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(RESEARCH ARTICLE)



## Self-medication with antimalarials drugs in Lubumbashi city (DR Congo)

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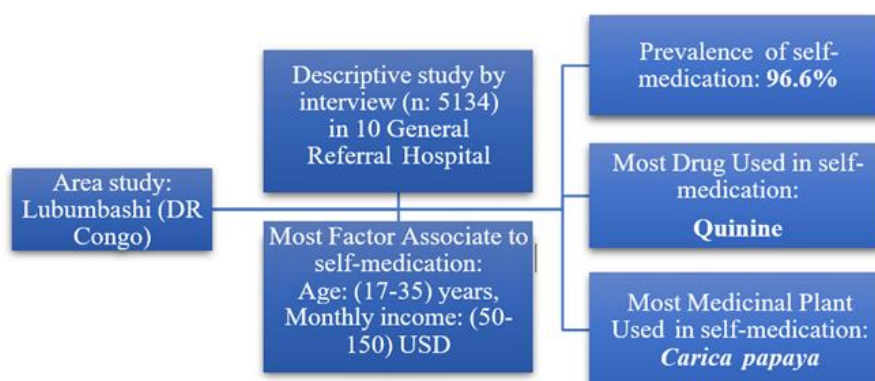
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### Abstract

Self-medication for malaria is very common in Sub-Saharan Africa where this parasitosis is endemic. In order to determine the extent, characteristics and factors associated with this practice in medical area in the city of Lubumbashi, a cross-sectional descriptive study was carried out by direct interview from January 2018 to June 2018, in the internal medicine departments of 10 General Referral Hospital (GRH). Five thousand one hundred and thirty-four patients were consulted among them, 96.6% (average age  $38.7 \pm 8$  years; average income:  $100 \pm 12$  USD; gender male/ female ratio: 0.86) practice self-medication with antimalarials. They used it for the first time at an average age of 13-17 years. Quinine (36.4%) and *Carica papaya* (0.4%) are the most used remedies in conventional and non-conventional medicine, respectively. Several risks are incurred during this practice when the most cited are worsening side effects (53%), incomplete treatment (37%) and appearance to health sciences (37%). Age (17-35 and > 65 years old), low income (50-150 USD), membership in a health sector and the claim to know antimalarial drugs, predispose patients to self-medication. There is an urgent need to regulate this practice to avoid its harmful consequences.



**Keywords:** Self-prescription; General Referral Hospital; Haut-Katanga; Antimalarial; Quinine; *Carica papaya*.

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## 1. Introduction

Malaria is the first parasitic disease in the world [1] and constitutes a major public health problem in Sub-Saharan Africa [2,3], particularly in Democratic Republic Congo (DRC) [4,5]. In DRC there is no social security system, [6,7], the majority of the population lives below the poverty line, causing the emerging phenomenon of self-medication.

This practice is very a common in both developing countries [8,9] as well as developed ones [10,11]. Although several negative consequences, including appearance of antimicrobial resistance, drug poisoning, non-beneficial drug interactions, drug dependence or addiction, have been reported during this practice [12]. Reasons allowing this practice to subsist are often mentioned, in particular the cost of treatment, the low purchasing power, the trivialization of some diseases or the complicity of some pharmacy salespeople who do not respect the rules for dispensing drugs and longtime waiting in hospitals [8,13–15].

In DRC, few works have been devoted to self-medication [16,17]. In Lubumbashi, cases of self-medication have been reported in Kasapa university campus [12], and when managing febrile episodes in children under the age of 5 years [18]. These works did not focus mainly on the practice of self-management of malaria by the general population. This study intends to describe the practice of self-medication by the population of Lubumbashi to treat malaria. It presents the frequency of this phenomenon; its characteristics as well as the factors associated.

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## 2. Material and methods

### 2.1. Experimental setting

The study was carried out from January 2018 to June 2018, in the internal medicine departments of 10 public hospitals in the city of Lubumbashi in the southern part of DRC. Their global hospitalization capacity is approximatively 1000 beds. These hospitals are namely: Hakika, Jason Sendwe, Kamalondo, Kampemba, Katuba, Kenya, Kowe, Mumbunda, SNCC and Vangu.

### 2.2. Patients and methods

This cross-sectional descriptive study was carried out by a direct interview using a guide questionnaire, with all patients, aged over 15 years old, met in the internal medical services of these 10 GRHs in good condition speaking and having provided informed consent. The questionnaire included 20 items related to antimalarials self-medication practices as well as socio-demographic characteristics of respondents. The sample size precalculated with Schwartz's formula:  $n = z^2 \times p \times (1-p) / m^2$  (where  $z$  = confidence level, set at 99%,  $p$  = prevalence of self-medication in Lubumbashi set at 50%,  $m$  = margin of error fixed at 5%) was 663 patients. However, we have taken all the patients who met the inclusion criteria to improve the accuracy.

### 2.3. Ethical Considerations

Ethical approval was granted from the Department of Pharmacology of the Faculty of Pharmaceutical Sciences of the University of Lubumbashi and all participants were asked for their consent to participate in the study before being given the survey. The responses were anonymous and confidential, and the participants were informed that before start answering the questionnaire.

### 2.4. Statistical data analysis

Graph Pad prism version 6 software was used to analyze the data statistically. The chi-square test and odd ratio established the factors associated with self-medication, a probability level  $p < 0.05$  was considered significant.

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## 3. Results and discussion

### 3.1. Socio-demographic characteristics of respondents

Five thousand one hundred thirty-four patients have been met the internal medicine departments of 10 GRHs in the city of Lubumbashi from January 2018 to June 2018. Their majority, 4,960 (96.6%) admit having already practiced self-medication against malaria and most of them are women (male-female sex ratio: 0.86), with an average age of  $38.7 \pm 8$

years (extremes: 16 and 65). The respondents were from the 7 municipalities of the city of Lubumbashi and exercise several trades, most represented by traders (23%) and public employees (19.5%). Most respondents of this study were from secondary school education level (47.6%), with less access to health services (86.8%). They have an average monthly income of  $100 \pm 12$  USD (extremes: 50 and 900 USD) and are 50% Catholic (Table 1).

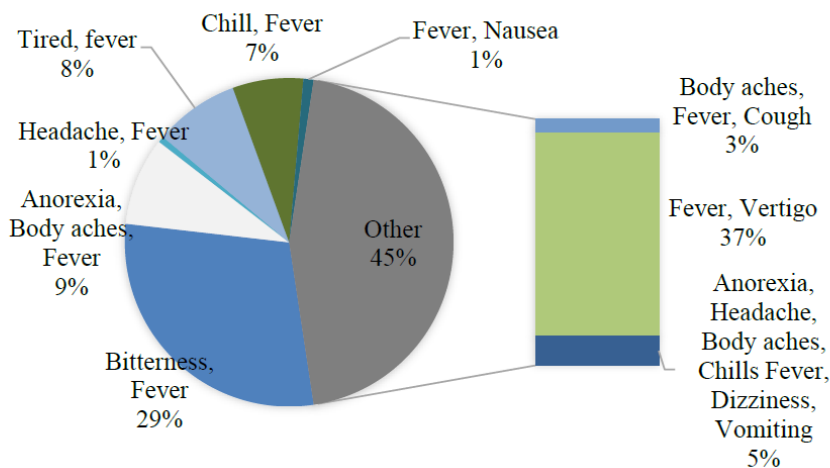
**Table 1** Socio-demographic features of respondents

	<b>Variable</b>	<b>Ni</b>	<b>Fi (%)</b>
Gender	Male	2289	46.1
	Female	2671	53.9
Marital status	Single	2221	44.8
	Divorced	220	4.44
	Married	2383	48
	Widower	136	2.74
Age class	] 16 – 31]	397	8
	] 31 – 46]	2779	56
	] 35 – 61]	1569	31.6
	>61	215	4.33
District of residence	Annexe	480	9.7
	Kamalondo	350	7.1
	Kampemba	723	15
	Katuba	280	5.6
	Kenya	1015	20
	Lubumbashi	1753	35
	Ruashi	359	7.2
Profession	Any	671	13.5
	Trader	1140	23
	Farmer	384	7.7
	Teacher	671	13.5
	Public employee	966	19.1
	Artisanal digger	201	4.1
	Service provider	927	18.7
Level of study	Any	277	5.58
	Primary	372	7.5
	Secondary	2360	47.6
	Higher School-University	1951	39.3
Study	Another sector	4303	86.8
	Health sector	657	13.2
Monthly income	≤50	836	16.9
	] 50 – 100]	2045	41.2
	] 100 – 150]	1284	25.9
	] 150 – 200]	453	9.13
	] 200 – 250]	192	3.87
	> 300	150	3.02
Religion	Adventist	32	0.6
	Buddhist	12	0.2
	Catholic	2457	50
	Garengaze	10	0.2
	Kimbanguist	30	0.6
	Lutheran	3	0.1
	Methodist	103	2.1
	Muslim	176	3.5
	Non-practicing	22	0.4
	Protestant	1089	22
	Revival Church	1026	21

Ni=Effective; Fi =Ni\*100/N: Citation frequency. N=4960.

### 3.2. Knowledge of respondents on malaria

The surveyed people associate several signs to diagnose malaria, the first two groups of which consist of fever and dizziness (37%) followed by bitterness and fever (29%). Fever is the most common sign in each of the symptom groups (Fig. 1).



**Figure 1** Signs of malaria identification by respondents (n=4960).

### 3.3. Impact of self-medication according to the GRH

The frequency of self-medication varies considerably from one hospital to another between 84.9% (GRH Kamalondo) and 99.7% (Katuba). It was higher in patients who attended GRH Jason Sendwe (30.5%) followed by GRH Kenya (18.9%) (Table 2).

**Table 2** Distribution of respondents according to the GRH

GRH	N	Ni	Fr (%)	Fa (%; N=5134)
Hakika	138	134	97.1	2.6
Jason Sendwe	1572	1565	99.6	30.5
Kamalondo	251	213	84.9	4.2
Kampemba	279	270	96.8	5.3
Katuba	609	607	99.7	11.8
Kenya	1001	972	97.1	18.9
Kowe	178	159	89.3	3.1
Mumbunda	801	787	98.3	15.3
SNCC	100	59	59	1.1
Vangu	205	194	94.6	3.8
Total	5134	4960	NA	96,6

N: total number of patients encountered in the GRH; Ni: number of patients who practiced self-medication in the GRH; Fr (relative frequency of self-medication in the medium concerned (= Ni \* 100 / N); Fa (absolute frequency of self-medication in the medium concerned (= Ni \* 100/5134). NA: Not applicable.

### 3.4. Reasons for patients to practice self-medication and their knowledge of the risks incurred during this practice

Several reasons have pushed interviewed patients to practice self-medication among which, we note search for time saving (32%) and the difficult to confide in a health professional (18%), are the most mentioned alongside a claim knowledge of effective remedies (8.5%), less mentioned. Although they resort to self- medication, the patients

nevertheless recognized certain risks incurred, the most and the least cited of which were worsening side effects (22%) and inadequate treatment respectively (fig.2).

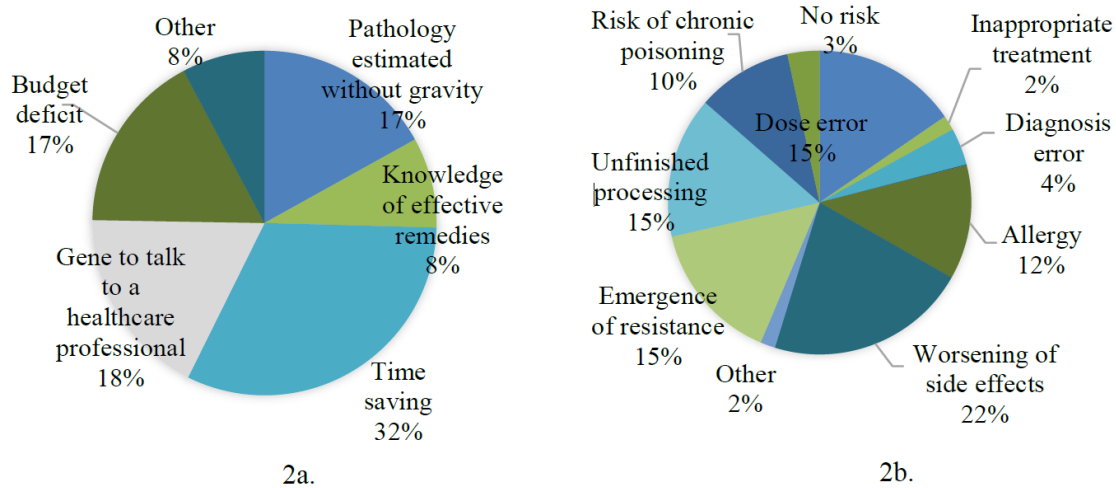


Figure 2 Reasons for self-medication (a) and knowledge of its risks (b) (n=4960).

### 3.5. Cost of malaria treatment in modern health care and traditional medicine in Lubumbashi

The average cost of treating malaria over three days in the health facilities in which this study was carried out is 37.9 ± 9.95 USD/7 days or 12.3 USD per day. The highest cost is observed in two GRHs, Jason Sendwe (56.3 USD) and Mumbunda (57 USD) and the lowest cost is observed in GRHs, Hakika (30 USD) and Kowe (30 USD). In traditional medicine, treatment for malaria is ≤ \$ 5 and in most cases (45%), it is free (Fig. 3).

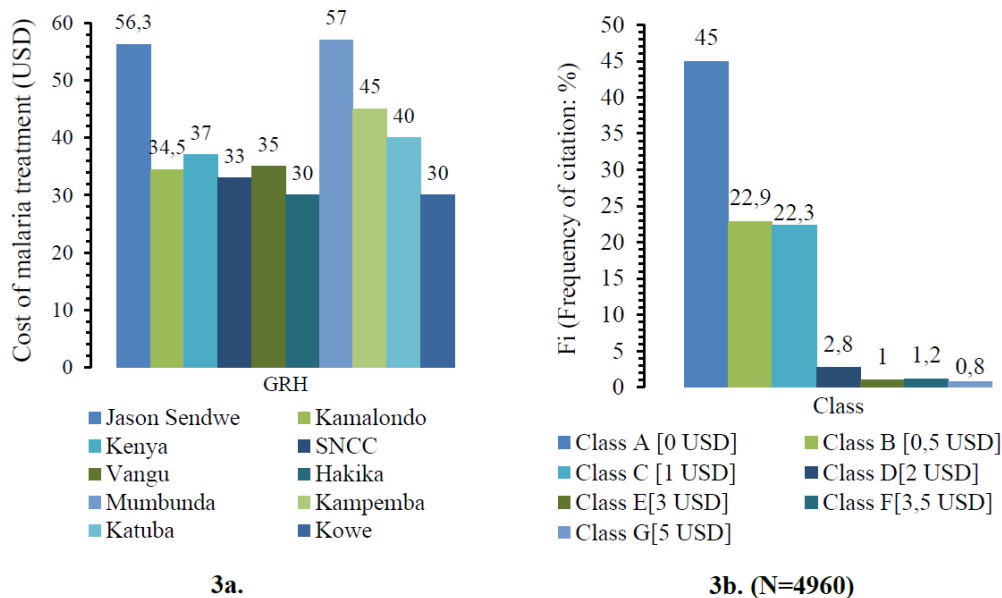
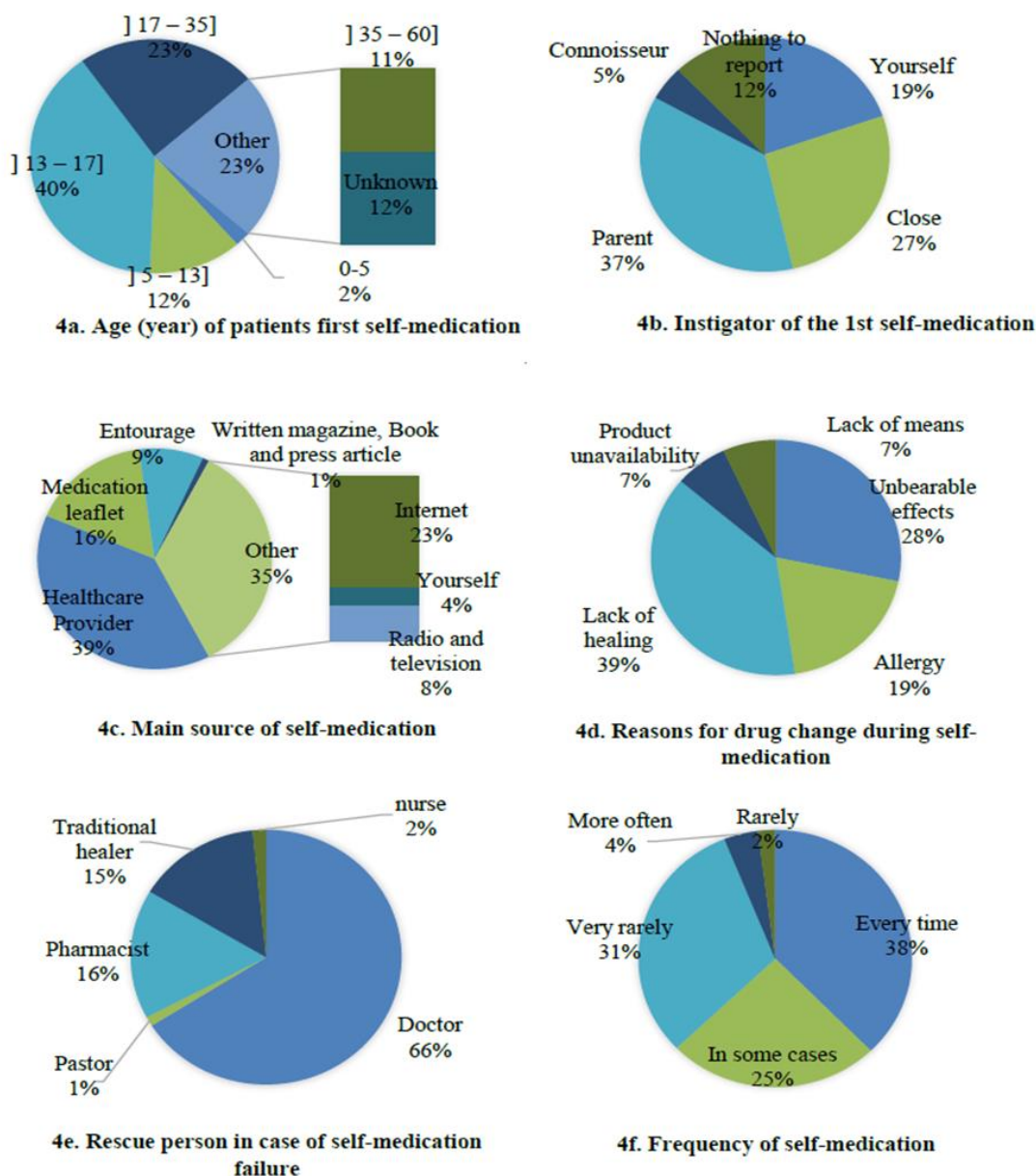


Figure 3 Cost of management of malaria by self-medication in biomedicine (a) and traditional medicine (b).

Age, instigator of first self-medication, main sources, person of recourse in the event of failure, reasons for changing medication and frequency of self-medication depending on the patients Almost 40% of patients resort to self-medication whenever the need arises (fig 4f) and more than a third (40%) started it as a teenager between 13 and 17

years old (Fig. 4a) although a large fraction do not know the exact age. The instigator of the 1st most incriminated self-medication is the parent (37%) and the main sources of information during this practice are providers in the health services (39%) and the internet (23%). People sometimes change medications for several reasons, the most mentioned of which are the lack of healing (39%) and the appearance of unbearable effects (28%). In the event of failure to self-medicate, the patients's resort to several people, preferably the doctor (66%) (Figure 3).



**Figure 4** Age, instigator of first self-medication, main sources, person of recourse in the event of failure, reasons for changing medication and frequency of self-medication depending on the patients (N=4960)

### 3.6. Antimalarial drugs used in self-medication in Lubumbashi

Fourteen antimalarial specialties are used by our informants for self-medication in biomedicine. Among them, Quinine® (36.4%), Artedped® (29.6%), Co-Artem® (26.5%) and Cether-L® (24.3%) are the first 4 most used and, Asaq® (0.06%), Alphater® (0.1% and Abithar (0.4%) are the least used. Artemether- Lumefantrine is the most used combination and Pharmakina the most requested firm (Table 3).

**Table 3** Biomedicine drugs used in self-medication against malaria

Registered trademark	Active ingredient	Firm	Effective	Fi (n = 4960)
Abithar®	$\alpha$ - $\beta$ Arteether	Promed	20	0.4
Alfather®	Artemether & Lumefantrine	Cato	7	0.14
ARH®	$\alpha$ - $\beta$ Artemether	Unique pharma	573	11.6
ASAQ®	Amodiaquine & Artesunate	Sanofi	3	0.06
Cether-L®	Artemether & Lumefantrine	New Cesamex	1205	24.3
Co-Artem®	Artemether & Lumefantrine	Novartis Pharma	1315	26.5
Fansidar®	Sulfadoxine & Pyrimethamine	Alisons	415	8.37
Lumeart®	Artemether & Lumefantrine	Promed	140	2.82
Luther®	Artemether & Lumefantrine	Unique pharma	826	16.7
Quinine®	Quinine	Pharmakina	1805	36.4
Luther DP®	Artemether-Lumefantrine	Zest Pharma	271	5.46
Arte Ped®	Artemether-Lumefantrine	Vardhman	1465	29.5
Amonate A®	Artesunate-Amodiaquine	Dafra-Pharma	180	3.63
Maladox®	Sulfadoxine & Pyrimethamine	Shalina	680	13.7

### 3.7. Situation of the treatment of malaria in self-medication by the patients

Several antimalarials are used with an incorrect dosage. This is the case of  $\alpha$ - $\beta$  Arteether, quinine as well as the associations, Artemether & Lumefantrine, Amodiaquine & Artesunate, Sulfadoxine & Pyrimethamine. Many drugs are combined with antimalarials like amoxicillin, Normegyl, Cadiphen, Gentamycin, Ampicillin, vitamin B, Polygel, Vermox and paracetamol (75%) followed by amoxicillin (53%) are the drugs most associated with antimalarials by patients (Table 4).

**Table 4** Way patients take medication during self-medication for the management of malaria

Antimalarial active ingredient	Aberrant dosage	PA associated	Ni	Fi (%)
$\alpha$ - $\beta$ Arteether	3x1 amp/D W 2D	Amoxicillin	36	0.73
		Normegyl	39	0.79
		Cadiphen	35	0.71
		Gentamycin	44	0.89
Artemether & Lumefantrine	2x2Tab/D W 7D	Paracetamol	2771	55.9
		Vitamin B	1830	36.9
		Vermox	1050	21.2
		Amoxicillin	2301	46.4
Amodiaquine & Artesunate		Paracetamol	989	19.9
		Ampicillin	651	13.1
Sulfadoxine & Pyrimethamine	1x3 Tab/D W 7D	Amoxicillin	315	6.35
		Polygel	685	13.8
		Paracetamol	36	0.73
Quinine	2x2 Tab W 5D	Gentamycin	665	13.4

Amp: ampoule, Tab: tablet, W: while D: Day

### 3.8. Medicinal Plants used in self-medication against malaria in Lubumbashi

Several patients interviewed (3661 or 73.6%) also use medicinal plants, 18 of which have been mentioned. These plants belong to 13 families dominated by Asteraceae (23%). From these plants flow 20 recipes which mainly use (80%) leaves as a decoction (75%) and which are administered orally (100%). *Carica papaya* (18), *Cymbopogon citratus* (15) and *Eucalyptus abdita* (15) are the three most cited plants (Table 5) and *Cissus aralioides* is the only one whose anti-malarial use has not been reported in the literature.

**Table 5** Medicinal Plants used by patients during self-medication with malaria in Lubumbashi

Scientific name	Vernacular name	Citation	Antimalarial recipe	Posology	Ei
<i>Acalypha homblei</i> De Wild. (Euphorbiaceae)	Kalafulu	[19]	R1. Decoction of 5 handfuls of root bark in 1 L of water	1x2V /D W 5D	10
<i>Aloe megalacantha</i> Baker (Asphodelaceae)	Mpanga	[20]	R2. Decoction of 3 handfuls of leaves in 1 L of water.	2x3V/ D W 7D	5
<i>Solanum nigrum</i> L. (Solanaceae)	Mutete	[21]	R3. Infusion or decoction of a handful of the leaves.	2x1V/D W 3D	1
<i>Carica papaya</i> L. (Caricaceae)	Kipapayi	[1]	R4. Decoction of 5 handfuls of leaves in 0.5 L of water. R5. Infuse a handful of the leaves in 1 L of water in 15 minutes.	2x3V/D W 7D 4 x ½V/D W 5D	18
<i>Cinchona officinalis</i> L. (Rubiaceae)	Kinkina	[1]	R6. Decoction of 5 bark stem handles in 0.5 L of water.	1V/ D W 3D	2
<i>Cissus aralioides</i> (Welw. Baker) Planch (Vitaceae)	Ex Mbwa mpimbidi		R7. Decoction of 5 handfuls of leaves in 0.5 L of water.	2x 3V/D W 7D	1
<i>Crossopteryx febrifuga</i> (Afzel. G.Don) Benth. (Rubiaceae)	Ex Mbinzo	[22]	R8. Decoction of 5 handfuls of leaves in 0.5 L of water.	1x 3V/D W 4D	10
<i>Cymbopogon citratus</i> (DC.) Stapf (Poaceae)	Kilulukunja	[1]	R9. Decoction of the 10 leaves in 1.5 L of water in 10 minutes.	2 x ½ V/D W 3D	15
<i>Pleurolobus gangeticus</i> (L.) J.St.-Hil. Ex H.Ohashi & K.Ohashi (Fabaceae)	Dintata	[23]	R10. Decoction of 5 handfuls of root bark in 0.75 L of water.	1x2V/D W 5D	1
<i>Dichrostachys cinerea</i> R.Vig. (Fabaceae)	Nsendi-mwanga	[24]	R11. Decoction of 5 handfuls of leaves in 0.75 L of water.	1x2 V/D W 7D	1
<i>Erigeron floribundus</i> Sch.Bip. (Asteraceae)	(Kunth) Fumu di buila	[25]	R12. Decoction of 5 handfuls of leaves in 0.5 L of water.	1x 3 V/D W 4D	1
<i>Eucalyptus camaldulensis</i> Dehnh. (Myrtaceae)	Eucalptus	[26]	R13. Decoction of 5 handfuls of leaves in 0.5 L of water.	1x4 V/D W 4D	15
<i>Moringa oleifera</i> Lam. (Moringaceae)	Moringa	[1]	R14. Decoction of 5 handfuls of root bark in 0.75 L of water.	1x2 V/D W 5D	7
<i>Psidium guajava</i> L. (Myrtaceae)	Mapela	[27]	R15. Decoction of 5 handfuls of root bark in 0.75 L of water.	1x2 V D W 5D	2



<i>Tetradenia riparia</i> (Hochst.) Mutuzo <i>Codd</i> (Lamiaceae)	[28]	R16. Decoction of 5 handfuls of leaves in 0.5 L of water and take.	3x3 V/D W 3D	1
<i>Tithonia diversifolia</i> (Hemsl.) Mayani <i>A.Gray</i> (Asteraceae)	[1]	R17. Decoction of 5 bark stem handles in 1 L of water and take.	2x2V/D W 7D	5
<i>Gymnanthemum amygdalinum</i> Kongo bololo <i>(Delile) Sch.Bip.</i> (Asteraceae)	[29]	R18. Decoction of 5 handfuls of leaves in 0.5 L of water and take.	1x 3V/D W 7D	7
<i>Zingiber officinale</i> <i>Roscoe</i> (Zingiberaceae)	Tangawisi [30]	R19. Infuse a handful of the leaves in 1 L of water in 15 minutes.	4x1/4 V /D W 5D	
		R20. Infusion of two spoonful of tuber powder or decoction.	2x2V/D W 3D	1

D: day, V: glass (200-300 mL)

### 3.9. Factors associated with self-medication during this study

Six factors are associated with self-medication with antimalarials in this study. These are age (17-35 years and over 60), monthly income (] 50 - 150] years), membership in a health science, prior use of traditional medicine and the pretension of knowledge of antimalarials (table 6).

**Table 6** Factors associated with self-medication in Lubumbashi

Variable	Factor	Yes	No	OR	p ( $\chi^2$ )
Gender	Male	801	45	1.817	0.2111
	Feminine	1156	118	1.5504	0.1278
Age	] 13 – 17]	223	20	0.9195	0.8344
	] 17 – 35]	1079	56	1.0155	0.0045
	] 35 – 60]	942	75	0.8651	0.127
	>60	113	12	0.8768	0.0407
Monthly income	≤50	945	65	0.9268	0.0888
	] 50 – 150]	770	50	1.0231	0.0012
	] 150 – 200]	252	12	1.8598	0.196
	] 200 – 250]	97	10	0.7979	0.1643
Religion	> 300	93	5	1.5766	0.4294
	Adventist	32	1	1.7595	0.2323
	Buddhist	12	2	0.4967	0.4006
	Catholic	618	56	0.8819	0.9352
	Garengaze	10	1	0.9786	0.9172
	Kimbanguism	10	0	-	0.9897
	Lutheran	5	0	-	0.9438
	Methodist	103	13	0.641	0.6171
	Muslim	72	2	3.0748	0.9917
Protestant	576	51	0.916	0.6822	
Revival Church	500	37	1.1686	0.8975	
Sans religion	19	0	-	0.7533	

Profession	Trader	451	26	1.578	0.1601
	Farmer	85	0	-	0.0416
	Teacher	285	21	1.1526	0.0358
	State worker	128	54	0.1413	0.1305
	Artisanal digger	17	0	-	0.1651
	Service provider	407	24	1.5208	0.6022
	No	584	38	1.3992	0.9504
Marital status	Single	1407	156	0.23	0.056
	Divorced	114	21	0.18	0.0978
	Married	1089	141	0.97	0.568
	Widower	72	3	0.31	0.1598
Belonging to SS	Yes	1059	759	2.82	0.0012
	No	126	126	2.8	0.01254
Use of MT	Yes	2875	3	23.56	0.0045
	No	122	3	0.24	0.0987
Knowledge of antimalarials	Yes	2653	121	15.84	0.0041
	No	29	200	0.97	0.098

SS: Health Sciences, MT: traditional medicine, OR: odd ratio, Ei: number of citations

#### 4. Discussion

This study completes the extent, associated factors, and characteristics of self-medication during the management of malaria in people attending 10 public hospitals in the city of Lubumbashi between January 2018 and June 2018. The results show that the city is experiencing self-medication using both conventional and traditional medicine.

Despite respondents are informed about self-medication risks (Figure 2), many of them resort to it with a much higher frequency (96.6%) than that observed in other regions such as the Middle East: 43% [31], Mbeya in Tanzania : 19 % [32], Antananarivo : 22 % [33] or Addis-Ababa : 75,5 % [34] but close to that of Saudi Arabia [15], Jordan [35] or Bangladesh [36]. In Lubumbashi a study carried out in the university campus of UNILU had reported a frequency of the same amplitude for any pathology concerned [12].

Fever associated to one or more other symptoms (Fig. 1) was the major sign conducting people to self-diagnosed malaria; as fever is known to be a major symptom of malaria according to WHO and many other accepted guidelines for the management of malaria [37]. Self-medication with antimalarials products would be favored by the low level of education (Table 1) and the easy access to antimalarials drugs, which are supposed to be dispensed only on medical prescription. Furthermore, the various signs of self-diagnosis of malaria mentioned by interviewed (fig. 1) suggest that, the kind of malaria generally treated in self-medication concerns the simple malaria. In this context, the high use of quinine by self-medicated people (36.4%) would be considered as an irrational use of medication, as is observed in most cases of self-treatment [38–40] especially since quinine is normally used in 2nd or 3rd intention or in case of severe malaria [3,41,42].

People resorting to self-medication have given several reasons motivating them such as time saving and the low cost of self-treatment as mentioned in other previous studies [43–45]. A possible approximation can be established between the average monthly income of respondents ( $100 \pm 12$  USD) and the average cost of malaria care in biomedicine ( $37.9 \pm 9.95$  USD) suggesting that very likely, the use of self-medication would be very related to financial reasons which is also one of the factors associated with self-medication during this study (table 6).

The first instigator of self-medication is the parent as in some previous studies [12,15]. In a country where almost, the entire population does not have health insurance, it seems very likely that the practice of self-medication will start

within the family. This familiarity is also observed in the transmission of self-medication information (fig 4) where the informants mainly use the knowledge that underpins the health sciences.

In this study, the malaria self-medication is associated with drug misuse (table 4), in particular, the duration of treatment with Arteether, the correct dosage of which is one ampoule once a day for 3 days in the case of simple malaria. *P. falciparum* chloroquino resistant [37] and for cerebral malaria, 25 mg (J1-3) / kg to 12.5 mg (J3-5) / kg [41]. Another misuse concerned the combination of Artemether-Lumefantrine whose treatment duration is normally 3 days [46,47]. These irrational uses of drugs, which are moreover frequent in self-medication, are responsible for the development of antimalarials resistance [48,49]. On the other hand, they expose to antimalarials toxicity as stated elsewhere [50,51].

The use of medicinal plants as the first line approach is a practice recognized by 80% of the world population for the primary health care [52–54]. In this study, we observed a high rate (73,6%) of malaria self-medication with medicinal plants suggesting that the use of medicinal plants in Lubumbashi is a popular knowledge. This situation can be compared to the fact that almost all (94.4%) of the plants were subsequently reported as antimalarials (Table 5) and the only species that antimalarial activity is not reported is *Cissus aralioides*.

Six factors are associated with antimalarials self-medication in this study: age, monthly income, membership in a health science, previous use of traditional medicine and the claim of knowledge of antimalarials unlike two studies where the associated factor was education [55,56], and in accordance with the works for which the age [57,58] and previous self-medication [57,59] were associated factors.

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## 5. Conclusion

Malaria self-treatment is a very common practice in Lubumbashi in both modern and traditional medicine. The self-medication with antimalarials products involves several notable abuses. It is important to get more implication from health regulatory authorities to significantly reduce the extent of this phenomenon which has a negative impact in the fight against malaria at the national level.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors declare that they have not known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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