widely used. Actually, recent reports on the quality of essential medicines keep to highlight the need of strengthening national and international strategic measures against the spread of poor quality medicines (counterfeit/falsified, substandard, and degraded), especially in resource limited countries where national medicine regulatory authorities (NMRA) are weak, and not able to fulfill their mission fully and efficiently.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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Fernand Gbaguidi and Joëlle Quetin Leclercq conceived the study. Victoria Crickboom, Benjamin Muhigirwa and Agnès Ngoya collected the samples. Achille Yemoa and Victoria Crickboom conducted the TLC analysis. Védaste Habyalimana and Jérémie Mbinze performed the HPLC testing, Achille Yemoa and Védaste Habyalimana contributed to writing the manuscript; Pierre-Yves Sacré performed the Raman Spectroscopy analysis. Roland D. Marini supervised the study and revised the manuscript. Philippe Hubert graciously provided the facilities.

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