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Botanicals from nine selected Cameroonian edible plants displayed Anti-pseudomonas effects and potentiated the activities of antibiotics against multidrug-resistant phenotypes over-expressing MexAB-OprM efflux pumps

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Abstract

Background: Despite the recognized efficiency of antibiotic therapy, the annual cases of deaths related to bacterial diseases are still growing in developing countries. In the present study, the *in vitro* antipseudomonal activity of the methanol extracts of nine food plants from Cameroon against the multidrug-resistant strains and isolates of *Pseudomonas aeruginosa* overexpressing active efflux pumps was determined. These plants included *Persea americana*, *Syzygium jambos*, *Mangifera indica, Garcinia kola*, *Citrus sinensis*, *Passiflora edulis*, *Vernonia amygdalina*, *Aframomum letestuanum*, and *Artocarpus heterophylus*.

Methods: The liquid microplate dilution method using the rapid para-Iodonitrotetrazolium chloride (INT) colorimetric method was applied to evaluate the antipseudomonal activities of botanicals, as well as their association with the efflux pump inhibitor and antibiotics.

Results: All botanicals displayed an antibacterial activity that varies from one bacterium to another, in the minimal inhibitory concentration (MIC) range of 64 µg/mL to 2048 µg/mL. The extracts from a mixture of leaves and bark of *Syzygium jambos* and *Mangifera indica*, the bark of *Garcinia kola*, and the leaves of *Persea americana* had the highest spectrum of antipseudomonal activity, with their inhibitory effects being noted in 100% of the 15 tested bacteria. Botanical from the leaves of *Garcinia cola*, were active against 90% of the strains tested, that from the bark of *Persea americana* and the leaves of *Citrus sinensis* were active against 70% and 60% of tested strains and isolates. Botanicals from the leaves and bark of *Mangifera indica* were very active against the isolates P124 and P57 with a MIC value of 64 µg/mL. At the concentration of MIC/2 and MIC/4, the extract from the leaves of Mangifera indica and *Syzygium jambo*s potentiated the activity of four antibiotics (Penicillin, Ampicillin, Imipenem, Augmentin) on 100% (7/7) of the strains and isolates tested. Persea americana leaf extract also enhanced the activity of penicillin, tetracycline, chloramphenicol, levofloxacin, ampicillin, and augmentin in 85% (6/7) of strains and isolates tested. The activity of all tested antibiotics increased in the presence of botanicals against at least one bacterial strain. The extract of leaves and bark of *Persea americana*, *Psidium guajava*, and leaves of *Syzygium jambos* potentiated the activity of 80% of the antibiotics on the strains and isolates tested.

Conclusion: Finally, the methanol extracts from the leaves and bark of *Mangifera indica* could be used effectively alone or in combination with antibiotics in the treatment of bacterial infection caused by *Pseudomonas aeruginosa* including antibiotic-resistant phenotypes expressing efflux pumps.

Keywords: Antibacterial activity; bacteria; Cameroon; edible plants; multidrug resistance; *Pseudomonas aeruginosa.*

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Background

Despite the recognized efficiency of antibiotic therapy, the annual number of deaths caused by bacterial diseases is still growing in many developing countries. These diseases represent a major public health concern globally, due to bacteria developing new resistance mechanisms leading to the failure of antibiotic therapy [1-3]. Natural product from the plant kingdom constitutes a good reservoir of pharmacologically active substances. Several medicinal plants and phytochemicals from the flora of Africa have been efficient against various types of drug-resistant pathogens including Plasmodia, worms, bacteria, as well as cancer cells [4-14]. In the last 15 years, an intensive investigation of the resource of the African flora as a potential source of botanicals and phytoconstituents to tackle bacterial drug resistance have done [15-17]. *Pseudomonas aeruginosa* is an important nosocomial pathogen highly resistant to clinically used antibiotics, causing a wide spectrum of infections, and leading to substantial morbidity and mortality [18, 19]. Earlier antibacterial screenings of the African medicinal plants allowed the detection of several botanicals with activity against the multidrug-resistant (MDR) phenotypes of *Pseudomonas aeruginosa.* Some of the most active plants include *Allanblackia gabonensis* and *Combretum mole* [20], *Capsicum frutescens* [21], *Dioscorea bulbifera* [22], *Albizia adianthifolia* and *Laportea ovalifolia* [23]. In our continuous search of new antibacterials from natural sources, the present investigation was undertaken to evaluate the *in vitro* antipseudomonal activity of methanol extracts of nine food plants from Cameroon against strains and multidrug-resistant *Pseudomonas aeruginosa* isolates, as well as the effect of their combination with PAβN and some clinically used antibiotics. The investigated plants included *Persea americana* Miller (Lauraceae), *Syzygium jambos* (L.) Alst. (Myrtaceae), *Mangifera indica* Linn. (Anacardiaceae), *Garcinia kola* Heckel (Guttiferae), *Citrus sinensis* Linn. (Rutaceae), *Passiflora edulis* Sims (Passifloraceae), *Vernonia amygdalina* Del. (Asteraceae), *Aframomum letestuanum* Gagnep. (Zingiberaceae), and *Artocarpus heterophylus* Lam. (Moraceae). These plants are traditionally used for various health conditions.

P. americana is used in cases of worms, microbial infections, malaria, diabetes, high blood pressure, stimulates uterine contractions and relief painful menstruations, urinary infections, bronchitis, rheumatism, anemia, exhaustion, hypercholesterolemia, hypertension, gastritis, and gastroduodenal ulcer, cancer, food, analgesic, as anti-inflammatory, hypoglycemic, anticonvulsant, and vasorelaxant [24-26]. The previously reported pharmacological activities of this plant include anti-inflammatory, antibacterial, antiproliferative, analgesic, anti-diabetic, cardiovascular, antihypertensive, antiviral, and wound healing activities [24, 25, 27-33]. *S. jambos* has been used in folk medicines to treat digestive tract disorders, as a stimulant and remedy for dental disorders, and to treat fever, diarrhea, dysentery, and catarrh [34, 35]. Earlier documented biological activities of the plant include the antibacterial, analgesic, antiproliferative, and antioxidant activities [34-37]. *M. indica* is used in traditional medicine for the treatment of syphilis, vomiting, inflammation, cough, hiccup, hyperdipsia, burning sensation, hemorrhages, hemoptysis, hemorrhoids, wounds, ulcers, diarrhea, dysentery, pharyngoplasty, scorpion string, wounds, ulcers, anorexia, dyspepsia, gastric disorders, asthma, mouth sores, liver diseases, urinary tract infections, diabetes, rheumatism, leucorrhea, lung hemorrhage, nerve disorders, and jaundice [38-40]. It has been shown to be anti-inflammatory [41], antibacterial and antifungal [39], antiproliferative [42-45], antinociceptive [46], analgesic [47], neuroprotective [48], anti-diabetic [49], hepatoprotective [50], antimalarial [51], immunomodulatory [52], anthelmintic [53], anti-hyperlipidemia [54], and gastroprotective [55]. *G. kola* is used in health conditions such as nervous alertness and induction of insomnia, wound healing, cancer, stomachache, gastritis, malaria, venereal diseases, laryngitis, and poison antidote [56]. *G. kola* had anti-inflammatory, diabetic, analgesic, antibacterial, antiproliferative, antimalarial, antimalarial, anti-diabetic, hepatoprotective, nephroprotective, antinociceptive, neuroprotective, gastroprotective, and antiparasitic activities [56-70]. *C. sinensis* is traditionally used in the cases of constipation, cramps, colic, diarrhea, bronchitis, tuberculosis, cough, cold, obesity, menstrual disorder, angina, hypertension, anxiety, depression, and stress, sore throats, indigestion, relieve intestinal gas and bloating, resolve phlegm, and additive for flavoring [71]. Some reported biological activities of *C. sinensis* include the antibacterial, antifungal, antiproliferative, anxiolytic, antimalarial, anti-Trypanosoma, anti-obesity, antiosteoporosis, and insecticidal activities [39, 72-80]. *P. edulis* has been traditionally used to treat anxiety, insomnia, nervousness, antifungal, anti-inflammatory, antihypertensive [81], gastric trouble [82], cancer [83], tonic, digestive, sedative, diuretic, antidiarrheal, insecticide, cough, dry throat, constipation, insomnia, dysmenorrhea, colic infants, joint pain, and dysentery [84]. The pharmacological investigated of *P. edulis* revealed its Anti-inflammatory, antibacterial, antiproliferative, anti-diabetic, analgesic, anxiolytic, anti-depressant, anti-hypertensive, hepatoprotective, and anti-hyperlipidemia activities [81, 85-97]. *V. amygdalina* is used in the folk medicine in many countries to cure the microbial infections, hiccups, kidney problems and stomach, discomfort, stomach-ache, gastrointestinal infections, malarial fever, cough remedy [98], malaria, purgative, parasitic infections, blood glucose levels control, and eczema [99]. It has shown anti-inflammatory, antibacterial, antiproliferative, antimalarial, neuroprotective, antinociceptive, and anti-diabetic activities [99-109]. *A. letestuanum* is traditionally in the treatment of Hemorrhage, muscular pains, nausea, and to stop vomiting [110]. Its preliminary antibacterial activity has been documented [110]. *A. heterophylus* is used for health condition including fracture, diabetes, laxative, increases breast milk in nursing mother, promotes anemia, diarrhea, and cough [111]. Its antibacterial activities were earlier reported [112].

Methods

Plant material and extraction

The plant material used in the present work included seven food plants from Cameroon. They were collected in Dschang (West Region) and Loum (Littoral Region) in Cameroon and identified in the Cameroon national herbarium (HNC). They were *Syzygium jambos* leaves and bark (30458/HNC), *Mangifera indica* leaves and bark (1846/HNC), *Vernonia amygdalina* leaves (31149/SRFC), *Garcinia kola* leaves, bark, and fruits (27839/SRF-CAM), *Citrus sinensis* leaves (25859/HNC), *Passiflora edulis* whole plant (65104/HNC), *Afromomum alboviolaceum* seeds and pulps (34888/HNC), *Artocarpus heterophylus* leaves (43993/HNC), and *Persea americana* leaves and bark (57756/HNC). These plant materials were air-dried, powdered, and soaked in methanol for 48 hours. The filtrate obtained using Whatman filter paper no. 1 was

evaporated over a vacuum to yield the crude extract or botanical. The botanicals were kept at 4°C until further use.

Chemicals

The chemicals used include the bacterial growth indicator, para-Iodonitrotetrazolium chloride ≥97% (INT), ten (10) antibiotics belonging to different families: beta-lactams (Ampicillin, Penicillin), cyclines (tetracycline and doxycycline), phenicols (chloramphenicol), cephalosporins (Ceftriazole, Cefixine), fluoroquinolones (Levofloxacin), a carbapenem (imipenem), aminopenicillin (Augmentin), and the efflux pump inhibitor, phenylalanine arginine beta naphthylamide (PAβN). They were all obtained from Sigma-Aldrich (St. Quentin Fallavier). Dimethylsulfoxide (DMSO, Sigma-Aldrich) was used to dissolve the tested samples.

Culture media

The culture media used were the Mueller Hinton Agar (MHA)used for the activation of bacterial strains and isolates, the Cetrimide agar (TITAN BIOTECH LTD, Rajasthan, India), also activate strains and isolates but more specifically for the identification of the bacterial species, the Mueller Hinton Broth (MHB), for the determination of minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC).

Bacterial strains and isolates

The *Pseudomonas aeruginosa* strains tested in the present were PA124 and PA01, and the clinical isolate available in the Laboratory of Microbiology and Antimicrobial Substances of the University of Dschang, P61, P120, P124, P57, P29, P2, P121, P97, P060, P021, P1, and P081 (Table 1). They were sub-cultured in the MHA for their activation 24 hours prior to any use while the antibacterial testing was done in the MHB.

Antibacterial evaluations

The MIC and MBC determinations on the used bacterial strains were performed using a rapid colorimetric INT test [10, 113, 114]. The different plant extracts and the reference drug were dissolved in DMSO-MHB. The bacterial inoculum used was 1.5×10^6 CFU/mL and the incubation conditions were 37°C for 18 h. DMSO with concentrations less than 2.5% was used as the control solvent. MIC was defined as the lowest sample concentration that prevented this change and exhibited complete inhibition of microbial growth. The MBC of the samples was further determined as previously reported [114]. Botanicals were also tested in the presence of PAβN at the concentration of 30 µg/mL to evaluate the role of efflux pumps on the resistance of the bacteria to the samples [18, 19]. A preliminary assay was also performed by evaluating a combination of the plant extracts at different sub-inhibitory concentrations (MIC/2, MIC/4, MIC/8, and MIC/16) with antibiotics on KP55 (Data not shown), which allowed us to select the appropriate sub-inhibitory concentration to further potentiate the effect on other bacteria. Therefore, MIC/2 and MIC/4 values were subsequently used for the combination of antibiotics in the sample on a larger number of bacteria [39, 115]. Activity ameliorating factor (AAF) was calculated as the ratio of the MIC of the antibiotic alone versus MIC in the combination with the botanical ($MIC_{\text{of the antibiotic alone}}/MIC_{\text{of the antibiotic with botanical}}$) [116].

Data Analysis

Generally, botanicals were considered significantly active, moderately active, and weakly active when their MIC values were less than 100 µg/mL, between 100 and 625 µg/mL, and greater than 625 µg/mL, respectively; for antibiotics and isolated compounds, the sample was considered to have strong activity when the MIC value≤ 10 µg/mL, moderate 10 < MIC≤ 100 µg/mL, and weak MIC> 100 µg/mL [117]. For in-depth analyses, the established cutoff point for the antibacterial activity of botanicals towards *Pseudomonas aeruginosa* was used as follows: outstanding activity when MIC ≤ 32 µg/mL; excellent activity when 32 < MIC ≤ 128 µg/mL; very good activity when 128 < MIC ≤ 256 µg/mL; good activity when 256 < MIC ≤ 512 µg/mL, average activity when 512 < MIC ≤ 1024 µg/mL, weak activity or not active when MIC values >1024 µg/mL [118]. The bactericidal or bacteriostatic effect of botanicals was determined using the ratio MBC/MIC [119].

Results

In vitro antibacterial activity of botanicals

The MICs and MBCs of botanicals were determined against two strains and twelve isolates of *Pseudomonas aeruginosa*. To determine whether they had bacteriostatic or bactericidal effects, the BMC/MIC ratio was calculated. The results are summarized in Table 2. All the plant extracts displayed an antibacterial activity that varies from one bacterium to another, in the range of 64 µg/mL to 2048 µg/mL. The extracts from the leaves and bark of *Syzygium jambos* and *Mangifera indica*, the bark of *Garcinia kola*, and the leaves of *Persea americana* had the highest spectrum of antipseudomonal activity, with their inhibitory effects being noted in 100% of the 15 tested bacteria. Botanical from the leaves of *Garcinia cola*, were active against 90% of the strains tested, that from the bark of *Persea americana* and the leaves of *Citrus sinensis* were active against 70% and 60% of tested strains and isolates. However, extracts from the leaves of *Artocarpus heterophylus* and *Passiflora edulis* were less active, with their effect being recorded in 50% of the strains and isolates tested. Botanicals from the leaves and bark of *Mangifera indica* were very active against the isolates P124 and P57 with a MIC value of 64 µg/mL. Similarly, extracts of leaves and bark of *Syzygium jambos* and *Mangifera indica* showed significant activity against isolates P87, P61, P120, P29, and P060. Botanicals from the leaves and bark of *Garcinia cola* showed the same activity vis-a-vis the P121 and P1 isolates; the extracts of the leaves of *Mangifera indica* and from *Garcinia cola* showed a bactericidal effect against 75% of the strains and isolates of *Pseudomonas aeruginosa* while botanicals from the leaves of *Citrus sinensis* and *Passiflora edulis* had the weakest bactericidal effects, on 10% and 7%, respectively.

Effect of combinations of PAβN and botanicals

Table 3 shows that in the presence of PaβN, the activity of the extracts was increased on 100% (8/8) of the strains and isolates tested. In addition, the extract from the leaves of *Persea americana* and *Vernonia amygdalina* had the highest significant values including: >256-fold increase on isolates P081 and P121.

Effect of combinations of antibiotics with botanicals

A preliminary test of associations between plant extracts and antibiotics on strain PA124 was performed at the botanical

subinhibitory concentrations of MIC/2, MIC/4, MIC/8, and MIC/16 (Data not shown). It was found that at the different concentrations of MIC/2 and MIC/4, all the extracts of the leaves of *Mangifera indica* potentiated all the antibiotics 100% (10/10) used during this association test, the extract from the leaves of *Persea americana*, the bark of *Psidium guajava*, the leaves of *Vernonia amygdalensis*, the leaves of *Artocarpus heterophylus* each potentiated 90% of the antibiotics tested. Many cases of synergy were observed with an increase AAF between 2 and 16. In addition, the activity of all the antibiotics used was improved in the presence of at least one extract against at least one strain tested. As the results of the preliminary test, the botanicals from the leaves and bark *of Persea americana*, *Psidium guajava*, *Mangifera indica*, and the leaves of *Syzygium jambo* were selected for further botanical-antibiotic association in more bacteria. The selected sub-inhibitory concentrations of the extracts were MIC/2 and MIC/4. The results obtained from the extract/antibiotic association test against another strain and six other isolates of Pseudomonas aeruginosa are presented in Table 4. At MIC/2 and MIC/4, the botanical from the leaves of Mangifera indica and *Syzygium jambos* potentiated the activity of four antibiotics (Penicillin, Ampicillin, Imipenem, Augmentin) on 100% (7/7) of the strains and isolates tested. *Persea americana* leaf extract also enhanced the activity of penicillin, tetracycline, chloramphenicol, levofloxacin, ampicillin, and augmentin in 85% (6/7) of strains and isolates tested. All antibiotics have seen their activity improved by plant extracts against at least one strain. The extract of leaves and bark of *Persea americana, Psidium guajava*, and leaves of *Syzygium jambos* potentiated the activity of 80% (8/10) of the antibiotics on the strains and isolates tested. In addition, *Syzygium jambos* and *Mangifera indica* leaf extract improved the activity of penicillin and ampicillin against 100% (7/7) of strains and isolates tested; However, there was a slight improvement in the antibacterial activity of tetracycline against 40% (3/7) of strains and isolates tested. Similarly, the extract from the bark of *Mangifera indica* potentiated the activity of Ceftriaxone and Imipenem against 100% (7/7) of strains and isolates tested. However, the activity of Cefixime, Doxycycline, Levofloxacin, Ampicillin, and Augmentin was improved by the extract of the same plant against 70% (5/7) strains and isolates tested. It is worth noting that a few cases of indifference. In effect, the extract of the bark of *Persea americana* in association with Doxycycline, showed indifference in the presence of the strain PA01 and the isolate P124, while the same association with Ceftriaxone, showed indifference towards isolates P124, P1, and P97. Some cases of antagonism were also recorded. This is the case of the extract of the leaves of *Vernonia amygdalina* and the bark of *Mangifera indica* which, in association with levofloxacin, have shown indifference towards the isolate P081.

Discussion

In accordance with the established threshold values for the classification of the antibacterial activity of plant-derived products, two plant extracts had interesting activity against at least one isolate of *Pseudomonas aeruginosa* [117, 118]. In effect, excellent antipseudomonal activity (32 < MIC ≤ 128 µg/mL) was recorded with the extracts of *Syzygium jambos* leaves towards PA124, PA01, P24, and P57, Mangifera indica leaves toward P124, P57, and P97, and bark toward P124, P57. The extracts of leaves and bark of Mangifera indica, Garcinia kola, *Persea americana*, and the seeds and pulps of *Aframomum letestuanum* had a spectrum of activity of 100% against strains and isolates tested. The differences in activity obtained with the extracts would be due either to their differences in composition in secondary metabolites or to the different interactions between the compounds or to the amount of active molecule. Nguenang et al. have previously recorded a MIC value of 1024 µg/mL for *Aframomum letestuanum* leaf extract on *Pseudomonas aeruginosa* PAO1 strain was 1024 µg/mL [110]. Wamba et al. highlighted the presence of tannins and many other metabolites in the leaf and bark extracts of this plant [34]. Lacmata et al. demonstrated moderate activity of Garcinia kola seeds against several multidrug-resistant bacteria including Pseudomonas aeruginosa with MIC values of 512 µg/mL against PA01 and 1024 µg/mL for PA124 [56]. All isolates used in the present work are resistant phenotypes overexpressing MexAB-OprM as evidenced by the increase of the activity in the presence of PAβN [18, 19]. The activity of strains and isolates generally increased in the presence of PAβN. These results corroborate those of Dzotam et al. [86], Noumedem et al. [99], Fankam et al. [120] who demonstrated that bacterial strains and isolates use efflux pumps as a mechanism of antibiotic resistance.

Table 1. Bacterial features of the studied Pseudomonas aeruginosa strains.

Bacterial strains	Features	References
PA124	MDR clinical strains overexpressing MexAB-OprM pumps	[121]
PA01	Reference strain	[20]
P61	Clinical isolate : PCR^r, CAZ^r, CIP^r, OFX^r, LEV^r, DO^r, TOB^r	Laboratory Collection
P120	Clinical isolate: PRL^r, CAZ^r, IMP^r, ATM^r, FEP^r, TOB^r, GEM^r, ATM^r, MEM^r,	Laboratory Collection
P124	AMK^r, OFX^r, LEV^r, PCR^r	Laboratory Collection
P57	Clinical isolate: GEN^r, TOB^r, TIC^r, CRO^r, IMP^r	Laboratory Collection
P29	Clinical isolate: FRC^r, CAZ^r, CIP^r, OFX^r, LEV^r, TOB^r, CN^r, AK^r, CRO^r, MEM^r, IMP^r, FCP^r, TC^r	Laboratory Collection
P2	Clinical isolate : DO^r, TOB^r, CN^r, AK^r, MEM^r, IMP^r, GEN^r	Laboratory Collection
P121	Clinical isolate: FRC^r, CAZ^r, CIP^r, ATM^r, DO^r, CRO^r, IMP^r, TC^r	Laboratory Collection
P97	Clinical isolate: FRC^r, CAZ^r, ATM^r, DO^r, CN^r, TOB^r, IMP^r, MEM^r	Laboratory Collection
P060	Clinical isolate: FRC^r, CAZ^r, CIP^r, OFX^r, LEV^r, TOB^r, CN^r, AK^r, CRO^r, MEM^r, IMP^r, FCP^r, TC^r	Laboratory Collection
P021	Clinical isolate: PRC^r, CAZ^r, OFX^r, ATM^r, DO^r, CRO^r, MEM^r, FEP^r, IMP^r	Laboratory Collection
P1	Clinical isolate: PCR^r, CAZ^r , CIP^r, OFX^r, LEV^r, DO^r, TOB^r	Laboratory Collection
P081	Clinical isolate: DO^r, TOB^r, CN^r, AK^r, MEM^r, IMP^r	Laboratory Collection

PRL^r, CAZ^r, ATM^r, MEM^r, IMP^r, FEP^r, CRO^r, TIC^r, TOB^r, GEN^r, AMK^r, DOX^r, CIP^r, OFX^r, LEV^r: resistance to Piperacillin, Ceftazidine, Aztreonan, Meropenem, Imipenem, Cefipime, Ceftriaxone, Ticarcillin, Tobramycin, Gentamycin, Amikacin, Doxycycline, Ciprofloxacin, Ofloxacin and Levofloxacin respectively.

Table 2. Minimal inhibitory and bactericidal concentration of the tested botanicals against *P. aeruginosa* strains (in µg/mL).

Bacterial strains	*Syzygium jambos*						*Mangifera indica*					
	Leaves			Bark			Leaves			Bark		
	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R
PA124	128	256	2	256	1024	4	512	512	1	256	2048	8
PA01	128	512	4	512	512	1	512	1024	2	512	512	1
P081	512	2048	4	256	512	2	256	256	1	256	512	2
P61	512	512	1	512	512	1	512	512	1	512	1024	2
P120	256	512	2	512	2048	4	512	1024	2	512	2048	4
P124	128	1024	8	128	1024	8	**64**	512	8	**64**	1024	16
P57	**64**	512	8	512	2048	4	**64**	512	8	**64**	1024	16
P29	128	2048	16	2048	>2048	nd	512	2048	4	1024	2048	2
P2	512	1024	2	1024	2048	2	512	1024	2	1024	2048	2
P121	1024	2048	2	1024	2048	2	512	2048	4	512	2048	4
P97	512	2048	4	256	2048	8	**64**	1024	16	512	512	1
P060	256	2048	8	256	2048	8	512	2048	4	512	1024	2
P21	1024	2048	2	1024	2048	2	1024	2048	2	1024	2048	2
P1	512	1024	2	256	512	2	256	512	2	256	512	2

MIC: minimal inhibitory concentration (in µg/mL); MBC: minimal bactericidal concentration (in µg/mL); R: MBC/MIC ratio; nd: not determined.

Table 2. Continued…

Bacterial strains	*Vernonia amygdalensis*			*Garcinia kola*			*Garcinia kola*			*Citrus sinensis*			*Passiflora edulis*			*Artocarpus heterophylus*		
	Leaves			Leaves			Bark			Leaves			Leaves			Leaves		
	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R
PA124	>2048	>2048	Nd	>2048	>2048	nd	512	512	1	>2048	>2048	Nd	>2048	>2048	Nd	2048	>2048	Nd
PA01	2048	2048	1	1024	2048	2	1024	1024	1	512	1024	2	2048	>2048	Nd	>2048	>2048	Nd
P081	>2048	>2048	Nd	1024	2048	2	1024	1024	1	1024	2048	2	2048	>2048	nd	1024	2048	Nd
P61	>2048	>2048	Nd	2048	>2048	nd	512	1024	2	2048	>2048	Nd	2048	2048	1	>2048	2048	Nd
P120	>2048	>2048	Nd	2048	2048	1	512	2048	4	2048	>2048	Nd	2048	>2048	Nd	>2048	>2048	Nd
P124	1024	2048	2	512	2048	4	512	1024	2	1024	>2048	Nd	1024	>2048	Nd	1024	>2048	Nd
P57	>2048	>2048	Nd	256	>2048	nd	128	1024	8	1024	>2048	Nd	>2048	>2048	Nd	2048	>2048	Nd
P29	1024	2048	2	512	1024	2	256	512	2	>2048	>2048	Nd	>2048	>2048	Nd	>2048	>2048	Nd
P2	2048	>2048	Nd	2048	2048	1	1024	2048	2	>2048	>2048	Nd	>2048	>2048	Nd	>2048	>2048	Nd
P121	2048	>2048	Nd	512	1024	2	256	1024	4	>2048	>2048	Nd	2048	>2048	Nd	1024	>2048	Nd
P97	1024	>2048	Nd	1024	1024	1	512	1024	2	512	>2048	Nd	>2048	>2048	Nd	>2048	>2048	Nd
P060	2048	>2048	Nd	1024	2048	2	512	2048	4	2048	>2048	Nd	>2048	>2048	Nd	>2048	>2048	Nd
P21	>2048	>2048	Nd	512	1024	2	512	1024	2	>2048	>2048	Nd	2048	>2048	nd	1024	>2048	Nd
P1	2048	>2048	Nd	1024	2048	2	256	512	2	2048	>2048	Nd	>2048	>2048	Nd	2048	>2048	Nd

Table 2. Continued and end.

Bacterial strains	*Persea americana*						*Aframomum letestuanum*						CHL		
	Leaves			Bark			Seeds			Pulps					
	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R
PA124	512	2048	4	>2048	>2048	Nd	1024	>2048	nd	256	1024	4	256	>256	nd
PA01	1024	1024	1	512	1024	2	512	2048	4	256	1024	4	256	>256	nd
P081	2048	2048	1	>2048	>2048	Nd	512	2048	4	512	>2048	Nd	128	>256	nd
P61	2048	>2048	Nd	>2048	>2048	Nd	512	2048	4	128	1024	8	256	>256	nd
P120	512	512	1	>2048	>2048	Nd	1024	>2048	nd	128	512	4	128	>256	Nd
P124	256	2048	4	256	1024	4	512	>2048	nd	128	1024	8	128	>256	Nd
P57	256	512	2	128	256	2	512	2048	4	256	2048	8	128	>256	Nd
P29	512	512	1	512	2048	4	512	512	1	256	>2048	Nd	128	>256	Nd
P2	512	2048	4	512	2048	4	1024	1024	1	128	512	4	128	>256	Nd
P121	1024	2048	2	256	>2048	Nd	1024	>2048	nd	128	1024	8	128	>256	Nd
P97	512	1024	2	1024	>2048	Nd	512	2048	4	128	1024	8	128	>256	Nd
P060	512	>2048	Nd	128	2048	16	512	>2048	nd	256	512	2	128	>256	Nd
P21	1024	2048	2	256	>2048	Nd	512	>2048	nd	128	2048	16	128	>256	nd
P1	256	2048	8	512	2048	4	1024	>2048	nd	512	2048	4	128	>256	Nd

Table 3. Anti-Pseudomonas activity (MIC in µg/mL) of the botanicals in the presence of PAβN.

Bacterial strains	*Persea americana* (Leaves)			*Persea ameicana* (Bark)			*Syzygium jambos (*Leaves*)*		
	MIC alone	+PAβN	Alone	Alone	Alone	R	Alone	+PAβN	R
PA124	512	<8	128	128	128	Nd	256	<8	>32
PA01	1024	64	128	128	128	32	1024	<8	>128
P97	512	<8	512	512	512	>128	128	>8	>16
P21	1024	<8	1024	1024	1024	>32	512	<8	>64
P081	2048	<8	512	512	512	nd	512	<8	>64
P121	1024	<8	1024	1024	1024	>32	1024	<8	>128
P124	256	16	128	128	128	2	256	128	2
P1	256	32	512	512	512	32	256	128	2

(R): Ratio of MIC (+PAβN)/MIC (alone)

Table 3. *Continued and end.*

Bacterial strains	*Mangifera indica* (Leaves)			*Mangifera indica* (Bark)			*Vernonia amygdalina* (Leaves)			CHL		
	Alone	+PAβN	R	Alone	+PAβN	R	Alone	+PAβN	R	Alone	+PAβN	R
PA124	512	<8	>32	256	<8	>32	-	<8	Nd	256	<8	>32
PA01	512	32	8	512	32	8	2048	128	16	256	128	2
P97	64	<8	>64	512	<8	>16	1024	256	4	128	16	8
P21	1024	<8	>64	1024	>8	>16	-	16	Nd	128	<8	>16
P081	256	<8	>64	256	<8	>16	-	64	Nd	128	128	1
P121	512	<8	>64	512	<8	>16	2048	<8	>256	128	<8	>16
P124	64	128	4	64	64	8	512	64	64	128	64	2
P1	256	128	4	256	64	8	2048	64	32	128	<8	>16

Table 4. Antipseudomonal activity of antibiotics (MIC in µg/mL) in the association with botanicals and activity increasing factors (AAF)

Bacterial strains	**MIC**	**Botanicals and MIC values (µg/mL) and activity increasing factors (in bracket)**			
		***Syzygium jambos* (Leaves)**		***Mangifera indica* (Leaves)**	
	0	**MIC/2**	**MIC/4**	**MIC/2**	**MIC/4**
Penicillin					
PA01	16	16(1)	16(1)	8**(2)**	8**(2)**
P081	64	8**(8)**	8**(8)**	8**(8)**	16**(4)**
P124	32	16(2)	16**(2)**	8**(4)**	16**(2)**
P21	64	4**(16)**	4**(16)**	4**(16)**	4**(16)**
P1	64	4**(16)**	16**(4)**	32**(2)**	32**(2)**
P121	32	16**(2)**	16**(2)**	8**(4)**	16**(2)**
P97	32	8**(2)**	8**(2)**	8**(2)**	8**(2)**
Ceftriaxone					
PA01	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P081	16	4**(4)**	4**(4)**	8**(2)**	8**(2)**
P124	64	32**(2)**	32**(2)**	32**(2)**	32**(2)**
P21	32	2**(16)**	2**(16)**	8**(4)**	8**(4)**
P1	32	16**(2)**	16**(2)**	8**(4)**	**16(2)**
P121	32	8**(4)**	8**(4)**	8**(4)**	8**(4)**
P97	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
PA01	256	256(1)	256(1)	128**(2)**	128**(2)**
Cefixime					
P081	128	4**(32)**	4**(32)**	8**(16)**	16**(8)**
P124	256	256(1)	256(1)	256(1)	256(1)
P21	64	4**(16)**	4**(16)**	8**(8)**	8**(8)**
P1	128	32**(4)**	128(1)	32**(4)**	128(1)
P121	128	32**(4)**	32**(4)**	128(1)	128(1)
P97	128	64**(2)**	64**(2)**	32**(4)**	64**(2)**
Doxycycline					
PA01	8	16(0.5)	16(0.5)	4**(2)**	8(1)
P081	32	2**(16)**	2**(16)**	2**(16)**	2**(16)**
P124	16	32(0.5)	32(0.5)	16(1)	16(1)
P21	32	16**(2)**	16**(2)**	8**(4)**	8**(4)**
P1	8	0.5**(16)**	0.5**(16)**	1**(8)**	1**(8)**
P121	8	**1(8)**	1**(8)**	1**(8)**	1**(8)**
P97	32	**16(2)**	16**(2)**	8**(4)**	8**(4)**
Tetracycline					
PA01	32	32(1)	32(1)	8**(4)**	8**(4)**
P081	8	0.25**(32)**	0.25**(32)**	8(1)	8(1)
P124	32	64(0.5)	64(0.5)	16**(2)**	16**(2)**
P21	32	16**(2)**	16**(2)**	32(1)	32(1)
P1	8	8(1)	8(1)	8(1)	8(1)
P121	8	4**(2)**	4**(2)**	2**(4)**	2(4)
P97	16	16(1)	16(1)	8(2)	16(1)
Chloramphenicol					
PA01	128	256(1)	256(1)	256(1)	256(1)
P081	256	32**(8)**	32**(8)**	32**(8)**	32**(8)**
P124	256	128**(2)**	128**(2)**	128**(2)**	128**(2)**
P21	256	64**(4)**	64**(4)**	256**(1)**	256(1)
P1	128	16**(8)**	64**(2)**	64**(2)**	64**(2)**
P121	128	32**(4)**	32**(4)**	32**(4)**	32**(4)**
P97	256	256(1)	256(1)	128**(2)**	128**(2)**
Levofloxacin					
PA01	8	2**(4)**	2**(4)**	2**(4)**	4**(2)**
P081	4	0.5**(8)**	0.5**(8)**	0.5**(8)**	0.5**(8)**
P124	4	2**(2)**	2**(2)**	4(1)	4(1)
P21	4	0.5**(8)**	0.5**(8)**	1**(4)**	1**(4)**
P1	8	2**(4)**	2**(4)**	2**(4)**	2**(4)**
P121	8	4**(2)**	4**(2)**	4**(2)**	4**(2)**
P97	4	1**(4)**	2**(2)**	2**(2)**	2**(2)**
Ampicillin					
PA01	32	16**(8)**	16**(8)**	16**(2)**	16**(2)**
P081	32	2**(16)**	2**(16)**	2**(16)**	2**(16)**
P124	128	16**(8)**	32**(4)**	64**(2)**	64**(2)**
P21	32	8**(2)**	8**(2)**	8**(2)**	8**(2)**
P1	64	16**(4)**	16**(4)**	16**(4)**	16**(4)**
P121	128	16**(32)**	16**(32)**	16**(32)**	16**(32)**
P97	64	16**(4)**	16**(4)**	16**(4)**	16**(4)**
Imipenem					
PA01	64	2**(32)**	2**(32)**	32**(2)**	32**(2)**
P081	32	2**(16)**	2**(16)**	8**(4)**	8**(4)**
P124	16	8**(2)**	8**(2)**	8**(4)**	8**(4)**
P21	16	4**(4)**	4**(4)**	4**(4)**	4**(4)**
P1	32	4**(8)**	4**(8)**	4**(8)**	8**(8)**
P121	32	2**(16)**	2**(16)**	4**(8)**	8**(4)**
P97	32	4**(8)**	8**(4)**	8**(4)**	8**(4)**
Augmentin					
PA01	32	2**(16)**	2**(16)**	2**(16)**	2**(16)**
P081	32	4**(8)**	8**(4)**	4**(8)**	16**(2)**
P124	16	8**(2)**	8**(2)**	16**(16)**	16**(16)**
P21	8	2**(4)**	2**(4)**	2**(4)**	2**(4)**
P1	32	4**(8)**	4**(8)**	4**(8)**	4**(8)**
P121	32	8**(4)**	8**(4)**	16**(2)**	16**(2)**
P97	32	0.5**(64)**	1**(32)**	1**(32)**	1**(32)**

Table 4. *continued and end.*

Bacterial strains	MIC	Botanicals and MIC values (µg/mL) and activity increasing factors (in bracket)			
		Mangifera indica (Bark)		*Vernonia amygdalina* (Leaves)	
	0	MIC/2	MIC4	MIC/2	MIC/4
Penicillin					
PA01	16	16(1)	16(1)	8**(2)**	8**(2)**
P081	64	16**(4)**	16**(4)**	16**(4)**	16**(4)**
P124	32	16**(2)**	16**(2)**	8**(4)**	8**(4)**
P21	64	16**(4)**	16**(4)**	16**(4)**	16**(4)**
P1	64	8**(8)**	16**(4)**	8**(8)**	8**(8)**
P121	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P97	8	4**(2)**	4**(2)**	4**(2)**	4**(2)**
Ceftriaxone					
PA01	32	8**(4)**	16**(2)**	4**(8)**	16**(2)**
P081	16	8**(2)**	8**(2)**	8**(2)**	16(1)
P124	64	32**(2)**	32**(2)**	32**(2)**	64(1)
P21	32	8**(4)**	16**(2)**	8**(4)**	16**(2)**
P1	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P121	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P97	64	32**(2)**	32**(2)**	16**(4)**	32**(2)**
Cefixime					
PA01	256	64**(4)**	128**(2)**	256(1)	256(1)
P081	128	32**(4)**	32**(4)**	4**(32)**	4**(32)**
P124	256	128**(2)**	128**(2)**	256(1)	256(1)
P21	64	8**(8)**	16**(2)**	8**(8)**	16**(2)**
P1	128	32**(4)**	128(1)	128(1)	128(1)
P121	128	128(1)	128(1)	128(1)	128(1)
P97	128	32**(4)**	64**(2)**	64**(2)**	64**(2)**
Doxycycline					
PA01	8	8(1)	8(1)	8(1)	8(1)
P081	32	8**(4)**	8**(4)**	4**(8)**	4**(8)**
P124	16	16(1)	16(1)	16(1)	16(1)
P21	32	8**(4)**	8**(4)**	8**(4)**	8**(4)**
P1	8	2**(4)**	2**(4)**	2**(4)**	2**(4)**
P121	8	1**(8)**	2**(4)**	2**(4)**	2**(4)**
P97	32	8**(4)**	16**(2)**	8**(4)**	16**(2)**
Tetracycline					
PA01	32	8**(4)**	8**(4)**	8**(4)**	8**(4)**
P081	8	4**(2)**	4**(2)**	1**(8)**	1**(8)**
P124	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P21	32	32(1)	32(1)	16**(2)**	16**(2)**
P1	8	8(1)	8(1)	8(1)	8(1)
P121	8	4**(2)**	4**(2)**	4**(2)**	4**(2)**
P97	16	16(1)	16(1)	16(1)	16(1)
Chloramphenicol					
PA01	128	128(1)	128(1)	256(0.5)	256(0.5)
P081	256	128**(2)**	128**(2)**	128**(2)**	128(2)
P124	256	64**(4)**	64**(4)**	128**(2)**	128**(2)**
P21	256	256(1)	256(1)	256(1)	256(1)
P1	128	128(1)	128(1)	64**(2)**	64**(2)**
P121	128	64**(2)**	64**(2)**	64**(2)**	64**(2)**
P97	256	128**(2)**	128**(2)**	128**(2)**	128(2)
Levofloxacin					
PA01	8	4**(2)**	4**(2)**	4**(2)**	4**(2)**
P081	4	1(0.25)	1(0.25)	0.5(0.125)	0.5(0.125)
P124	4	4(1)	4(1)	4(1)	4(1)
P21	4	1**(4)**	1**(4)**	0.5**(8)**	0.5**(8)**
P1	8	8(1)	8(1)	8(1)	8(1)
P121	8	4**(2)**	8(1)	4**(2)**	4**(2)**
P97	4	2**(2)**	2**(2)**	2**(2)**	2**(2)**
Ampicillin					
PA01	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P081	32	4**(8)**	8**(4)**	4**(8)**	8**(4)**
P124	128	128(1)	128(1)	128(1)	128(1)
P21	32	8**(4)**	8**(4)**	8**(4)**	8**(4)**
P1	64	64(1)	64(1)	16**(4)**	16**(4)**
P121	128	32**(4)**	32**(4)**	32**(4)**	32**(4)**
P97	64	8**(8)**	16**(4)**	16**(4)**	16**(4)**
Imipenem					
PA01	64	16**(4)**	16**(4)**	16**(4)**	16**(4)**
P081	32	8**(4)**	16**(8)**	8**(4)**	8**(4)**
P124	16	2**(8)**	2**(8)**	2**(8)**	2**(8)**
P21	16	4**(4)**	4**(4)**	8**(2)**	8**(2)**
P1	32	16**(2)**	16**(2)**	4**(8)**	8**(4)**
P121	32	16**(2)**	16**(2)**	16**(2)**	16**(2)**
P97	32	4**(8)**	4**(8)**	4**(8)**	4**(8)**
Augmentin					
PA01	32	2**(16)**	2**(8)**	2**(8)**	2**(8)**
P081	32	32(1)	32(1)	16**(2)**	16**(2)**
P124	16	16(1)	16(1)	8**(2)**	16(1)
P21	8	2**(4)**	2**(4)**	2**(4)**	2**(4)**
P1	32	16**(2)**	16(2)	8**(4)**	16**(2)**
P121	32	16**(2)**	16**(2)**	8**(4)**	16**(2)**
P97	32	2**(16)**	2**(16)**	2**(16)**	2**(16)**

Conclusion

In the present study, we have demonstrated the antipseudomonal activity of ten botanicals from the Cameroonian food plants against MDR Pseudomonas aeruginosa overexpressing efflux pumps. The leaves and bark of *Mangifera indica* and *Syzygium jambos* had interesting spectra of antipseudomas activity. Botanicals from the bark and

leaf of *Mangifera indica* and *Persea americana* improved the activity of the antibiotics used on at least 55% of the strains and isolates tested. The activity of all the extracts increased in the presence of PAβN against all the strains and isolates tested. Conclusively, the extracts of *Syzygium jambos* leaves and *Mangifera indica* leaves and bark have antipseudomonal activities and can also be used in combination with certain antibiotics to combat infections caused by *Pseudomonas aeruginosa*.

Abbreviations

AAF, activity ameliorating factor; DMSO, dimethylsulfoxide, HNC, Cameroon national herbarium; INT, para-Iodonitrotetrazolium chloride; MDR, multidrug-resistant; PAβN, phenylalanine arginine beta naphthylamide; MBC, minimal bactericidal concentrations; MHA, Mueller Hinton Agar; MHB, Mueller Hinton Broth; MIC, minimum inhibitory concentrations.

Authors' Contribution

RST carried out the study; ATM wrote the manuscript; VK and ATM supervised the study; All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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