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Research Article

Antibacterial and Antibiotic-Potentiating Activities of Thirteen Cameroonian Edible Plants against Gram-Negative Resistant Phenotypes

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This work was designed to investigate the antibacterial activities of methanol extracts from thirteen Cameroonian edible plants and their antibiotic-potentiating effects against Gram-negative multidrug-resistant (MDR) phenotypes. The broth microdilution method was used to evaluate the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of the extracts, as well as their antibiotic-potentiating activities. The phytochemical screening of the extracts was carried out according to the standard methods. The results of phytochemical tests revealed the presence of sterols, polyphenols, and tannins in most of the tested extracts, with the other classes of secondary metabolites being selectively distributed. Tested extracts showed variable antibacterial activities with MIC values ranging from 64 to 1024 μg/mL. However, some extracts were significantly active against certain bacterial strains: seeds extract of *Theobroma cacao* (64 μg/mL) against *Escherichia coli* AG100Atet and *Klebsiella pneumoniae* K24, and the bark extract of *Uapaca guineensis* against *E. coli* ATCC 8739. The leaves extract of *T. cacao* displayed the best MBC values (256 μg/mL) against *E. aerogenes* EA27. Some tested extracts included extracts from the leaves of *T. cacao* and *P. vulgaris,* and the seeds of *D. edulis* and barks *A. indica* has selectively improved (2- to 64-fold) the antibacterial activities of some of the tested antibiotics, chloramphenicol (CHL), tetracycline (TET), kanamycin (KAN), streptomycin (STR), and erythromycin (ERY), against more than 70% of tested MDR bacteria. The findings of this work showed that tested plant extracts and particularly those from *T. cacao* and *Phaseolus vulgaris* can be used alone or in combination with conventional antibiotics in the treatment of infections involving multiresistant bacteria.

1. Introduction

The advent of antibiotics has been a tremendous therapeutic progress as it has significantly reduced mortality due to bacterial infections [1]. However, their misuse in humans and animals has contributed to the emergence of drug-resistant bacteria [2]. These bacteria are often more difficult to be combatted, and the infections they caused are more difficult and expensive to be treated. This can therefore lead to serious disability and even death [3, 4]. According to World Health Organization [4], antibiotic resistance has drastically increased to high levels all over the world. The multidrug-resistant (MDR) genes may be carried on the bacterial chromosome, plasmid, or transposons, and their expression allows bacteria to overcome the effects of many antibiotics [5]. Among the antibiotic resistance mechanisms, the most common are enzymatic inactivation of antibiotics, changes in cell permeability, and induction/activation of efflux pumps [6]. The Gram-negative bacteria are among the bacteria that drastically impair the efficacy of antibacterial agents and therefore limit their clinical use [3, 7]. In fact, to guide research, discovery, and development of new antibiotics against MDR bacteria, WHO has developed a global priority list of antibiotic-resistant bacteria where Gram-negative multidrug-resistant (MDR) bacteria, particularly *Pseudomonas aeruginosa* and *Enterobacteriaceae*, constitute the most critical group [4]. These groups of bacteria are particularly characterized by the expression of efflux pumps belonging to the Resistance Nodulation-cell Division (RND) family, which constitutes one of their main resistance

mechanisms [8, 9]. Tackling antibiotic resistance mechanisms like efflux pumps expression is therefore a high priority for WHO and scientists over the world. Plant sources used since ancient time to fight microbial infections appear as an interesting alternative for the discovery of new antibacterial substances against MDR bacteria [10–12]. For instance, a number of plant-deriving compounds with possible efflux pump inhibitor (EPI) activities such as reserpine [13], berberine [13, 14], and curcumin [15] have been discovered, but they are still unused clinically. In our previous studies, we have also shown that edible plants could be used alone and/or in combination with commonly used antibiotics to fight infections involving Gram-negative MDR bacteria [16–19]. In the continuous search for natural substances effective in MDR bacteria, this study was aimed at investigating the *in vitro* antibacterial and antibiotic-potentiating activities of methanol extracts of thirteen Cameroonian edible plants (*Azadirachta indica* A. Juss, *Citrus grandis* (L.) (Red), *Citrus grandis* (L.) (White), *Cucurbita maxima* Duch., *Dacryodes edulis* [G. Don] H. J. Lam, *Hibiscus esculentus* L., *Ipomoea batatas* (L.) Lam., *Irvingia gabonensis* (Aubry. Lec. ex O. Rorke) Baill., *Phaseolus vulgaris* L., *Saccharum officinarum* L., *Spondias mombin* L., *Theobroma cacao* L., and *Uapaca guineensis* Muell. Arg.) against Gram-negative MDR phenotypes. Some of these plants or their related genera are known for their antimicrobial properties, but not as antibiotic modulators (Supplementary Materials, Table S1).

2. Material and Methods

2.1. Plant Material and Extraction. Plants used in this study were collected in West, Southwest, and Centre regions of Cameroon from March to April 2016. All plants collected were identified at the National Herbarium (Yaoundé, Cameroun) where the voucher specimens were deposited. The names as well as the reference numbers of the studied plants are shown in Table S1 (Supplementary Materials). For the extraction, each plant material was cleaned and air-dried, and the powder (200 g) was soaked in methanol (MeOH, 1 L) for 48 h at room temperature. The extract obtained was collected by filtration using Whatman filter paper n°.1 and concentrated under reduced pressure using a rotary evaporator to yield a residue which constituted the plant extract. All the extracts were then kept at 4°C until further use.

2.2. Preliminary Phytochemical Investigations. The major phytochemical classes such as triterpenes (Liebermann-Burchard test), sterols (Salkowski's test), alkaloids (Mayer's test), polyphenols (ferric chloride test), flavonoids (aluminum chloride test), anthraquinones (Borntrager's test), saponins (foam test), and tannins (gelatin test) were investigated as previously described [20, 21].

2.3. Chemicals for Antibacterial Assays. Eight reference antibiotics were used in this study: ampicillin (AMP), cefepime (CEF), chloramphenicol (CHL), ciprofloxacin (CIP), erythromycin (ERY), kanamycin (KAN), streptomycin (STP), and tetracycline (TET) which were obtained from Sigma-Aldrich, St Quentin Fallavier, France. *p*-Iodonitrotetrazolium (INT) (Sigma-Aldrich) chloride was used as microbial growth indicator; dimethylsulfoxide (DMSO) was used to dissolve the plant extracts [22].

2.4. Bacteria Strains and Culture Media. In this study, we used a panel of 21 strains belonging to Gram-negative bacteria including sensitive and multidrug-resistant strains of *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Providencia stuartii*, and *Pseudomonas aeruginosa*. Their features were previously reported (Supplementary Materials, Table S2). These bacteria were maintained at 4°C and subcultured on a fresh Mueller Hinton Agar (MHA) for 24 h before any antibacterial assay. Mueller Hinton Broth (MHB) was used for antibacterial assays [23].

2.5. Antibacterial Assays. MIC and MBC values of the different samples were determined by microdilution using INT colorimetric assay as previously described [22, 24]. Briefly, the samples were dissolved in 10% dimethyl-sulfoxide (DMSO)/Mueller Hinton Broth (MHB) and serially diluted twofold (in a 96-well microplate). Then, 100 μL of inoculum (2×10^6 CFU/mL) prepared in MHB was added in each well. Chloramphenicol was used as reference drug and the well containing the vehicle (DMSO 2.5%) as control. The plates were then covered with a sterile plate sealer and gently shaked to mix the contents of the wells. After 18 h of incubation at 37°C, the MIC value of each sample, defined as the lowest sample concentration that inhibited complete bacteria growth, was detected following addition of 40 μL INT (0.2 mg/mL) and incubation at 37°C for 30 min. Viable bacteria reduced the yellow dye to pink. The MBC value was determined by adding 50 μL aliquots of the preparations, which did not show any growth after incubation during MIC assays, to 150 μL of MHB. Then, these preparations were incubated at 37°C for 48 h. The MBC was regarded as the lowest concentration of samples, which did not produce a color change after addition of INT as mentioned above [24]. Each assay was performed in three independent tests in triplicate. In case there was difference, the MIC or MBC values were taken as the most frequently occurring values.

2.6. Antibiotic Resistance Modifying Assay. The resistance modifying activity of the extracts was evaluated by determining the MICs of antibiotics in the presence or absence of the plant extracts in the 96-wells modulation assay as previously described [13, 25]. Briefly, after serial dilutions of antibiotics (256–0.5 μg/mL), the plant extracts were added at their subinhibitory concentrations (MIC/2 and MIC/4) selected after preliminary study assessed against *P. aeruginosa* PA124 (Supplementary Materials, Table S3). The MIC of each treatment was determined as described above. Each assay was performed in three independent tests in duplicate. Modulation factors (MF), calculated as MIC of antibiotic alone/MIC of antibiotic + extract, were used to express the antibiotic-potentiating effects of the plant extracts [11, 26, 27].

Table 1: Extraction yields and phytochemical composition of the plant extracts.

Plant extract	Part used	Yields (%)	ALK	POL	FLAV	ANTHR	TAN	TRI	STER	SAP
Azadirachta indica	Bark	10.3	+	+	-	-	+	-	+	+
***Citrus grandis* (Red)**	Pericarp	13.4	+	+	+	-	+	+	+	-
	Leaves	6.2	-	-	-	-	-	+	+	-
***Citrus grandis* (White)**	Leaves	2.6	+	+	-	-	+	+	+	-
Cucurbita maxima	Beans	2.6	-	+	-	-	+	+	+	+
Dacryodes edulis	Leaves	6.2	-	+	+	+	+	+	+	+
	Bark	9.1	-	+	-	+	+	+	+	+
	Seeds	6.9	-	+	+	+	+	+	+	+
Hibiscus esculentus	Leaves	1.9	-	+	-	-	+	-	+	-
Ipomoea batatas	Beans	3.3	+	+	+	+	+	+	-	+
Irvingia gabonensis	Leaves	6.7	-	+	-	-	+	-	+	+
Phaseolus vulgaris	Leaves	1.2	-	+	-	-	+	-	+	+
Spondias mombin	Leaves	21.4	-	+	-	-	+	+	+	-
Saccharum officinarum	Leaves	8.4	-	+	-	-	+	-	+	+
Theobroma cacao	Leaves	3.1	-	+	-	-	+	+	+	+
	Beans	6.2	+	+	+	+	+	+	+	+
Uapaca guineensis	Leaves	7.3	-	+	-	-	+	+	+	+
	Bark	6.1	+	+	-	-	+	+	+	+

(-): absent; (+): present; yield calculated as the ratio of the mass of the obtained methanol extract/mass of the plant powder; ALK: alkaloids; ANTH: anthocyanins; ANTHR: anthraquinones; FLAV: flavonoids; POL: polyphenols; SAP: saponins; STER: steroids; TAN: tannins; TRI: triterpenes.

3. Results

3.1. Qualitative Phytochemical Composition of the Tested Extracts. The results of the phytochemical screening (Table 1) showed that only *Theobroma cacao* broad bean (TCBB) extract contained all the classes of screened secondary metabolites. These metabolites were selectively distributed in other tested plant extracts. In addition, results showed that polyphenols, tannins, triterpenes, and steroids were the most represented metabolites in the tested extracts.

3.2. Antibacterial Activity of the Tested Extracts. Nineteen extracts from thirteen plants as well as chloramphenicol were tested for their antibacterial activities on a panel of 21 Gram-negative bacteria. The results of Table 2 show that the tested extracts (*A. indica* bark, *P. vulgaris* leaves, *H. esculentus* leaves, *U. guineensis* leaves, and *D. edulis* seed) presented selective antibacterial activity with the recorded MIC values ranging from 64 to 1024 μg/mL. Some extracts presented broad spectrum of antibacterial activity. Their inhibitory activities were observed on 18/21 (85, 71%, *A. indica* bark and *P. vulgaris* leaves), 17/21 (80.95%, *H. esculentus* leaves), and 16/21 (76,19%, *U. guineensis* leaves and *D. edulis* seeds). The lowest MIC value (64 μg/mL) was recorded with the extract of *T. cacao* broad bean (TCBB) against *E. coli* ATCC 8739, AG100A$_{Tet}$, and *K. pneumoniae* K24 and that from bark of *U. guineensis* against *E. coli* ATCC 8739. In general, MBC values were not detected at up to 1024 μg/mL extract concentrations. Extract from *I. batatas* leaves (IBL) and *T. cacao* leaves (TCL) displayed the best MBC values (256 μg/mL) against *E. aerogenes* EA27.

3.3. Antibiotic Resistance-Modifying Activities of the Extracts. The antibacterial activity of 6 commonly used antibiotics was evaluated in the presence of plant extracts at the concentrations equivalent to MIC/2 and MIC/4. The results obtained are summarized in Tables 3–9. From these tables, it was observed that some extracts selectively improved the antibacterial activities of tested antibiotics against the selected MDR bacteria (2- to 64-fold decrease of MIC). *D. edulis* seeds extract has significantly improved the antibacterial activities of CHL and KAN against 90% (8/10) and 80% (8/10) of the tested MDR bacteria, respectively (Table 4). The bark extract of *A. indica* (Table 3) and leaves extract of *P. vulgaris* (Table 6) also improved the activities of CHL, STP, and TET to about 80% (8/10) and 70% (7/10) of the tested MDR bacteria, respectively. The modulating effects were also observed after the combination of *T. cacao* leaves extract with STP, CHL, CIP, TET, and STP against 80% to 70% of the tested MDR bacteria (Table 8) whilst other extracts were less active.

4. Discussion

Plants constitute an undeniable source of substances named secondary metabolites which are known for their direct or indirect antimicrobial activities; some examples include flavonoids, phenols, terpenoids and sterols, saponins, and tannins [28–30]. The results of the phytochemical screening carried out on the tested extracts indicated the presence of at least one of these metabolites in each of the tested extracts (Table 1). This may explain the antibacterial activities of the extracts tested.

Table 2: MIC and MBC of the plant extracts and chloramphenicol against bacteria strain.

Bacterial strains[a]	Samples[b] MIC and MBC in μg/mL (in Bracket)																		
	Plant extracts																		Antibiotic
	AIB	CGrP	CGrL	CGwL	CMB	DEB	DEL	DES	HEL	IBL	IGB	PVL	SML	SOL	TCBB	TCL	UGB	UGL	CHL
E. coli																			
ATTC8739	1024 (-)	1024 (-)	1024 (-)	1024 (-)	1024 (-)	-	-	1024 (-)	512 (-)	1024 (-)	-	512 (-)	-	1024 (-)	**64 (-)**	1024 **(-)**	**64** (1024)	256(1024)	8 (64)
ATCC10536	1024 (-)	1024 (-)	1024 (-)	-	1024 (-)	-	-	-	1024 (-)	-	-	512 (-)	-	-	-	-	128 (-)	1024 (-)	4 (16)
AG100	1024 (-)	-	1024 (-)	512 (-)	1024 (-)	-	1024 (-)	-	512 (-)	-	1024 (-)	512 (1024)	-	1024 (-)	1024 **(-)**	-	512 (-)	512 (-)	32 (64)
AG102	1024 (-)	-	512 (-)	-	1024 (-)	-	-	-	1024 (-)	-	-	512 (-)	-	512 (-)	256 **(-)**	-	256 (1024)	-	32 (256)
AG100Atet	1024 (-)	1024 (-)	256 (-)	512 (-)	-	-	1024 (-)	-	1024 (-)	1024 (-)	-	-	-	-	**64 (-)**	1024 **(-)**	256 (-)	512 (-)	4 (32)
MC4100	1024 (-)	-	256 (-)	-	128 (1024)	-	1024 (-)	1024 (-)	512 (-)	-	-	256 (512)	-	1024 (-)	-	-	-	512 (-)	128 (-)
W3110	1024 (-)	-	1024 (-)	-	-	1024 (-)	-	1024 (-)	512 (1024)	-	-	1024 (-)	-	1024 (-)	-	-	-	512 (-)	8 (32)
E. aerogenes																			
ATCC13048	1024 (-)	-	-	-	-	1024 (-)	512 (-)	512 (-)	256 (-)	256 (-)	-	1024 (-)	-	512 (-)	-	256 **(-)**	-	512 (-)	8 (128)
EA27	512 (1024)	-	-	1024 (-)	-	1024 (-)	512 (1024)	1024 (-)	512 (1024)	256 (256)	-	512 (1024)	-	512 (-)	256 **(-)**	256 (256)	1024 (-)	1024 (-)	128 (256)
EA289	1024 (-)	-	1024 (-)	128(-)	512 (-)	512 (-)	256 (1024)	512 (-)	512 (-)	1024 (-)	-	1024 (-)	1024 (-)	1024 (-)	1024 **(-)**	1024 **(-)**	-	-	4 (64)
EA294	1024 (-)	-	1024 (-)	-	-	1024 (-)	512 (-)	128 (512)	-	-	-	512 (-)	-	-	-	-	-	512 (-)	2 (256)
EA 298	512 (-)	1024 (-)	-	1024 (-)	-	-	-	1024 (-)	256 (-)	512 (-)	-	1024 (-)	1024 (-)	512 (-)	-	512 **(-)**	1024 (-)	1024 (-)	8 (128)
K. pneumoniae											-								
ATCC11296	-	1024 (-)	1024 (-)	128(-)	-	-	-	1024 (-)	512 (-)	512 (-)	1024 (-)	512 (-)	-	-	-	512 **(-)**	-	1024 (-)	8 (256)
K24	1024 (-)	-	128 (512)	-	-	1024 (-)	512 (-)	-	512 (-)	-	-	512 (-)	-	1024 (-)	**64 (-)**	-	128 (-)	512 (-)	16 (128)
KP55	1024 (-)	-	-	-	128 (1024)	-	-	1024 (-)	512 (-)	512 (-)	-	-	1024 (-)	512 (-)	1024 **(-)**	512 **(-)**	512 (-)	1024 (-)	64 (128)
KP63	512 (1024)	-	-	-	-	1024 (-)	-	512 (-)	-	256 (-)	-	512 (-)	-	-	1024 **(-)**	256 **(-)**	-	-	16(128)
P. stuartii																			
PS2636	-	-	-	-	-	512 (-)	512 (-)	512 (-)	512 (1024)	-	-	512 (-)	-	-	-	-	-	1024 (-)	64 (256)
NEA16	-	-	-	-	-	512 (-)	512 (-)	256 (-)	512 (-)	-	-	-	-	1024 (-)	-	-	-	1024 (-)	64 (128)
E. cloacae																			
ECCI69	512 (-)	1024 (-)	-	-	-	128 (-)	256 (1024)	128 (-)	-	512 (-)	-	512 (-)	-	-	1024 **(-)**	512 **(-)**	-	512 (-)	128 (-)
P. aeruginosa																			
PA01	1024 (-)	-	1024 (-)	-	-	512 (-)	1024 (-)	512 (1024)	-	-	-	512 (1024)	-	1024 (-)	1024 **(-)**	-	128 (-)	-	128 (-)
PA124	1024 (-)	1024(-)	512 (-)	512 (-)	-	-	-	1024 (-)	512(-)	1024 (-)	-	512 (-)	-	1024 (-)	-	-	512 (-)	-	32 (-)

[a]Bacterial strain [*E.c*: *Escherichia coli*, *E.a*: *Enterobacter aerogenes*, *K.p*: *Klebsiella pneumoniae*, *P.s*: *Providencia stuartii*, *E.cl*: *Enterobacter cloacae*, *P.a*: *Pseudomonas aeruginosa*]. [b]Samples [AIB: *Azadirachta indica* bark, CGrP: *Citrus grandis* (red) pericarp, CGrL: *Citrus grandis* (red) leaves, CGwL: *Citrus grandis* (white) leaves, CMB: *Cucurbita maxima* beans, DEB: *Dacryodes edulis* bark, DEL: *Dacryodes edulis* leaves, DES: *Dacryodes edulis* seeds, HEL: *Hibiscus esculentus* leaves, IBL: *Ipomoea batatas* leaves, IGB: *Irvingia gabonensis* beans, PVL: *Phaseolus vulgaris* leaves, SML: *Spondias mombin* leaves, SOL: *Saccharum officinarum* leaves, TCBB: *Theobroma cacao* beans, TCL: *Theobroma cacao* leaves, UGB: *Uapaca guineensis* bark, UGL: *Uapaca guineensis* leaves, CHL: chloramphenicol]. MIC: minimal inhibitory concentration, MBC: minimal bactericidal concentration, -: MIC and MBC at up to 1024 μg/mL; MIC in bold: significant activity.

Table 3: Antibiotic resistance modulatory activity of leaves extract of *Azadirachta indica*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P.aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL	0	64	8	64	64	64	64	32	64	64	32	
	CMI/2	16 (**4**)	8 (1)	32 (**2**)	64 (1)	8 (**8**)	32 (**2**)	1 (**16**)	16 (**4**)	32 (**2**)	8 (**4**)	**80.00**
	CMI/4	32 (**2**)	8 (1)	32 (**2**)	64 (1)	64 (1)	32 (**2**)	4 (**8**)	32 (**2**)	32 (**2**)	8 (**4**)	**70.00**
KAN	0	32	4	16	32	64	64	16	32	16	64	
	CMI/2	16 (**2**)	4 (1)	16 (1)	32(1)	64 (1)	64 (1)	16 (1)	4 (**4**)	4 (**4**)	16 (**4**)	40.00
	CMI/4	16 (**2**)	4 (1)	16 (1)	32(1)	64 (**1**)	64 (1)	16 (1)	4 (**8**)	16(1)	32 (**2**)	40.00
STP	0	128	256	256	64	64	256	256	16	256	64	
	CMI/2	128(1)	256(1)	256(1)	**32 (2)**	**8 (8)**	**32 (8)**	**128 (2)**	16(1)	256(1)	32 (**2**)	50.00
	CMI/4	128(1)	256(1)	256(1)	64 (1)	128 (2)	**32(8)**	256 (1)	32 (2)	256(1)	32 (**2**)	20.00
CIP	0	8	1	1	1	8	4	16	2	2	16	
	CMI/2	8(1)	1 (1)	1 (1)	1 (1)	**<0.5(≥16)**	4 (1)	16 (1)	**<0.5(>4)**	1(**2**)	8 (**2**)	20.00
	CMI/4	8(1)	2(1)	1 (1)	1(1)	16 (1)	4 (1)	16 (1)	2 (1)	2(1)	16(1)	00.00
TET	0	8	< 0.5	64	32	16	32	4	32	16	16	
	CMI/2	1(**8**)	< 0.5(na)	64 (1)	8(**4**)	2(**8**)	16 (**2**)	1 (**4**)	16 (**2**)	2 (**8**)	2 (**8**)	**80.00**
	CMI/4	4 (**2**)	< 0.5(na)	64 (1)	8(**4**)	4(**4**)	16 (**2**)	1 (**4**)	32 (1)	2 (**8**)	2 (**8**)	**70.00**
ERY	0	64	8	16	64	64	32	16	32	16	32	
	CMI/2	32 (**2**)	2 (**4**)	16 (1)	32 (**2**)	4 (**32**)	32 (1)	2 (**8**)	32 (1)	8 (**2**)	16 (**4**)	**70.00**
	CMI/4	32 (**2**)	4 (**2**)	16 (1)	64 (1)	32 (**2**)	32 (1)	4 (**4**)	32 (1)	16 (1)	32(1)	40.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

Table 4: Antibiotic resistance modulatory activity of seeds extract of *Dacryodes edulis*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL	0	64	8	64	64	64	64	32	64	64	32	
	CMI/2	<2(≥**32**)	2 (**4**)	32 (**2**)	64 (1)	16 (**4**)	16 (**4**)	16 (**2**)	16 (**4**)	32 (**2**)	4 (**8**)	**90.00**
	CMI/4	8 (**8**)	2 (**4**)	32 (**2**)	64 (1)	32 (**2**)	64 (1)	16 (**2**)	32 (**2**)	64 (1)	4 (**8**)	**70.00**
KAN	0	32	4	16	32	64	64	16	32	16	64	
	CMI/2	8 (**4**)	2 (**2**)	8 (**2**)	32(1)	64 (1)	32 (**2**)	2 (**8**)	4 (**8**)	8 (**2**)	1 (**64**)	**80.00**
	CMI/4	16 (**2**)	2 (**2**)	16 (0.5)	32(1)	64 (1)	32 (**2**)	2 (**8**)	8 (**4**)	16 (1)	32 (**2**)	60.00
STP	0	128	256	256	64	64	256	256	16	256	64	
	CMI/2	64 (**2**)	128(**2**)	256(1)	64(1)	128(0.5)	256(1)	256(1)	32 (**2**)	256(1)	1 (**64**)	40.00
	CMI/4	64 (**2**)	256(1)	256(1)	64(1)	128(0.5)	256(1)	256(1)	32 (**2**)	256(1)	32 (**2**)	20.00
CIP	0	8	1	1	1	8	4	16	2	2	16	
	CMI/2	8(1)	0.5 (**2**)	2 (0.5)	1(1)	2(**4**)	2 (**2**)	4 (**4**)	2 (1)	1 (**4**)	1 (**16**)	60.00
	CMI/4	8(1)	2 (2)	2 (0.5)	1(1)	2(**4**)	2 (**2**)	16 (1)	2 (1)	2 (1)	4 (**4**)	30.00
TET	0	8	< 0,5	64	32	16	32	4	32	16	16	
	CMI/2	2 (**8**)	< 0,5 (na)	-(na)	8(**4**)	1(**16**)	16 (**2**)	1 (**4**)	32 (1)	2 (**8**)	1 (**16**)	**70.00**
	CMI/4	2 (**8**)	< 0,5 (na)	- (na)	8(**4**)	2(**8**)	16 (**2**)	1 (**4**)	32 (1)	2 (**8**)	4 (**4**)	**70.00**
ERY	0	64	8	16	64	64	32	16	32	16	32	
	CMI/2	16 (**4**)	2 (**4**)	16 (1)	64 (1)	16 (**4**)	32 (1)	2 (**8**)	64 (0.5)	8 (**2**)	**8 (4)**	60.00
	CMI/4	16(**4**)	2 (**4**)	16 (1)	64 (1)	32 (**2**)	32 (1)	16 (1)	64 (0.5)	8 (**2**)	32 (1)	40.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

Table 5: Antibiotic resistance modulatory activity of leaves extract of *Ipomea batatas*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL	0	64	8	64	64	64	64	32	64	64	32	
	CMI/2	32 (**2**)	8 (1)	16 (**4**)	64 (1)	64 (1)	32 (**2**)	32 (1)	32 (**2**)	32 (**2**)	16 (**2**)	60.00
	CMI/4	32 (**2**)	8 (1)	32 (**2**)	64 (1)	64 (1)	16 (**4**)	32 (1)	32 (**2**)	32 (**2**)	16 (**2**)	60.00
KAN	0	32	4	16	32	64	64	8	32	16	64	
	CMI/2	32 (1)	4 (1)	8 (**2**)	32 (1)	64 (1)	32 (**2**)	4 (**2**)	16 (**2**)	8 (**2**)	16(**4**)	60.00
	CMI/4	32 (1)	4 (1)	8 (**2**)	32 (1)	64 (1)	32 (**2**)	4 (**2**)	16 (**2**)	8 (**2**)	32 (**2**)	60.00
STP	0	128	256	256	64	64	256	>256	16	256	64	
	CMI/2	64 (**2**)	256 (1)	64 (**4**)	64 (1)	32(**2**)	64 (**4**)	128 (≥**2**)	32(**2**)	64(**4**)	64 (1)	**70.00**
	CMI/4	64 (**2**)	256 (1)	64 (**4**)	128(1)	64(1)	64 (**4**)	256 (≥**2**)	32(**2**)	64(**4**)	64 (1)	60.00
CIP	0	8	1	1	1	8	1	4	2	2	16	
	CMI/2	2 (**4**)	0.5 (**2**)	1 (1)	1(1)	8 (1)	<0.5(≥**2**)	1 (**4**)	2 (1)	<0.5(≥**4**)	16(1)	40.00
	CMI/4	2 (**4**)	0.5 (**2**)	1 (1)	1 (1)	8 (1)	<0.5(≥**4**)	2 (**2**)	4 (1)	<0.5(≥**4**)	16(1)	50.00
TET	0	8	< 0.5	64	32	16	32	4	32	16	16	
	CMI/2	8 (1)	< 0.5 (na)	64 (1)	8 (**4**)	16 (1)	32(1)	2 (**2**)	4 (**8**)	4 (**4**)	8(**2**)	50.00
	CMI/4	8 (1)	< 0.5 (na)	64 (1)	8 (**4**)	16 (1)	16 (**2**)	2 (**2**)	16 (**2**)	4 (**4**)	8(**2**)	60.00
ERY	0	64	8	16	64	64	32	16	32	16	32	
	CMI/2	16 (**4**)	8 (1)	8 (**2**)	64 (1)	16 (**4**)	16 (**2**)	2 (**8**)	8 (**4**)	16 (1)	32 (1)	60.00
	CMI/4	16 (**4**)	8 (1)	8 (**2**)	64 (1)	32 (**2**)	16 (**2**)	4(**4**)	8 (**4**)	16 (1)	32 (1)	60.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

Table 6: Antibiotic resistance modulatory activity of leaves extract of *Phaseolus vulgaris*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL	0	64	8	64	64	64	64	32	64	64	32	
	CMI/2	32 (**2**)	2 (**4**)	64(1)	32 (**2**)	32 (**2**)	32 (**2**)	8 (**4**)	32 (**2**)	64 (1)	16 (**2**)	**80.00**
	CMI/4	32 (**2**)	4 (**2**)	64(1)	64 (1)	32(**2**)	32 (**2**)	8 (**4**)	32 (**2**)	64 (1)	16 (**2**)	**70.00**
KAN	0	32	4	16	32	64	64	8	32	16	64	
	CMI/2	8 (**4**)	4 (1)	8 (**2**)	32(1)	64 (1)	16 (**4**)	2 (**4**)	16(**4**)	16 (1)	16(**4**)	60.00
	CMI/4	16 (**2**)	4 (1)	8 (**2**)	32(1)	64(1)	32 (**2**)	2 (**4**)	16 (**2**)	16 (1)	32 (**2**)	60.00
STP	0	128	256	256	64	64	256	>256	16	256	64	
	CMI/2	64 (**2**)	128 (**2**)	16 (**16**)	32 (**2**)	8 (**8**)	4(**64**)	256(≥**2**)	16(1)	256(1)	64 (1)	**70.00**
	CMI/4	64 (**2**)	256(1)	64 (**4**)	64(1)	32 (**2**)	8(**32**)	256(1)	16(1)	256(1)	64 (1)	40.00
CIP	0	8	1	1	1	8	1	4	2	2	16	
	CMI/2	8(1)	<0.5 (≥**2**)	1(1)	1(1)	4(**2**)	1 (1)	4 (1)	2 (1)	1 (**2**)	16(1)	30.00
	CMI/4	8(1)	<0.5(<0.5)	1 (1)	1(1)	4(**2**)	1 (1)	4 (1)	2 (1)	2 (1)	16(1)	10.00
TET	0	8	< 0.5	64	32	16	32	4	32	16	16	
	CMI/2	0.5 (**16**)	< 0.5 (na)	64 (1)	16 (**2**)	2(**8**)	8 (**4**)	1 (**4**)	32 (1)	2 (**8**)	8(**2**)	**70.00**
	CMI/4	4 (**2**)	< 0.5 (na)	64 (1)	16 (**2**)	8(**2**)	8 (**4**)	1 (**4**)	32 (1)	2 (**8**)	8(**2**)	**70.00**
ERY	0	64	8	16	64	64	32	16	32	16	32	
	CMI/2	16(**4**)	2 (**4**)	16 (1)	32 (**2**)	32 (**2**)	16 (**2**)	4 (**4**)	32 (1)	16 (1)	32 (1)	60.00
	CMI/4	16(**4**)	2 (**4**)	16 (1)	32 (**2**)	32 (**2**)	16 (**2**)	8 (**2**)	32 (1)	16 (1)	32 (1)	60.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

Table 7: Antibiotic resistance modulatory activity of broad bean extract of *Theobroma cacao*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL		64	8	64	64	64	64	32	64	64	32	
	CMI/2	32 (**2**)	8 (1)	32 (**2**)	128 (0.5)	128 (0.5)	16 (**4**)	8 (**4**)	16 (**4**)	64 (1)	32 (1)	50.00
	CMI/4	32 (**2**)	8 (1)	32 (**2**)	128 (0.5)	128 (0.5)	64 (1)	8 (**4**)	16 (**4**)	64 (1)	32 (1)	40.00
KAN	0	32	4	16	32	64	64	8	32	16	64	
	CMI/2	16 (**2**)	4 (1)	8 (**2**)	64 (1)	64 (1)	64 (1)	2 (**4**)	8 (**4**)	16 (1)	32 (**2**)	50.00
	CMI/4	16 (**2**)	4 (1)	8 (**2**)	64 (1)	64 (1)	64 (1)	4 (**2**)	16 (**2**)	16 (1)	32 (**2**)	50.00
STP	0	128	256	256	64	64	256	>256	16	256	64	
	CMI/2	128 (1)	- (na)	256 (1)	64 (1)	32(**2**)	128(**2**)	32(<**8**)	16 (1)	256 (1)	32 (**2**)	40.00
	CMI/4	128 (1)	- (na)	256 (1)	128(**2**)	32(**2**)	256(1)	16(<**16**)	16(1)	256 (1)	32 (**2**)	40.00
CIP	0	8	1	1	1	8	1	4	2	2	16	
	CMI/2	4 (**2**)	1(1)	1 (1)	0.5 (**2**)	16 (0.5)	0.5 (**2**)	<0.5(<**8**)	2 (1)	0.5 (**4**)	8(**2**)	60.00
	CMI/4	4 (**2**)	1(1)	2 (1)	1(1)	16 (0.5)	0.5 (**2**)	<0.5(<**8**)	4 (0.5)	1 (2)	8(**2**)	40.00
TET	0	8	< 0.5	64	32	16	32	4	32	16	16	
	CMI/2	8(1)	< 0.5 (na)	64 (1)	16 (**2**)	16 (**2**)	8(**4**)	0.5 (**8**)	4 (**8**)	8 (**2**)	8(**2**)	**70.00**
	CMI/4	8(1)	< 0.5 (na)	64 (1)	32 (1)	16(1)	16 (**2**)	0.5 (**8**)	4 (**8**)	4 (**4**)	8(**2**)	50.00
ERY	0	64	8	16	64	64	32	16	32	16	*32*	
	CMI/2	32 (**2**)	8 (1)	8 (**2**)	128 (0.5)	16 (**4**)	8 (**4**)	16 (1)	4 (**8**)	16 (1)	16 (**2**)	60.00
	CMI/4	32 (**2**)	8 (1)	16 (1)	128 (0.5)	32(**2**)	16 (**2**)	16 (1)	16 (**2**)	16 (1)	16 (**2**)	50.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

Table 8: Antibiotic resistance modulatory activity of leaves extract of *Theobroma cacao*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL	0	64	8	64	64	64	64	32	64	32	64	
	CMI/2	32 (**2**)	2 (**4**)	32 (**2**)	16 (**4**)	16 (**4**)	32 (**2**)	32 (1)	16 (**4**)	32 (1)	64 (1)	**70.00**
	CMI/4	32 (**2**)	2 (**4**)	64 (1)	64 (1)	32 (**2**)	32 (**2**)	8 (**4**)	32 (**2**)	32 (1)	64 (1)	60.00
KAN	0	32	4	16	32	64	64	8	32	64	16	
	CMI/2	32(1)	4 (1)	8 (**2**)	16 (**2**)	32 (**2**)	16 (**4**)	< 2 (≥**4**)	16 (**4**)	64 (1)	16 (1)	60.00
	CMI/4	32 (1)	4 (1)	32 (**2**)	16 (**2**)	64 (1)	16 (**4**)	2 (**4**)	16 (**2**)	64 (1)	16 (1)	50.00
STP	0	128	256	256	64	64	256	256	16	32	256	
	CMI/2	64 (**2**)	128 (**2**)	128 (**2**)	64 (1)	32(**2**)	32(**4**)	8 (**32**)	32 (1)	8 (**4**)	128 (**2**)	**80.00**
	CMI/4	128 (1)	256(1)	**128 (2)**	64 (1)	64 (1)	32**(4)**	128 **(2)**	32(1)	16 (**2**)	128 (**2**)	50.00
CIP	0	8	1	1	1	8	1	4	2	16	2	
	CMI/2	4 (**2**)	1 (1)	1 (1)	0.5 (**2**)	8 (1)	<0.5(≥**2**)	0.5(**8**)	0.5 (**4**)	8 (**2**)	0.5 **(4)**	**70.00**
	CMI/4	8 (1)	1 (1)	4 (0.25)	2 (2)	16 (2)	<0.5(≥**2**)	4 (1)	2 (1)	8 (**2**)	0.5 **(4)**	30.00
TET	0	8	< 0.5	64	32	16	32	4	32	16	16	
	CMI/2	4 (**2**)	< 0.5 (na)	32 (**2**)	16 (**2**)	16(1)	16 (**2**)	4 (1)	4 (**8**)	8 (**2**)	4 (**4**)	**70.00**
	CMI/4	8(1)	< 0.5 (na)	32 (**2**)	16 (**2**)	16(1)	16 (**2**)	8 (**2**)	16 (**2**)	8 (**2**)	4 (**4**)	**70.00**
ERY	0	64	8	16	64	64	32	16	32	32	16	
	CMI/2	32 (**2**)	8 (1)	8 (**2**)	128 (1)	32(**2**)	8 (**2**)	16 (1)	8 (**4**)	8 (**4**)	**8 (2)**	**70.00**
	CMI/4	32 (**2**)	8 (1)	8 (**2**)	64 (1)	32(**2**)	16 (**4**)	16 (1)	8 (**4**)	16 (**2**)	16(1)	60.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

Table 9: Antibiotic resistance modulatory activity of barks extract of *Uapaca guineensis*.

Antibiotics	Extract concentration	Bacteria MIC (μg/mL) and modulating factors (in bracket)										Modulating effect (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		AG102	AG100Atet	EA27	EA289	KP55	KP63	PS2636	NEA16	PA01	PA124	
CHL	0	64	8	64	64	64	64	32	64	64	32	
	CMI/2	32 (**2**)	8 (1)	32 (**2**)	128(0.5)	64 (1)	16 (**4**)	8 (**4**)	16 (**4**)	64 (1)	32 (1)	50.00
	CMI/4	32 (**2**)	8 (1)	32 (**2**)	128(0.5)	64 (1)	64 (1)	8 (**4**)	16 (**4**)	64 (1)	32 (1)	40.00
KAN	0	32	4	16	32	64	64	8	32	16	64	
	CMI/2	16 (**2**)	4 (1)	8 (**2**)	64 (**2**)	64 (1)	128 (1)	2 (**4**)	8 (**4**)	16 (1)	32 (**2**)	60.00
	CMI/4	16 (**2**)	4 (1)	8 (**2**)	64 (**2**)	64 (1)	64 (1)	4 (**2**)	16 (**2**)	16 (1)	32 (**2**)	60.00
STP	0	128	256	256	64	64	256	>256	16	256	64	
	CMI/2	128 (1)	- (na)	256 (1)	64 (1)	32(**2**)	128 (**2**)	32(≥**8**)	16 (1)	256 (1)	32 (**2**)	40.00
	CMI/4	128 (1)	- (na)	256 (1)	128(**2**)	32(**2**)	256(1)	16(≥**8**)	16 (1)	256 (1)	32 (**2**)	40.00
CIP	0	8	1	1	1	8	1	4	2	2	16	
	CMI/2	4 (**2**)	1(1)	1 (1)	0.5 (**2**)	16 (**2**)	0.5 (**2**)	<0.5 (≥**8**)	2 (1)	0.5 (**4**)	8(**2**)	**70.00**
	CMI/4	4 (**2**)	1(1)	1 (1)	1(1)	16 (**2**)	0.5 (**2**)	<0.5 (≥**8**)	2 (1)	1 (**2**)	8(**2**)	60.00
TET	0	8	< 0.5	64	32	16	32	4	32	16	16	
	CMI/2	8(1)	<0.5 (na)	64 (1)	16 (**2**)	16 (**2**)	8(**4**)	0.5 (**8**)	4 (**8**)	8 (**2**)	8(**2**)	**70.00**
	CMI/4	8(1)	<0.5 (na)	64 (1)	32 (1)	16(1)	16 (**2**)	0.5 (**8**)	4 (**8**)	4 (**4**)	8(**2**)	50.00
ERY	0	64	8	16	64	64	32	16	32	16	32	
	CMI/2	32 (**2**)	8 (1)	8 (**2**)	64 (1)	16 (**4**)	8 (**4**)	16 (1)	4 (**8**)	16 (1)	16 (**2**)	60.00
	CMI/4	32 (**2**)	8 (1)	16 (1)	64 (1)	32(**2**)	16 (**2**)	16 (1)	16 (**2**)	16 (1)	16 (**2**)	50.00

CHL: chloramphenicol, KAN: kanamycin, STP: streptomycin, CIP: ciprofloxacin, TET: tetracycline, ERY: erythromycin; −: MIC not detected at up to 256 μg/mL; ( ): modulating factor; MIC: minimal inhibitory concentration; values in bold represent modulating factor ≥ 2.

According to Tamokou et al. [31], an edible plant extract is very active if it has a MIC<100 μg/mL, significantly active if 100 ≤ MIC<512 μg/mL, moderately active when 512<MIC ≤ 2048 μg/mL, and weakly active for a MIC>2048 μg/mL. Thus, many of the tested extracts presented significant to moderate activities, 100≤ MIC<2048 μg/mL. Therefore, two extracts were very active (MIC<100 μg/mL), including the extract from seeds of *Theobroma cacao,* active against *E. coli* ATCC8739, AG100Atet, and *K. pneumoniae* K 24 and the extract from bark of *Uapaca guineensis* which was very active on *E. coli* ATCC 8739 (Table 2). Several other studies have already demonstrated the *in vitro* antibacterial activity of at least one of the parts of these two plants or those belonging to the same genus. Previous study has already demonstrated the antibacterial potential of extracts of bark and pulp of *T. cacao* on many bacterial strains including *E. coli* [32]. Singh et al. [33] have also demonstrated the antibacterial activity of *T. cacao* seed extract against *K. pneumoniae*. In addition, the bark of several species of the *Uapaca* genus has shown very good antibacterial activity against certain sensitive and resistant strains [34, 35]; the results obtained in this work reinforce those previous works done with some of the tested extracts. The extracts of seeds of *Theobroma cacao* and that from bark of *Uapaca guineensis* could be used to fight infections involving multidrug-resistant bacteria.

In addition to their direct antibacterial activities, secondary metabolites have been found to act indirectly as modulators of the activity of antibacterial agents [10, 28, 36]. In this work, some antibiotics (CHL, TET, KAN, STR, and ERY) activities were improved (2 to 64 times) on more than 70% of the multidrug-resistant bacteria tested in the presence of *T. cacao* leaves, *P. vulgaris* leaves, *D. edulis* seeds, and *A. indica* barks extracts (Tables 3–9). The bacteria used in this work are multiresistant and overexpress efflux pumps as a resistance mechanism (Supplementary Materials, Table S2). This suggests that aforesaid extracts could contain substances which are able to inhibit the efflux pumps expressed in these bacteria [37], thus leading to an increase in the effectiveness of antibiotics [38]. Several studies have shown that polyphenols, especially flavonoids, could improve the activity of antibiotics against resistant bacterial strains [39, 40]. Thus, the presence of these metabolites in the most active extracts may be the origin of the observed antibiotic-potentiating activity. Many cases of antagonism were also observed and this could be due to the negative interactions between the antibiotics and the compounds of the plant extract, leading, for example, to the inhibition of the active groups of the antibiotics. These results of this study indicate, for the first time, the potential of the tested plant extracts, mainly extracts from *D. edulis*, *P. vulgaris, A. indica*, and *T. cacao*, to reverse antibiotic resistance.

5. Conclusion

This work has provided informative data related to the antimicrobial activity of the tested plant extracts. It suggests that plant extracts and particularly those from *Theobroma cacao* and *P. vulgaris* can be used alone or in combination with conventional antibiotics in the treatment of bacterial infections involving multiresistant phenotypes.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Brice E. N. Wamba, Paul Nayim, Aimé G. Fankam, and Joachim K. Dzotam carried out the study; Armelle T. Mbaveng and Victor Kuete designed the experiments. Aimé G. Fankam and Victor Kuete wrote the manuscript; Armelle T. Mbaveng and Victor Kuete supervised the work and provided the facilities for antibacterial assays; all authors read and approved the final manuscript.

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Supplementary Materials

Supplementary file.docx. Table S1: information on the studied plants; Table S2: further details on the antibiotic resistance profiles of tested Gram-negative bacteria; Table S3: results of preliminary evaluation of antibiotic resistance modulatory activity of selected extracts at subinhibitory concentrations against *Pseudomonas aeruginosa* PA124. *(Supplementary Materials)*

References

[1] H. Lode, "Safety and tolerability of commonly prescribed oral antibiotics for the treatment of respiratory tract infections," *American Journal of Medicine*, vol. 123, no. 4, pp. S26–S38, 2010.

[2] World Health Organization, "Antibiotic resistance," http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/, Accessed on 09 November 2017.

[3] E. Cerceo, S. B. Deitelzweig, B. M. Sherman, and A. N. Amin, "Multidrug-resistant gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options," *Microbial Drug Resistance*, vol. 22, no. 5, pp. 412–431, 2016.

[4] World Health Organization, "Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics," http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1, Accessed on 09 November 2017.

[5] S. Santajit and N. Indrawattana, "Mechanisms of antimicrobial resistance in ESKAPE pathogens," *BioMed Research International*, vol. 2016, Article ID 2475067, 8 pages, 2016.

[6] D. Schillaci, V. Spanò, B. Parrino et al., "Pharmaceutical approaches to target antibiotic resistance mechanisms," *Journal of Medicinal Chemistry*, vol. 60, no. 20, pp. 8268–8297, 2017.

[7] T. N. Gandhi, D. D. Depestel, C. D. Collins, J. Nagel, and L. L. Washer, "Managing antimicrobial resistance in intensive care units," *Critical Care Medicine*, vol. 38, no. 8, pp. S315–S323, 2010.

[8] O. Lomovskaya and K. A. Bostian, "Practical applications and feasibility of efflux pump inhibitors in the clinic - A vision for applied use," *Biochemical Pharmacology*, vol. 71, no. 7, pp. 910–918, 2006.

[9] H. Nikaido and J.-M. Pagès, "Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria," *FEMS Microbiology Reviews*, vol. 36, no. 2, pp. 340–363, 2012.

[10] O. A. Aiyegoro and A. I. Okoh, "Use of bioactive plant products in combination with standard antibiotics: implications in antimicrobial chemotherapy," *Journal of Medicinal Plants Research*, vol. 3, no. 13, pp. 1147–1152, 2009.

[11] J. Kovač, N. Gavarić, F. Bucar, and S. S. Možina, "Antimicrobial and resistance modulatory activity of *Alpinia katsumadai* seed extract, essential oil and post-distillation extract," *Food Technology and Biotechnology*, vol. 52, no. 2, pp. 248–254, 2014.

[12] S. B. Tankeo, P. Tane, and V. Kuete, "In vitro antibacterial and antibiotic-potentiation activities of the methanol extracts from *Beilschmiedia acuta*, *Clausena anisata*, *Newbouldia laevis* and *Polyscias fulva* against multidrug-resistant Gram-negative bacteria," *BMC Complementary and Alternative Medicine*, vol. 15, article 412, 2015.

[13] M. Stavri, L. J. V. Piddock, and S. Gibbons, "Bacterial efflux pump inhibitors from natural sources," *Journal of Antimicrobial Chemotherapy*, vol. 59, no. 6, pp. 1247–1260, 2007.

[14] Y. Morita, K. Nakashima, K. Nishino et al., "Berberine is a novel type efflux inhibitor which attenuates the MexXY-mediated aminoglycoside resistance in *Pseudomonas aeruginosa*," *Frontiers in Microbiology*, vol. 7, 2016.

[15] K. A. Eshra and M. M. Shalaby, "Efflux Pump Inhibition effect of Curcumin and Phenylalanine Arginyl β-Naphthylamide (PAβN) against Multidrug Resistant *Pseudomonas aeruginosa* Isolated from Burn Infections in Tanta University Hospitals," *The Egyptian Journal of Medical Microbiology*, vol. 26, no. 1, pp. 113–119, 2017.

[16] A. G. Fankam, V. Kuete, I. K. Voukeng, J. R. Kuiate, and J.-M. Pages, "Antibacterial activities of selected Cameroonian spices and their synergistic effects with antibiotics against multidrug-resistant phenotypes," *BMC Complementary and Alternative Medicine*, vol. 11, article 104, 11 pages, 2011.

[17] I. K. Voukeng, V. Kuete, J. P. Dzoyem et al., "Antibacterial and antibiotic-potentiation activities of the methanol extract of some cameroonian spices against Gram-negative multi-drug resistant phenotypes," *BMC Research Notes*, vol. 5, p. 299, 2012.

[18] J. A. Seukep, A. G. Fankam, D. E. Djeussi et al., "Antibacterial activities of the methanol extracts of seven Cameroonian dietary plants against bacteria expressing MDR phenotypes," *SpringerPlus*, vol. 2, no. 1, pp. 1–8, 2013.

[19] J. K. Dzotam and V. Kuete, "Antibacterial and antibiotic-modifying activity of methanol extracts from six Cameroonian food plants against multidrug-resistant enteric bacteria," *BioMed Research International*, vol. 2017, Article ID 1583510, 19 pages, 2017.

[20] J. B. Harbone, *Phytochemical Methods: A Guide to Modern Techniques of Plant Analysis*, Chapman and Hall Ltd, London, UK, 1973.

[21] H. M. P. Poumale, R. Hamm, Y. Zang, Y. Shiono, and V. Kuete, "Coumarins and related compounds from the medicinal plants of Africa," in *Medicinal Plant*, V. Kuete, Ed., vol. 1, pp. 261–300, Elsevier, Oxford, UK, 2013.

[22] J. N. Eloff, "A sensitive and quick microplate method to determine the minimal inhibitory concentration of plant extracts for bacteria," *Planta Medica*, vol. 64, no. 8, pp. 711–713, 1998.

[23] V. Kuete, B. Ngameni, J. G. Tangmouo et al., "Efflux pumps are involved in the defense of gram-negative bacteria against the natural products isobavachalcone and diospyrone," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 5, pp. 1749–1752, 2010.

[24] V. Kuete, F. Nana, B. Ngameni, A. T. Mbaveng, F. Keumedjio, and B. T. Ngadjui, "Antimicrobial activity of the crude extract, fractions and compounds from stem bark of *Ficus ovata* (Moraceae)," *Journal of Ethnopharmacology*, vol. 124, no. 3, pp. 556–561, 2009.

[25] A. G. Fankam, J.-R. Kuiate, and V. Kuete, "Antibacterial and antibiotic resistance modulatory activities of leaves and bark extracts of *Recinodindron heudelotii* (Euphorbiaceae) against multidrug-resistant Gram-negative bacteria," *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, article 168, 2017.

[26] F. G. Figueredo, E. O. Ferreira, B. F. F. Lucena et al., "Modulation of the Antibiotic Activity by Extracts from *Amburana cearensis* A. C. Smith and *Anadenanthera macrocarpa* (Benth.) Brenan," *BioMed Research International*, vol. 2013, Article ID 640682, 5 pages, 2013.

[27] A. G. Fankam, J. R. Kuiate, and V. Kuete, "Antibacterial and antibiotic resistance modifying activity of the extracts from allanblackia gabonensis, combretum molle and gladiolus quartinianus against Gram-negative bacteria including multi-drug resistant phenotypes," *BMC Complementary and Alternative Medicine*, vol. 15, no. 1, 2015.

[28] M. Saleem, M. Nazir, M. S. Ali et al., "Antimicrobial natural products: an update on future antibiotic drug candidates," *Natural Product Reports*, vol. 27, no. 2, pp. 238–254, 2010.

[29] A. Basli, M. Chibane, K. Madani, and N. Oukil, "Activités antibactériennes des polyphénols extraits d'une plante médicinale de la flore d'Algérie: *Origanum glandulosum* Desf," *Phytothérapie*, vol. 10, no. 1, pp. 2–9, 2012.

[30] K. L. Compean and R. A. Ynalvez, "Antimicrobial activity of plant secondary metabolites: A review," *Research Journal of Medicinal Plant*, vol. 8, no. 5, pp. 204–213, 2014.

[31] J. D. D. Tamokou, A. T. Mbaveng, and V. Kuete, "Antimicrobial activities of African medicinal spices and vegetables," in *Medicinal Spices and Vegetables from Africa*, V. Kuete, Ed., Chapter 8, pp. 207–237, Academic Press, 2017.

[32] C. A. Panganiban, R. B. Reyes, I. Agojo et al., "Antibacterial activity of Cacao (*Theobroma* Cacao Linn.) Pulp Crude extract against selected bacterial isolates," *International Peer Reviewed Journal*, vol. 1, no. 1, 2010.

[33] N. Singh, S. Datta, A. Dey, A. R. Chowdhury, and J. Abraham, "Antimicrobial activity and cytotoxicity of *Theobroma cacao* extracts," *Der Pharmacia Lettre*, vol. 7, no. 7, pp. 287–294, 2015.

[34] A. J. Atibioke, I. George, N. Sallau, and S. Muhammed, "Phytochemical and antimicrobial studies of stem bark extracts from *Uapaca pilosa* (Hutch)," *World Journal of Pharmaceutical Sciences*, vol. 4, pp. 200–204, 2016.

[35] J. A. Seukep, L. P. Sandjo, B. T. Ngadjui, and V. Kuete, "Antibacterial activities of the methanol extracts and compounds from *Uapaca togoensis* against Gram-negative multi-drug resistant

phenotypes," *South African Journal of Botany*, vol. 103, no. 1, pp. 1–5, 2016.

[36] H. N. H. Veras, F. F. G. Rodrigues, A. V. Colares et al., "Synergistic antibiotic activity of volatile compounds from the essential oil of Lippia sidoides and thymol," *Fitoterapia*, vol. 83, no. 3, pp. 508–512, 2012.

[37] L. C. Braga, A. A. M. Leite, K. G. S. Xavier et al., "Synergic interaction between pomegranate extract and antibiotics against *Staphylococcus aureus*," *Canadian Journal of Microbiology*, vol. 51, no. 7, pp. 541–547, 2005.

[38] J. Pagès and L. Amaral, "Mechanisms of drug efflux and strategies to combat them: challenging the efflux pump of Gram-negative bacteria," *Biochimica et Biophysica Acta*, vol. 1794, no. 5, pp. 826–833, 2009.

[39] Y. Sato, H. Shibata, T. Arai et al., "Variation in synergistic activity by flavone and its related compounds on the increased susceptibility of various strains of methicillin-resistant Staphylococcus aureus to beta-lactam antibiotics," *International Journal of Antimicrobial Agents*, vol. 24, no. 3, pp. 226–233, 2004.

[40] T. P. Cushnie and A. J. Lamb, "Antimicrobial activity of flavonoids," *International Journal of Antimicrobial Agents*, vol. 26, no. 5, pp. 343–356, 2005.