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Evaluation of the Antibacterial ESBL Activity of some Extracts of Gabonese Medicinal Plants on Strains of Enterobacteria Isolated in a Hospital Environment

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ABSTRACT

Background: *The widespread spread of ESBLs worldwide is a major public health problem that urgently needs to be addressed. Medicinal plants represent a therapeutic alternative to combat ESBLs. The objective of this study was to evaluate in vitro the antibacterial activity of ethanolic extracts of some medicinal plants from Gabon on enterobacteria strains ESBL.*

Results: *The results show an inhibition activity of the ethanolic extract of Canarium schweinfurthii. Mitragyna ciliata and Solanum torvum on K. pneumoniae and E. cloacae. Anonidium manii showed narrow activity only on E. coli . However. the best spectrum of activity was obtained with the extract of Harungana madasgascariensis on more than 3 bacterial species (K. pneumoniae. E. coli and E. cloacae). However. we also observed very clear antagonistic effects for certain plants. Synergistic and sometimes even additive effects were observed for all the extracts used.*

Conclusion: *Five (5) ethanolic extracts of Gabonese medicinal plants exhibit ESBL-CTX-M antibacterial activity. Therefore. these plants can be used to develop drugs capable of treating infections due to enterobacteria resistant to third-generation cephalosporins.*

Keywords

ESBLs, Medicinal plants, Antibacterial activity, Enterobacteria ESBL-CTX-M. Gabon.

Abbreviations

ATP: Adenosine Triphosphate. BHI-D: Brain Heart Infusion Broth. blaCTX-M: Cefotaximase-Minuch type Beta-Lactamase gene. ESBL: Extended Spectrum Beta-Lactamase. MRB: Multidrug-Resistant Bacteria. C3G: Third Generation Cephalosporin. CFU: Colony Forming Unit. MIC: Minimum Inhibitory Concentration. CTX: Cefotaxime. CTX-M: Cefotaximase-Minuch. MH: Mueller Hinton Agar. TEM: Temoneira type ESBL. TRI: TEM Inhibitor Resistant.

Introduction

Antibiotics play an important role in the fight against bacterial infections and their development has revolutionized the treatment of infectious diseases. Their discoveries have allowed a considerable increase in life expectancy during the 20th century. However. as the use of these molecules increases. and in some cases overconsumption. bacteria have learned to defend themselves and adapt. and some have become resistant to antibiotics. This state of affairs is becoming worrying for the health of populations. The worsening of this situation is the consequence of various concomitant parameters. The environment. hygiene. the lack of development of new antibiotics. the overconsumption of the latter and their misuse have been determining factors in the expansion of this public health problem across the globe [1].

To overcome this problem of resistance. other more effective antibiotics have been developed. such as third-generation cephalosporins (C3Gs). However. the intense prescription of these during infections was quickly followed by the spread of bacterial resistance to these antibiotics. particularly through the production of extended-spectrum beta-lactamase (ESBL) [2].

Infections caused by ESBL-producing bacterial strains are associated with high morbidity and mortality. prolonged length of hospitalization. and increased hospitalization costs [3].

Unfortunately. the increase in these resistances jeopardizes the use of C3Gs. At the University Hospital of Libreville. Medzégué Nguema et al.. reported the presence of ESBL and BMR in clinical isolates from blood cultures [4]. Kouegnigan Rerambiah et al.. also reported a high resistance of enterobacteria strains to 3rd and 4th generation cephalosporins in Libreville [5]. In addition. cefotaxime. ceftriaxone and amoxicillin clavulanic acid are the antibiotics mainly used at CHUL for the treatment of bacterial infections and nearly 80% of the bacterial strains isolated in this hospital show resistance to these commonly prescribed antibiotics [5.6].

On the other hand. CTX-M (Cefotaxime Munich) is considered the most common type of ESBL in the world. Many studies report the continued global progression of this type of resistance [7]. In Gabon. resistance to CTX has also been reported. Indeed. Dikoumba et al.. in 2021 showed the exclusive presence of blaCTX-M-15 genes for CTX-M group 1 in 94% (79/84) of clinical isolates in eight (8) hospitals in Gabon [8].

Unfortunately. to date. no study has been devoted to a global therapeutic alternative for the management of bacterial infections of CTX-M-producing strains other than the usual antibiotics. Therefore. the study of new possibilities for treating infections caused by blaCTX -M bacteria is necessary. Medicinal plants represent a therapeutic alternative to combat ESBLs. more precisely ESBL-CTX-M bacteria.

Indeed. the increase in the number of antibiotic-resistant bacteria has revived interest in plant products as alternative/complementary antimicrobial agents to control pathogenic microorganisms and has brought phytomedicine back into the spotlight [9-11]. Moreover. the literature has shown significant antibacterial activities of many plants that are also traditionally used to treat infections. Research on the antibacterial effects of medicinal plants using clinical isolates has shown that crude extracts are a viable source of resistance-modifying phytochemicals [12-14].

Gabon is a tropical country covered 85% by forest with a large pharmacopoeia and especially by an indigenous population (pygmies) very renowned for its mastery of care through herbal medicine.

It is in this context that we were interested in the resistance to 3rd generation cephalosporins (Cefotaxime) of clinical strains of enterobacteria ESBL-CTX-M (E. *coli. Klebsiella spp and E. cloacae)* commonly isolated at the University Hospital Center of Libreville (CHUL) in order to evaluate *in vitro* the antibacterial activity of extracts of some plants of the Gabonese pharmacopoeia on these isolates.

Methods

Study Settings and Population

This was a prospective. descriptive. and cross-sectional study conducted in the city of Libreville over a period of 16 months. During this study. clinical strains of ESBL-producing Enterobacteriaceae of the CTX-M type were collected from various clinical samples (blood. urine. stool. vaginal secretions…) from patients hospitalized or attending outpatient clinics in the various departments of the CHUL.

At the same time. an ethnopharmacological survey was conducted among herbalists and individuals with knowledge of phytotherapy. This survey aimed to identify Gabonese medicinal plants used in the traditional treatment of certain infectious diseases.

Through this approach. 11 plant species used in the traditional treatment of fevers. diarrhea. wounds. and other infections were identified and collected. Ethanolic extracts of these plants were then tested on hospital isolates of ESBL-producing Enterobacteriaceae of the CTX-M type. Ethnopharmacology and harvesting of medicinal plants ethnopharmacological survey on plants used to treat infectious diseases was carried out among herbalists at the Peyrie market (Libreville. Gabon).

Plant material

One kilogram of the bark or leaves of the plants from the survey were provided by herbalists at the Peyrie market in Libreville (0.40113371290349753 N. 9.45426531812608 E) in February 2023 and one kilogram of wild eggplant leaves (*Solanum torvum*) were harvested in the town of Oyem in the Mekaga district (1.59977° N. 11.55630°E) in August 2023. Botanical authentication of plants was carried out at the herbarium of the Department of Biology.

Biological material

The bacteria used in this study came from clinical isolates from the samples of the different biological samples sent to the CHUL

microbiology laboratory for routine analyses. The selected isolates were only ESBL-CTX-M strains. These blaCTX-M were detected by phenotypic confirmation tests and synergy tests of amoxicillin + clavulanic acid disks and cefotaxime.

Preparation of ethanolic extracts

After harvesting. the plant material was washed and dried at room temperature away from sunlight for two weeks. Then. the barks were cut into small pieces and crushed and the leaves were crushed using an electric grinder. all rendered into powder. The latter was used for the preparation of ethanolic extracts.

For each plant. 20 g of powder were macerated in 100 ml of ethanol diluted to 70° in an Erlenmeyer flask and incubated in an oven at 37°C for about 24 hours. The macerate obtained was filtered once on Watman paper No. 1 and the filtrate was concentrated using a Rotavapor at 60°C. The extract obtained was stored cold between 4°C and 8°C until the antibacterial tests were carried out.

Extraction yield

The extraction yield. expressed as a percentage relative to the weight of the starting material. was determined by the following relationship: R = (Pc- Pv) x 100 ⁄ Q. With R: yield (in %); Pc: weight of the flask with contents (in g); Pv : weight of the empty flask (in g); Q: weight of the starting plant material (in g).

Microbial culture

Choice of sprouts

The choice of bacteria *Escherichia coli*. *Enterobacter cloacae and Klebsiella pneumoniae* is based on their pathological interest. in relation to problems of resistance to commonly used antibiotics and particularly for their resistance to cefotaxime. Six (6) strains of ESBL CTX-M-producing enterobacteria were used to study the antibacterial activity of medicinal plants.

Preparation of bacterial suspension

A well-isolated colony from a 24-hour young culture was introduced into 2.5 ml of physiological serum (0.09% NaCl) contained in a sterile test tube. The density of the inoculum was adjusted by a densitometer to 0.5 Mc Faland to have an inoculum of 10 ^{7} CFU/ ml. The bacterial inoculum thus obtained was inoculated in tight streaks with a swab on Muller Hinton agar. then incubated at 37°C.

Antibacterial activities

The agar diffusion test was applied in order to evaluate the antimicrobial activity of plant extracts. This evaluation was made *in vitro* by the Kirby Bauer solid medium diffusion method: previously sterilized Wattman No. 1 paper discs of 6 mm diameter were soaked for 15 min at 37°C with 50 µl of different extract solutions of concentrations ranging from 125 mg / ml to 250 mg / ml. The impregnated discs were deposited using sterile forceps on the surface of the solid Muller Hinton medium previously inoculated with the bacterial inoculum of a density of 0.5 Mc Farland. Petri dishes were incubated for 18 to 24 h at 37°C. Antibacterial activities were evaluated by measuring. using a caliper. the diameter of the inhibition zone in millimeters induced by the extracts. The results are expressed according to four levels of activity as described by Ababsa et al.. [15].

Water and ethanol-soaked disks were used as negative controls. Ceftriaxone and cefotaxime were used as positive controls.

Synergy test and determination of the Minimum Inhibitory Concentration (MIC)

The combinations of plant extracts with the antibiotic (cefotaxime) for synergistic study were evaluated in Petri dishes using the diffusion technique. Synergy is the result of the interaction between several compounds. so that the biological effects of a plant or a part of the plant are superior to the effect of its constituents studied in isolation [16]. Brain heart infusion broth (BHI-D; BioMerieux) was used for the MIC test and distributed in the microtiter plates. The Minimum Inhibitory Concentration (MIC) was determined by the liquid microdilution method with visual assessment of bacterial growth.

Synergy test

For this. a 6 mm diameter Wattman paper disk is aseptically placed on the surface of the Muller Hinton medium previously seeded with the bacterial suspension. the disk is impregnated with 50 µl of plant extract and combined with a volume of 50 µl of cefotaxime [17].

After incubation at 37°C for 24 hours. the antimicrobial effects of the combinations of these extracts and the antibiotic are defined in response to the interactions in the following ways:
Indifference: the activity of cefotaxime or the extract is not affected by the other: (A + B) = effect A or effect B.
Addition: the effect of the combination of cefotaxime and extract is equal to the sum of the effects of each studied in isolation: (A + B) = effect A + effect B.
Synergy: the effect is significantly greater than the sum of cefotaxime and the extract studied in isolation: (A + B) > effect A + effect B.
Antagonism: the association decreases the activity. It is less than the sum of the effects of cefotaxime and the extract taken separately: (A+B) < effect A or effect B [17].

Determination of the minimum inhibitory concentration (MIC)

After examining the antibacterial activity of the plant extracts. the MIC was determined using a Muller Hinton broth microdilution susceptibility test as recommended by the National Committee for Clinical Laboratory Standards [18].

Enterobacteriaceae strains were grown in Mueller-Hinton broth at 37°C for 24 h. The bacterial suspension was adjusted to a turbidity of 0.5 McFarland units. Dilutions of plant extracts ranging from 125 to 500 mg/ml were prepared in Mueller-Hinton broth (supplemented to a final concentration of 0.5%). Then. 100 µl of diluted extract and 100 µl of bacterial suspension were added to a 96-well plate and incubated at 37°C for 24 h. The Minimum Inhibitory Concentration (MIC) value is defined as the minimum

concentration of the extract that inhibits the growth of 90% of the bacterial population after 24 h of incubation at 37°C.

Statistical Analysis

Data were entered into Excel (version 2016) and in our statistical analysis. we utilized the Statistical Package for Social Sciences (SPSS) Version 25 by IBM. Inc. Descriptive statistics were used to summarize numerical variables using mean and standard deviations. Frequencies and percentages were displayed as Categorical variables. Associations between categorical variables were evaluated using the Chi-square test or Fisher's exact test. as appropriate. A p-value of <0.05 is deemed statistically significant.

Results

Ethnopharmacological survey and harvest of medicinal plants

The survey made it possible to list and collect 11 plant species used in the traditional treatment of fevers. diarrhea. wounds and various infectious or non-infectious diseases in Gabon (Table 1).

Extraction yield

Variability in extraction yields among plants was observed (Table 2). The highest yield was observed with ethanolic extracts of *Harungana madasgascariensis* with 13.06% and the lowest yield with ethanolic extracts of *Nymphaea lotus* with 0.4%.

Antibacterial activity

Hospital isolates were more represented and came mainly from urine samples (Table 3). The ESBL CTX-M phenotype was predominant and associated with both a quinolone resistance mechanism with phenotypes II to III.

Table 2: Yield of plant extracts.

Scientific names	Composition	Yield (%)
Bryophyllum pinnatum	Leaf	4.55
Celtic tessmanii Render	Bark	6.40
Coula edulis Bail	Bark	1.47
Desmodium salicifolium	Leaf	7.39
Guibourtia Tessmanii	Bark	11.93
Solanum torvum	Leaf	11.84
Harungana madasgascariensis	Bark	13.06
Mitragyna ciliata	Bark	4.08
Nymphaea lotus	Leaf	0.4
Canary Islands schweinfurthii	Bark	5.25
Anonidium manii	Bark	1.73

Antibacterial activities of plant extracts

The antibacterial activity concerned 11 ethanolic plant extracts including: *Bryophyllum pinnatum. Celtis tessmanii Render. Coula edulis Baill. Desmodium salicifolium. Guibourtia Tessmanii. Solanum torvum. Harungana madasgascariensis* And *Nymphae lotus.* On 11 plants listed to search for antibacterial activity on ESBL strains of type CTX-M. only 5 showed a considerable ESBL-CTX-M antibacterial activity. i.e. a frequency of 45.45% of antibacterial activity obtained. The other extracts showed no activity on ESBL CTX-M enterobacteria.

The sensitivity tests carried out with the extracts show that the susceptibility of the bacterial strains varies from one strain to

Table 1: Characteristics of selected plants.

Scientific name	Family	Voucher number	Vernacular name (Fang language)	Harvested part	Method of preparation	Mode of administration	Traditional use
*Bryophyllum pinnatu*m	Crassulaceae	Towns 679	Event	Leaf	Filtration	Instillation Juice of the leaves Infusion	Rhinitis. cough. fevers
Celtic tessmanii Returns	Ulmaceae	Reitsma 2569	Nsaaka	Bark	Decoction	Infusion. drink	Diarrhea. dysentery. malaria
Coula edulis Bail	Olacaceae	Bouroubou 622	Eweme	Bark	Decoction	Drink. Enema. Sitz Bath	Dysentery. respiratory tract infections.
Desmodium salicifolium	Fabaceae	Boupoya-Mapikou 521	Obogbe ze	Leaf	Decoction. maceration	Drink. friction	Cough. lung infection. fever. malaria. aphrodisiac.
Guibourtia Tessmanii	Fabaceae	Bidault 1450	Oveng	Bark	Maceration	Drink. purge	Malaria. anti-inflammatory. dysentery. fever
Canary Islands schweinfurthii	Burseraceae	Street 259	Abel	Bark	Decoction	Local application	Skin cancer. cough.
Anonidium manii	Annonaceae	Bourobou 324	Ebom	Bark	Maceration	Purge	Colorectal cancer
Mitragyna ciliata	Rubiaceae		Otsige-nzam	Bark	Decoction	Beverage	Dysentery. fever. malaria. gonorrhoea.
*Solanum torvu*m	Solanaceae	Wilde 9902	Nkoatoa'a	Leaf	Decoction-maceration	Poultice-Drink Local application	Wounds. fever. cough. bronchitis. dental caries
Harungana madasgascariensis	Clusiaceae	Bourobou 580	Atuiing	Bark	Decoction	Beverage	Liver cancer. Hepatitis. Wounds
Nymphaea lotus	Nymphaeaceae	Mouandza 108	abôbôre	Leaf	Infusion. decoction	Local application Drink. Purge	Fever. Anti-inflammatory. diabetes. Rheumatism aphrodisiac. anti-diarrheal

Table 3: Phenotypic characteristics of the resistances of the strains tested.

ID	*Bacterium*	*Origin*	Sample type	Resistance to beta-lactams	Resistance to quinolone
910	*Escherichia coli*	*Community*	Urine	ESBL	Phenotype III
1241	*Klebsiella pneumoniae*	Hospitable	Urine	ESBL	Phenotype III
817	*Enterobacter cloacae*	Hospitable	Blood	ESBL	Phenotype II
1200	*Klebsiella pneumoniae*	Hospitable	Urine	ESBL	Phenotype III
BAB	*Escherichia coli*	Community	Urine	ESBL	Phenotype II
864	*K. pneumoniae*	Hospitable	Vaginal secretion	ESBL	Phenotype IV

Table 4: Antibacterial activity of plants.

Plant	Bacteria	Diameter (mm) ± SD	Interpretation
Canary Islands schweinfurthii	*K. pneumoniae (1200)*	23.5 ± 0.707	ES
	Escherichia coli (910)	6 ± 0.00	R
	K. pneumoniae (1241)	24.5 ± 0.707	ES
	K. pneumoniae (864)	6 ± 0.00	R
	Escherichia coli (BAB)	6 ± 0.00	R
	Enterobacter cloacae (817)	6 ± 0.00	R
Mitragyna ciliata	*K. pneumoniae (1200)*	24.5 ± 0.707	ES
	Escherichia coli (910)	6 ± 0.00	R
	K. pneumoniae (1241)	17.5 ± 0.707	TS
	K. pneumoniae (864)	6 ± 0.00	R
	Escherichia coli (BAB)	6 ± 0.00	R
	Enterobacter cloacae (817)	10.5 ± 0.707	S
Harungana madasgascariensis	*K. pneumoniae (1200)*	18.5 ± 0.707	TS
	Escherichia coli (910)	11.5 ± 0.707	S
	K. pneumoniae (1241)	15.5 ± 0.707	TS
	K. pneumoniae (864)	6 ± 0.00	R
	Escherichia coli (BAB)	6 ± 0.00	R
	Enterobacter cloacae (817)	14.5 ± 0.707	S
Solanum torvum	*K. pneumoniae (1200)*	6 ± 0.00	R
	Escherichia coli (910)	6 ± 0.00	R
	K. pneumoniae (1241)	10.5 ± 0.707	S
	K. pneumoniae (864)	6 ± 0.00	R
	Escherichia coli (BAB)	6 ± 0.00	R
	Enterobacter cloacae (817)	11.5 ± 0.707	S
Anonidium manii var. mannii	*K. pneumoniae (1200)*	6 ± 0.00	*R*
	Escherichia coli (910)	*10.5* ± 0.707	*S*
	K. pneumoniae (1241)	6 ± 0.00	*R*
	K. pneumoniae (864)	6 ± 0.00	*R*
	Escherichia coli (BAB)	6 ± 0.00	*R*
	Enterobacter cloacae (817)	6 ± 0.00	*R*

D= inhibition diameter
R = resistant strain (D < 8 mm);
S = susceptible strain (9 mm ≤ D ≤ 14 mm);
TS = highly susceptible strain (15 mm ≤ D ≤ 19 mm);
ES = extremely susceptible strain (D > 20 mm).

another and depending on the plant extract studied. The results of the antibacterial activities of the plant extracts on the blaCTX -M strains are reported in Table 4.

The plant *Canary Islands schweinfurthii* (Aielé) has excellent antibacterial activity only on *Klebsiella spp* strains and showed no activity on other bacterial strains. *Canarium* extract *schweinfurthii* exhibited cumulative activity on ESBL beta-lactamase cumulatively with resistance mechanisms to quinolones of type II and III phenotype.

The plant *Mitragyna ciliata* gave antibacterial activities on strains of *Klebsiella spp* and *Enterobacter cloacae* (817) and showed no activity on other bacterial strains. *Mitragyna* extract *ciliata* has simultaneous antibacterial activity on the enzymes Beta-lactamase ESBL associated with activity on the quinolone resistance phenotype type II and III.

The plant *Harungana madasgascariensis* has shown antibacterial

activities against strains of *Klebsiella spp*. *E. coli (910)*. *Enterobacter cloacae* (817) and showed no activity on other bacterial strains. *Harungana* extract *madasgascariensis* has simultaneous antibacterial activity on the enzymes Beta-lactamase ESBL. TRI. associated with activity on the quinolone resistance phenotype type II and III.

The plant *Solanum torvum* gave antibacterial activities on a strain of *Klebsiella spp* and *Enterobacter cloacae* (817). no activity was observed on other bacterial strains. *Solanum torvum* extract inhibits the activity of ESBL enzymes and is associated with activity on the type III quinolone resistance phenotype.

The plant *Anonidium manii* showed antibacterial activity only on one strain of *Escherichia coli* (910). no activity was observed on other bacterial strains. The extract of *Anonidium manii* inhibits only the activity of ESBL enzymes. the strain tested having shown no other associated resistance mechanism.

Determination of the minimum inhibitory concentration (MIC)

The inhibitory potential of the extracts was confirmed by MIC determination tests. The results in Table 5 show that the MIC value was very high depending on the extracts.

Table 5: Minimum inhibitory concentrations (MIC) of plant extracts.

Plant extracts	MIC
Canary Islands schweinfurthii	254 ± 3.60 mg/ml
Anonidium manii	253.33 ± 3.51 mg/ml
Mitragyna ciliata	126 ± 1 mg/ml
Solanum torvum	126.66 ± 1.52 mg/ml
Harungana madasgascariensis	127.66 ± 2.51 mg/ml

Effect of combinations of plant extracts and standard antibiotic disks on ESBL enterobacteria CTX-M

After numerous tests of combinations between plant extracts and different concentrations of the antibiotic cefotaxime. it emerged that there were potentiating effects with the combinations of extracts and the antibiotic cefotaxime at different concentrations. Some combinations were effective. With these combinations. the concentration of cefotaxime required for strain inhibition was significantly reduced. as was the concentration of the extract. while the extract was only slightly active when used alone. Furthermore. some plant extracts cannot be combined with cefotaxime on certain bacterial strains. hence the antagonistic effects recorded. Overall. the plant extracts exhibited several synergistic and additive effects on blaCTX-M isolates. thus providing a wide range of therapeutic combinations.

Tests of combinations of plants associated with cefotaxime 30

Canarium extract *schweinfurthii* showed synergy with cefotaxime loaded at 30 µg/ml on *K. pneumoniae* strain. The extract offers a single therapeutic combination. *Mitragyna* extract *ciliata* presented three synergies. on 3 species of enterobacteria (*K. pneumoniae. Escherichia coli* and *Enterobacter cloacae)*. With these different effects. the extract of *Mitragyna ciliata* offers 3 possible therapeutic combinations. The extract of *Anonidium manii* presented four synergistics with a concentration of cefotaxime (30 µg/ml) on 4 species of enterobacteria. With these different effects. the extract offers 4 possible therapeutic combinations. *Harungana* extract *madasgascariensis* presented a single synergistic effect for an additive effect with a concentration of cefotaxime (30 µg/ml) on 2 species of enterobacteria. With these different effects. the extract offers 2 therapeutic combinations. *Solanum torvum* extract showed no synergistic effect with cefotaxime concentration of 30 µg/ml. The extract does not offer any therapeutic combination.

Results of tests of herbal combinations associated with cefotaxime 200

Ethanolic extract of *Canarium schweinfurthii* showed a single synergistic and two additive effects with a higher concentration of cefotaxime of 200 mg/ml on 3 bacterial strains. The extract offers three therapeutic combinations. *Mitragyna* extract *ciliata* showed three synergies and two additive effects with a higher concentration of cefotaxime (200mg/ml) on 5 species of enterobacteria. With these different effects. the extract of *Mitragyna ciliata* offers 5 possible therapeutic combinations. *Anonidium* extract *manii* showed two synergistic effects and one additive effect with a higher concentration of cefotaxime (200 mg/ml) on 3 species of enterobacteria. With these different effects. the extract offers only 3 therapeutic combinations. *Harungana* Excerpt *madasgascariensis* presented four synergistic effects with a higher concentration of cefotaxime (200 mg/ml) on 4 species of enterobacteria. With these different effects. the extract offers only 4 therapeutic combinations. *Solanum torvum* extract showed no synergistic effect even with higher concentration of cefotaxime (200 mg/ml). The extract does not offer any therapeutic combination (Table 7).

Discussion

Many plant extracts are used as alternative medicines and their antimicrobial properties have been recognized for several years [19]. The various pharmacological properties of the plants used in our study suggest that they potentially inhibit pathogenic bacteria. However. their antimicrobial effect on antibiotic-resistant bacteria. such as the ESBL Enterobacteriaceae strains CTX-M. has not been specifically studied before.

The aim of this work was to evaluate *in vitro* the antibacterial activity of ethanolic extracts of some medicinal plants from Gabon on ESBL CTX-M enterobacteriaceae strains.

However. it seemed appropriate to us to look for therapeutic combinations that could boost the antibacterial activity of the plant or the antibiotic cefotaxime.

The variability observed in extraction yields would probably be related to the chemical composition of the leaves and barks used. Indeed. the extraction capacity of a solvent depends on the one hand on the affinity of this solvent with respect to phytomolecules and on the other hand on the polarity of this solvent [20]. Extraction by maceration in ethanol can explain the low yields [21]. Other factors. such as pH. temperature. the ratio of the amount of

Table 6: Tests of plant combinations associated with cefotaxime 30.

Plant	Bacterium	Diameter (mm) ± SD CTX30	Diameter (mm) ± SD plant	Diameter (mm) ± SD plant+CTX30	Interpretation
	K. pneumoniae (1200)	22.5 ± 0.707	23.5 ± 0.707	24.5 ± 0.707	I
	Escherichia coli (910)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
Canarium schweinfurthii	*K. pneumoniae* (1241)	21 ± 0.00	24.5 ± 0.707	32 ± 0.00	S
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Enterobacter cloacae (817)	21 ± 0.00	6 ± 0.00	21 ± 0.00	I
	K. pneumoniae (1200)	22.5 ± 0.707	24.5 ± 0.707	27.5 ± 0.707	S
	Escherichia coli (910)	6 ± 0.00	6 ± 0.00 mm	8.5 ± 0.707	S
Mitragyna ciliata	*K. pneumoniae* (1241)	21.5 ± 0.707	17.5 ± 0.707	22.5 ± 0.707	I
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Enterobacter cloacae (817)	21.5 ± 0.707	10.5 ± 0.707	24.5 ± 0.707	S
	K. pneumoniae (1200)	22 ± 0.00	6 ± 0.00	25 ± 0.00	S
	Escherichia coli (910)	6 ± 0.00	*10.5* ± 0.707	15.5 ± 0.707	S
Anonidium manii	*K. pneumoniae* (1241)	21 ± 0.00	*6* ± 0.00	27 ± 0.00	S
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Enterobacter cloacae (817)	21 ± 0.00	6 ± 0.00	27 ± 0.00	S
	K. pneumoniae (1200)	22.5 ± 0.707	18.5 ± 0.707	22.5 ± 0.707	I
	Escherichia coli (910)	6 ± 0.00	11.5 ± 0.707	11 ± 0.00	I
Harungana madasgascariensis	*K. pneumoniae* (1241)	21 ± 0.00	15.5 ± 0.707	24 ± 0.00	S
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	17.5 ± 0.707	Ad
	Enterobacter cloacae (817)	21.5 ± 0.707	14.5 ± 0.707	22.5 ± 0.707	I
	K. pneumoniae (1200)	22 ± 0.00	6 ± 0.00	6 ± 0.00	A
	Escherichia coli (910)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
Solanum torvum	*K. pneumoniae* (1241)	21.5 ± 0.707	10.5 ± 0.707	19.5 ± 0.707	A
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	6 ± 0.00	I
	Enterobacter cloacae (817)	21 ± 0.00	11.5 ± 0.707	21 ± 0.00	I

I= Indifference: the activity of cefotaxime or the extract is not affected by the other: (A + B) = effect A or effect B;
Ad= Addition: the effect of the cefotaxime and extract combination is equal to the sum of the effects of each studied separately: (A + B) = effect A + effect B; **S= Synergy**: the effect is significantly greater than the sum of cefotaxime and the extract studied separately: (A + B) > effect A + effect B; **A= Antagonism**: the combination decreases activity. It is less than the sum of the effects of cefotaxime and the extract taken separately: (A + B) < effect A or effect B.

Table 7: Tests of plant combinations associated with cefotaxime 200.

Plant	Bacterium	Diameter (mm) ± SD CTX200	Diameter (mm) ± SD plant	Diameter (mm) ± SD plant+CTX200	Interpretation
	K. pneumoniae (1200)	27 ± 0.00	23.5 ± 0.707	32 ± 0.00	S
	Escherichia coli (910)	20 ± 0.00	6 ± 0.00	18 ± 0.00	A
Canarium schweinfurthii	*K. pneumoniae* (1241)	32.5 ± 0.707	24.5 ± 0.707	27.5 ± 0.707	A
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	20 ± 0.00	Ad
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	18 ± 0.00	Ad
	Enterobacter cloacae (817)	31 ± 0.00	6 ± 0.00	27 ± 0.00	A
	K. pneumoniae (1200)	27 ± 0.00	24.5 ± 0.707	24 ± 0.00	S
	Escherichia coli (910)	20 ± 0.00	6 ± 0.00	20 ± 0.00	I
Mitragyna ciliata	*K. pneumoniae* (1241)	32.5 ± 0.707	17.5 ± 0.707	34.5 ± 0.707	S
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	18 ± 0.00	Ad
	Escherichia coli (BAB)	6 ± 0.00	6 ± 0.00	17.5 ± 0.707	Ad
	Enterobacter cloacae (817)	30.5 ± 0.707	10.5 ± 0.707	32.5 ± 0.707	S

Anonidium manii	*K. pneumoniae* (1200)	27.5 ± 0.707	*6* ± 0.00	34.5 ± 0.707	S
	Escherichia coli (910)	20 ± 0.00	*10.5* ± 0.707	20 ± 0.00	I
	K. pneumoniae (1241)	32 ± 0.00	6 ± 0.00	30 ± 0.00	A
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	16 ± 0.00	Ad
	Escherichia coli (BAB)	18 ± 0.00	6 ± 0.00	18 ± 0.00	I
Harungana madasgascariensis	*Enterobacter cloacae* (817*)*	31.5 ± 0.707	*6* ± 0.00	33.5 ± 0.707	S
	K. pneumoniae (1200)	27.5 ± 0.707	18.5 ± 0.707	34.5 ± 0.707	S
	Escherichia coli (910)	20.5 ± 0.707	11.5 ± 0.707	23.5 ± 0.707	S
	K. pneumoniae (1241)	32.5 ± 0.707	15.5 ± 0.707	33.5 ± 0.707	S
	K. pneumoniae (864)	6 ± 0.00	6 ± 0.00	17 ± 0.00	S
	Escherichia coli (BAB)	18 ± 0.00	6 ± 0.00	18 ± 0.00	I
Solanum torvum	*Enterobacter cloacae* (817)	31 ± 0.00	14.5 ± 0.707	31 ± 0.00	I
	K. pneumoniae (1200)	39 ± 0.00	6 ± 0.00	39 ± 0.00	I
	Escherichia coli (910)	20 ± 0.00	6 ± 0.00	16.5 ± 0.707	A
	K. pneumoniae (1241)	32 ± 0.00	10.5 ± 0.707	32 ± 0.00	I
	K. pneumoniae (864)	18 ± 0.00	6 ± 0.00	18 ± 0.00	I
	Escherichia coli (BAB)	18 ± 0.00	6 ± 0.00	18 ± 0.00	I
	Enterobacter cloacae (817)	21 ± 0.00	11.5 ± 0.707	21 ± 0.00	I

material to the volume of the solvent. time intervals. the number and steps of individual extractions. the size of the sample particles. the chemical nature of the phytochemical compounds as well as the presence of interfering substances also affect the extraction yield [22].

Phenotypic characteristics of the resistances of the tested strains

Hospital isolates were more represented and mainly came from urine samples. The ESBL phenotype blaCTX -M was predominant and associated with a quinolone resistance mechanism. Judge et al.. have shown that many isolates producing ESBL CTX-M are often resistant to fluoroquinolones and aminoglycosides [23]. IncFII plasmids carrying the blaCTX -M genes also carry the aac (6')- Ib-cr gene. which codes for an enzyme that modifies aminoglycosides and fluoroquinolones. This could therefore explain why the same active ingredient of the plant can have simultaneous antibacterial activity on our isolates carrying both ESBL CTX-M and quinolone resistance mechanisms.

Indeed. to show the *in vitro antibacterial activity of Dacryodes* essential oil *edulis* and *Dacryodes buettneri* and their synergies with antibiotics commonly prescribed to treat bacterial gastroenteritis in children. Italen Bingangoye et al used bacterial isolates from hospital origins with phenotypes of resistance to beta-lactams of penicillinase and ESBL type [24]. In Thailand. Armassa et al in also used clinical strains multi-resistant to antibiotics to show the antibacterial activity of ethanolic extracts of the leaves and stems of *Tanao Si Kan Dang RD1* against antibiotic-resistant bacteria [25]. Ngangoue et al in to research the antibacterial activity of plants also worked on clinical isolates of multi-resistant bacteria [26].

Indeed. microbial resistance is a current topic and is a major public health problem. The use of clinical strains resistant to antibiotics commonly used in medicine makes it possible to seek a real alternative to the management of bacterial infections in hospitals.

Antibacterial activities of plant extracts

The ethanolic extract of *Canary Islands schweinfurthii has excellent antibacterial activity only on Klebsiella spp* strains with an inhibition diameter of 24.5±0.707 mm and showed no activity on other bacterial strains. Aiele extract showed cumulative activity on blaCTX -M and quinolones with type II and III resistance phenotype. In Gabon. Youssra Aghoutane in 2020 showed however antibacterial properties of Aielé essential oil for *Escherichia coli* with an inhibition zone ranging from 6 to 12 mm. On the other hand. our study shows in addition that Aelé also has antibacterial effects on *Klebsiella spp* isolates blaCTX-M [27].

Canarium extract *schweinfurthii* showed only one synergistic and two additive effects with a higher concentration of cefotaxime of 200 mg/ml on 3 bacterial strains (one isolate of *Eschericia coli*. and two isolates of *Klebsiella pneumoniae*). The extract offers three therapeutic combinations. The activity against E. *coli* could be justified by the presence of the chemical compounds highlighted such as triterpenoids. lactic acid and lantanic acid which showed a strong antibacterial activity against *E. coli* at a MIC of 0.08 µg/ ml [28,29]. The observed antimicrobial activity could be correlated with the chemical composition of the plants studied [30] and could justify their degree of activity.

The ethanolic extract of *Mitragyna ciliata* exhibits simultaneous antibacterial activities to blaCTX -M. TRI and quinolones (type II and III resistance phenotype) on isolates of *Klebsiella spp* (inhibition diameter 17.5±0.707 mm) and *Enterobacter cloacae* (10.5±0.707mm) and showed no activity on other bacterial strains. This antibacterial activity of *Mitragyna ciliata* is rarely corroborated in the literature. However. studies report other antimicrobial activities. Indeed. the plant has an antiplasmodial activity on *Plasmodium falciparum*. an effect that can be attributed to the alkaloids and more particularly to mitrinermine [31]. Despite the antiplasmodial activity noted in the literature. few studies

have reported to date specific antibacterial activities of *Mitragyna ciliata.* The present work confirms what is reported in the literature that this plant is also recognized for its antibacterial effects [32]. *Mitragyna* extract *ciliata* showed three synergies and two additive effects with a higher concentration of cefotaxime (200 mg/ml) on 5 species of enterobacteria. With these different effects. the extract of *Mitragyna ciliata* offers 5 possible therapeutic combinations.

The ethanolic extract of *Harungana madasgascariensis* gave simultaneous antibacterial activities to blaCTX -M. TRI and quinolones (type II and III resistance phenotype) on *Klebsiella spp* strains (inhibition diameter 18.5±0.707 mm). *E. coli (*11.5±0.707 mm *)* . *Enterobacter cloacae* (14.5±0.707 mm) and showed no activity on other bacterial strains. Indeed. our study corroborates with the literature review which reports that *Harungana madasgascariensis* exhibits a wide range of pharmacological activities; extracts possess antimicrobial. antiprotozoal. antisickle-cell. anti-inflammatory and antioxidant activities [33]. Furthermore. the aqueous extract of the leaves has been shown to possess antimicrobial activity against different bacterial strains including *Escherichia coli* and *Salmonella typhi* . thus justifying its use for gastrointestinal disorders [34].

Ethanolic extract of *Solanum torvum* simultaneously inhibits the activity of blaCTX -M. TRI enzymes and quinolones (type III resistance phenotype) on an isolate of *Klebsiella spp (10.5±0.707 mm)* and *Enterobacter cloacae* (11.5±0.707 mm). no activity was observed on other bacterial strains. Our study is in agreement with some authors who present antibacterial activities of this plant without however emphasizing its action on quinolone-resistant bacteria. Indeed. methanolic extracts of roots have presented encouraging antibacterial and antifungal effects. Some studies have shown that water-acetone and water-ethanol extracts of *S. torvum* have a high antimicrobial activity against *Bacillus cereus* LMG 13569 BHI. *Shigella dysenteriae* 5451 CIP. *Shigella dysenteriae* and *Neisseria gonorrhoeae* [35]. The antimicrobial activity of this plant could be explained by its great physicochemical diversity consisting of alkaloids. flavonoids. tannins. saponins. glycosides and with the discovery of nine (09) new chemical compounds. namely the derivatives of neochlorogenin. solagenin. isoquercetin. rutin. kaempferol and quercetin [26,36].

The ethanolic extract of *Anonidium manii* exhibited blaCTX -M antibacterial activity only on one strain (Escherichia *coli)* with a inhibition diameter of 10.5±0.707 mm not being associated with any other resistance mechanism. Our work is in agreement with the study of Ngangoue et al. Indeed. it shows that the crude extracts of the barks of *A.mannii* showed antibacterial activity on twelve (12) clinical isolates of multi-resistant bacteria including nine Gram-negative and three Gram-positive. In addition. the compounds tested were active on at least one isolate of all species (*E. coli. E. aerogenes. K. pneumoniae. P. stuartii. P. aeruginosa and S. aureus*) [26]. The good activity of this plant on multi-resistance isolates could be explained by its phytochemical composition with the presence of at least 23 chemical compounds. These are: Three alkaloids: manniindole. Arborinine and oxoanolobine; Thirteen triterpenes: β- amyrin. β- amyrin acetate. taraxerol. α- amyrin acetate. taraxerol acetate. polycarpol . erythrodiol . lanosta-7.9(11). 24-triene-3 ß.21-diol. ursolic acid. oleanolic acid. diopyric acid B; Six steroids: β-sitosterol. 3-O-β-D- β -sitosterol glucopyranoside. spinasterol. 3-O-β-D- spinasterol glucopyranoside. stigmasterol and 3-O-β-D-stigmasterol glucopyranoside; Two derivatives of benzoic acid: 3.4-dihydroxybenzoic acid. vanillic acid. a benzophenone: 3-C-β-D-glucopyranosyl-2.4'. 4.6-tetrahydroxylbenzophenone and many others [26].

Determination of the Minimum Inhibitory Concentration (MIC)

The MIC values were very high ranging from 126 ± 1 mg/ml to 254 ± 3.60 mg/ml depending on the extracts. This shows an interesting antibacterial activity compared to the concentrations used. This high antibacterial activity can be linked to the presence of certain chemical compounds. Indeed. these compounds such as phenolic derivatives. triterpenes. alkaloids. sterols. anthraquinones. flavonoids but also terpenoids are known for their antibacterial properties with a very broad spectrum [37]. Moreover. these chemical compounds are naturally present in the essences of most of the species of plants studied in our studies. The activity of these plants could be explained by the effects of plants in microbial cells that occur mainly due to their interaction with the cell membrane. increasing cell permeability and promoting interference in ATP and protein synthesis. disruption of cytoplasmic pH and inhibition of quorum sensing [35].

Effect of the association Ethanolic extract / antibiotic cefotaxime » on the enterobacteria blaCTX -M studied

In general. we obtained synergistic interactions with the association of cefotaxime and ethanolic plant extracts. Furthermore. the association of some plant extracts on some bacteria with the antibiotic cefotaxime did not show any synergistic or additive effects but antagonistic effects.

blaCTX -M antibacterial activity appears with the combinations of cefotaxime and the plant extracts studied. This association therefore presents a remarkable antibacterial effect against certain strains of enterobacteria.

In general. the antibacterial power of the different combinations of cefotaxime with the 5 plants varies according to the strains tested. the concentration of cefotaxime and the plant extracts used.

Our results showed that the ethanolic extracts of the plants studied could be used independently and/or in association with cefotaxime. However. we also observed very clear antagonistic effects for certain plants such as *Solanum torvum. Anonidium manii and Canarium schweinfurthii*. Synergistic and sometimes even additive effects were observed for all the extracts used.

These results are considered positive. encouraging and very interesting to consider in the field of therapeutic care.

Moreover. the association of plant extracts with antibiotics can be

used to increase the antibacterial spectrum. prevent the emergence of resistant mutants. minimize toxicity and minimize the side effects of the antibiotic. This association could be an alternative to monotherapy for patients with difficult-to-treat infections. such as those due to multidrug-resistant species [37].

Ethical Approval and Consent to Participate

This study is part of a prospecting work associated with the routine analysis of bacteriological examinations with a view to finding an alternative to the problem of bacterial resistance in hospital environments. Data confidentiality and patient anonymity were respected. Multidrug-resistant bacterial strains were stored in freezers with limited access and good laboratory practices were respected. The study and the protocol were approved by the scientific council of the doctoral school of fundamental and applied sciences (EDSFA) of the University of Science and Technology of Masuku (Gabon): Decision No. 004/2022/MESRSTT/USTM/R/05.

Conclusion

Ultimately. the ethanolic extracts of the 5 plants studied in this study contain chemical compounds likely to confer blaCTX -M antimicrobial properties. These include triterpenes. alkaloids. tannins. phenolic derivatives. sterols. anthraquinones. flavonoids and also terpenoids. The information provided by this study on these ethanolic extracts make them potential antibacterial ESBL of the CTX-M type. However. the phytomolecules should be purified. identified. their antimicrobial power and their cytotoxicity must be evaluated.

The very encouraging results obtained in this work suggest. through the effectiveness demonstrated by the plant extracts. that the fight against bacterial infections with multi-resistant germs. in monotherapy. bi or tritherapy or plant-antibiotic combination would be more than interesting.

These results also demonstrate the potential of plants for the research of innovative antibacterial molecules in their modes of action. The study of the chemical composition of these different plant extracts would therefore be more than necessary in order to identify and specify their different active ingredients to better understand their modes of action. Similarly. the association "plant extract-cefotaxime antibiotics" can be recommended in order to go further in the phytotherapy sector. and to arrive at the design of a medicinal formula that combines antibiotics and plant extracts. in order to effectively combat bacteria with resistance to third-generation cephalosporins.

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