Investigational
Medicinal Chemistry & Pharmacology

Research Article Open Access

Exploring *Mangifera indica* (Anacardiaceae) leaf and bark methanol extracts as potential adjuvant therapy in the management of multidrug-resistant *Staphylococcus aureus*

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Abstract

Background: After several decades of antibiotic use, pathogenic bacteria have reached alarming levels of resistance. *Staphylococcus aureus* is the most common cause of nosocomial infections, and treatment is difficult owing to the advent of multidrug-resistant (MDR) strains. This motivates the search for more potent drugs. Foremost, adjuvant compounds that increase the effectiveness of conventional antibiotics are also being researched extensively. The current study examined the anti-staphylococcal and antibiotic-resistance reversal effects of the methanol extracts of *Mangifera indica* (leaves and bark).

Methods: Botanicals were tested alone, in the presence of reserpine (efflux pump inhibitor), and in association with commonly prescribed antibiotics, using a 96-well broth microdilution method against a panel of seventeen MDR strains and clinical isolates of *S. aureus*, including methicillin-resistant strains (MRSA). The ability of the leaf extract to inhibit H^+-ATPase-mediated proton pumping was determined by controlling the acidification of the bacterial solution, whereas the influence on bacterial kinetic growth was determined by measuring absorbance (OD600 nm) after exposure to various concentrations of the test extract.

Results: *M. indica* leaf and bark extracts exhibited exceptional anti-staphylococcal capabilities, inhibiting 100% of the *S. aureus* strains tested. The minimal inhibitory concentrations (MICs) recorded varied from 256 to 2048 µg/mL; the effects were bactericidal (MBC/MIC ≤ 4) in most cases. The bark extract demonstrated an outstanding potential to improve the efficacy of conventional antibiotics. The activity of chloramphenicol, doxycycline, tetracycline, levofloxacin, and ampicillin was enhanced against 100% of studied MDR *S. aureus* in association with the bark extract at sub-inhibitory concentrations of MIC/2 and MIC/4. The leaf extract of *M. indica* induced a concentration-dependent inhibition of *S. aureus* MRSA4 growth over 20 hours of exposure at 0.5×MIC, MIC, and 2×MIC. The latent phase has been extended up to 6 hours after treatment with the extract. Similarly, *M. indica* leaf extract significantly reduced the acidity of the bacterial solution in a concentration-dependent manner, indicating a possible target of its antibacterial effect.

Conclusion: The present study revealed the remarkable activity of *M. indica* leaf and bark extracts against MDR strains and clinical isolates of *S. aureus*, including MRSA. The bark extract might be used as an adjuvant to antibiotic therapy, as indicated by its notable potentiation activity when combined with conventional antibiotics.

Keywords: Antibacterial activity; *Mangifera indica*; multidrug resistance; potentiation; *Staphylococcus aureus*.

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Citation on this article: Ekamgue B, Mbaveng AT, Seukep AJ, Matieta VY, Kuete JRN, Megaptche JF, Guefack MGF, Paul Nayim P, Kuete V. Exploring Mangifera indica (Anacardiaceae) leaf and bark methanol extracts as potential adjuvant therapy in the management of multidrug-resistant Staphylococcus aureus. Investigational Medicinal Chemistry and Pharmacology (2023) 6(2):84; Doi: https://dx.doi.org/10.31183/imcp.2023.00084

Background

The current antibiotic resistance crisis is a serious threat to public health [1, 2]. Resistance reduces the effectiveness of traditional treatments, preventing their clinical usage and leaving a major void in the therapeutic arsenal [3]. ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) refer to common pathogens exhibiting high resistance rates and providing the biggest obstacles in clinical practice [4]. *S. aureus* is the most common cause of hospital-acquired infections in this group. Exploration of new antibiotic sources, particularly for S. aureus management, is required. Furthermore, discovering resistance-breaking chemicals, which would allow the re-use of existing antibiotics that have lost their potency, would be a reasonably appealing option. Given the wide range of bioactive secondary metabolites generated by medicinal plants, they are the focus of several studies aimed at developing novel and efficient antibacterial agents against resistant microorganisms. Many botanicals and phytochemicals from the flora of Africa have been shown to have antibacterial properties [5-26], with a focus on edible plants as a possible adjuvant to conventional antibiotics [27-31]. *Mangifera indica* (Anacardiaceae), commonly known as mango, is one of many edible plants which possesses many pharmacological effects. Several uses are attributed to the plant in traditional medicine. The different parts of the plant (leaves, bark, roots) are exploited in the treatment of syphilis, parasitic diseases, worms, inflammation, cough, hiccups, hyperdipsia, burning sensation, hemorrhage, hemoptysis, hemorrhoids, diarrhea, dysentery, wounds, ulcers, anorexia, and dyspepsia [32]. The main compounds identified in the plant include carotenoids (provitamin A, beta-carotene, lutein, and alpha-carotene), polyphenols such as quercetin, kaempferol, gallic acid, caffeic acid, catechins, tannins, and mangiferin [33, 34]. Many studies have also correlated the presence of these bioactive constituents to biological activities, as well as their uses in traditional medicine. Mangiferin was revealed as an excellent antimalarial [35]. Methanolic, ethanolic, aqueous, and benzene extracts have shown significant antimicrobial effects [36, 37]. The antibacterial effects on MDR bacteria over-expressing efflux pumps have also been revealed [38]. Other biological effects include anti-amoebic and anticancer [39]. Although *M. indica* has been shown to have antibacterial action in prior studies, few have specifically targeted MDR *S. aureus*. As a result, the current study investigated *M. indica* leaf and bark extracts' anti-staphylococcal potential as well as their capacity to re-sensitize routinely used antibiotics against MDR strains and clinical isolates of *S. aureus*, including MRSA.

Methods

Plant material

The leaves and stem barks of *Mangifera indica* (Anacardiaceae) were harvested in September 2020, in Dschang (West Region, Cameroon, 5.4459° N, 10.0472° E). The identification of the plant material was done at the National Herbarium of Cameroon (HNC) and a reference number was provided (18646/HNC).

Plant extraction procedure

Methanol was employed as the extraction solvent. Air-dried plant powder (200 g) of each sample was macerated for 48 hours in methanol 95°C (1:3 w/v) with constant stirring. The filtration of the mixture followed, using Whatman paper grade 1. This procedure was repeated with the filtering residue, and crude extracts were produced following the concentration of all filtrates with a rotary evaporator (BÜCHI R-200) set at 40°C. For future tests, the crude extracts were dried to eliminate residual solvent and kept in dark sterile vials at 4°C.

Chemicals

para-Iodonitrotetrazolium chloride ≥ 97% (INT) was used as the bacterial growth indicator. Dimethyl sulfoxide (DMSO) served to solubilize plant extracts. The plant alkaloid Reserpine (RES) was used as the efflux pump inhibitor (EPI). The antibiotics selected are commonly prescribed comprising Ceftriaxone (CRO), Tetracycline (TET), Chloramphenicol (CHL), Ciprofloxacin (CIP), Doxycycline (DOX), Imipenem (IPM), Ampicillin (AMP), Penicillin (PCN), Augmentin (AUG), and Levofloxacin (LVX). All chemicals were purchased from Sigma-Aldrich (St. Quentin Fallavier, France).

Staphylococcus aureus strain and isolates

Seventeen bacteria were used, all expressing multi-drug resistance phenotypes, among which the reference strain from American Type Culture Collection (ATCC 25923), seven methicillin-resistant *S. aureus* isolates (MRSA3, MRSA4, MRSA6, MRSA8, MRSA9, MRSA11, and MRSA12) and nine clinical laboratory collection (ST20, ST39, ST50, ST52, ST76, ST132, ST135, ST218, and ST674). Their features were previously described [40-42]. Culture media used included Chapman (Mannitol Salt Agar) for the identification of strains/isolates of *S. aureus*, Mueller Hinton agar (MHA) for the activation of *S. aureus* strain and isolates, and Mueller Hinton broth (MHB) for microdilution assays which involved the determination of the minimal inhibitory concentration (MIC) and minimal bactericidal concentrations (MBC) of test herbals, as well as the combination between test extracts and antibiotics. All media were purchased from Titan Biotech Ltd (Rajasthan, India) and their preparation followed the instructions of the manufacturer.

Anti-staphylococcal activities

The bacterial inoculum was prepared as previously described [43-46] in comparison to the turbidity of a standard McFarland 0.5 ($1.5x10^8$ CFU/mL). The various plant extracts and the reference drug (CIP) were dissolved in DMSO-MHB. Leaf and stem bark extracts of *M. indica* were prepared at 8192 µg/mL, and antibiotics at 1024 µg/mL. Reserpine was prepared at the concentration of 100 µg/mL. Botanicals were tested alone, then in the presence of reserpine (EPI). The combination of plant extracts with reserpine was intended to evaluate the function of efflux pumps in bacterial resistance to the test extracts [47-49]. The minimal inhibitory (MIC) and bactericidal (MBC) concentrations of test extracts alone were determined using a 96-well broth microdilution method, with INT serving as a bacterial growth indicator [50]. The full description of the experimental procedure was as reported in our previous investigations [49, 51, 52]. The reference drug used was CIP for positive control, whereas DMSO 2.5%+MHB and MHB alone were used as negative controls. MIC was considered the smallest concentration of plant extract which produced complete inhibition of bacterial growth (the least concentration for which no color change is observed) after 18 to 24 hours of incubation at 37°C, whereas

MBC was considered the lowest concentration of a sample that did not induce a color change with the addition of INT [50]. Each experiment was repeated three times in triplicate.

Combination assay of M. indica extracts with conventional antibiotics

The effects of the association of test herbals with antibiotics were assessed against the most resistant microorganisms. Extracts were used at the sub-inhibitory concentrations of MIC/2, MIC/4, MIC/8, and MIC/16 for a preliminary assay on ATCC25923, which then allowed the selection of appropriate sub-inhibitory concentrations for further combination testing on extended MDR *S. aureus* isolates. As a result, MIC/2 and MIC/4 values of extracts were then utilized on a larger number of bacteria in association with antibiotics [53-55]. Antibioc-resistance modulating factor (AMF) was calculated as the ratio of the MIC of the antibiotic alone versus MIC in combination with the plant extract. The potentiation effect was considered for AMF ≥ 2 [56].

Modes of action of M. indica extracts

The effects of leaf methanol extract of *M. indica* were assessed on the kinetic growth and H^+-ATPase-mediated proton pumping of *S. aureus* MRSA4, at 0.5×MIC, MIC, and 2×MIC. The same concentrations were used for the positive control CIP. The action on kinetic growth consisted of measuring the absorbance (600 nm) of the bacterial solution treated with extracts at various concentrations over 20 hours, whereas the action on H^+-ATPase-mediated proton pumping was done by controlling the acidification of the bacterial growth medium over 60 min. Elaborated procedures were previously described [57, 58].

Results

Anti-staphylococcal activity

The results following MIC and MBC determination of *M. indica* leaf and bark methanol extracts are presented in Table 1. Both extracts exhibited inhibitory activities against all studied microorganisms with MIC values ranging from 256 to 2048 µg/mL. Except for the MIC value of 2048 µg/mL recorded with both extracts on *S. aureus* ST132, MICs ≤ 1024 µg/mL were registered against all tested MDR strains and isolates of *S. aureus*. The lowest MIC (best activity) of 256 µg/mL was obtained with the leaf extract on MRSA4 and MRSA11, as well as the bark extract on MRSA8. The MBC/MIC ratio was ≤ 4 in twelve and fifteen strains and isolates, respectively with leaf and bark extracts. The MIC was equal to MBC with the leaf extract on MRSA3, ST76, ST135, and ST218. Likewise, similar values were obtained with the bark extract on six strains including MRSA3, ATCC25923, ST52, ST96, ST132, ST135, and ST128.

Influence of reserpine on the anti-staphylococcal activity of test herbals

The bark methanol extract of *M. indica* was tested in the presence of reserpine, an efflux pump inhibitor, against selected strains over-expressing MDR phenotypes. The results are shown in Table 2. Significant reduction (improved activity) of the MIC of the test extract was recorded once associated with reserpine. Up to a 32-fold reduction of the initial MIC of bark extract was obtained against the reference strain ATCC25923.

Combination assay

An evaluation of the effects of conventional antibiotics in association with the bark extract was performed against strains and isolates over-expressing MDR. A preliminary test on ATCC25923 was done at sub-inhibitory concentrations of the extracts (MIC/2, MIC/4, MIC/8, and MIC/16). Best synergistic effects were recorded at MIC/2 and MIC/4 (data not shown), which were then used for further testing on seven MDR strains (Table 3). The bark methanol extract demonstrated an outstanding potential to improve the efficacy of conventional antibiotics, with AMF ranging from 2 to 128-fold. The activity of CHL, DOX, TET, LVX, and AMP was enhanced against all studied MDR microorganisms at sub-inhibitory concentrations of MIC/2 and MIC/4 of the extract. However, some cases of AMF = 1 were recorded in association with CIP at MIC/4 on MRSA4, PEN at MIC/2 and MIC/4 on MRSA11, and CRO at the two sub-inhibitory concentrations on MRSA8 and MIC/4 on MRSA11.

Modes of action

The leaf extract of *M. indica* induced a concentration-dependent inhibition of MRSA4 growth over 20 hours of exposure at 0.5×MIC, MIC, and 2×MIC (Figure 1). The latent phase has been extended up to 4 hours after treatment with both the test extract and the positive control (CIP). Likewise, *M. indica* leaf extract also produced a significant and concentration-dependent reduction of the acidification of the bacterial solution at various concentrations tested, as compared with negative control (Figure 2).

Discussion

Plants and their derivatives [59]possess a wide variety of bioactive ingredients with large applications in the management of several diseases such cancer, microbial and parasitic infections, viral infections amongst others [60-75]. Indeed, several established antibacterial compounds have been unveiled from medicinal plants, with the majority showing noteworthy efficacy against MDR strains [76]. *S. aureus* appears as one of the worrisome bacterial species in hospital settings and the community [77], and management remains challenging due to the emergence of MDR strains. The present work investigated the effects of *M. indica* leaf and bark methanol extracts on the sensitivity of *S. aureus* strains and clinical isolates, including MRSA. More so, the effects of the association of extracts with conventional antibiotics were performed, followed by the possible modes of action. The inhibitory effects of test extracts were recorded on all the seventeen strains and isolates used. Based on the established interpretation criteria for the antibacterial activity of food plants [78], the MICs obtained (ranging from 256 to 2048 µg/mL) indicate significantly to moderately active anti-staphylococcal activity. However, the updated cutoff-points for the classification of antibacterial agents from plants in various species of bacteria have been previously established [79-82]. In Gram-positive bacteria, these thresholds values for botanicals were defined as follows: Outstanding activity: minimal inhibitory concentration (MIC) ≤ 8 µg/mL; Excellent activity: 8 < MIC ≤40 µg/mL; Very good activity: 40 < MIC ≤128 µg/mL; Good activity: 128 < MIC ≤ 320 µg/mL; Average activity: 320 < MIC ≤ 625 µg/mL; Weak activity: 625 < MIC ≤ 1024 µg/mL; Not active: MIC values > 1024 µg/mL [82]. Consequently, the obtained anti-staphylococcal activities of botanicals from Mangifera indica were ranged from good activity to not active effects. Because of the MDR

characteristics of the microorganisms examined, these findings are noteworthy. Interestingly, the MBC/MIC ratio was ≤ 4 in the majority of MDR strains and isolates, among which MBC = MIC was recorded with the test extracts on several MDR strains (Table 1). These results suggest bactericidal effects [83] of leaf and bark extracts of *M. indica*. Previous studies reported on the antimicrobial and particularly the anti-staphylococcal potential of *M. indica* and derived phytochemicals. For instance, the compounds isolated from the bark part of the plant including 1,2-benzenedicarboxylic acid mono(2-ethylhexyl) ester, 9,12-tetradecadien-1-ol-acetate, and 3-chloro-N-(2-phenylethyl) propanamide exhibited remarkable antimicrobial activity [84]. Similarly, the mango leaf extract was reported as an effective, non-mutagenic anti-staphylococcal agent containing phytochemicals such as tannins, saponins, flavonoids, phenols, and coumarins [85]. The findings highlight the need for more research into the development of phytopharmaceuticals based on *M. indica* extracts for the treatment of *S. aureus* infections. Furthermore, the activity of mango extracts reported in this study supports the plant's usage in traditional medicine to treat a variety of diseases, including S. aureus-related infections. Because of the decreased effectiveness of traditional antibiotics, many researchers are looking for novel compounds as well as molecules capable of increasing or restoring the efficacy of existing antibiotics against resistant bacteria. Microorganisms have evolved several strategies to diminish the efficiency of antibiotics, one of which is the overexpression of active pumps, which expels all harmful substances (including antibiotics) from the cytoplasm, preventing them from reaching their intracellular destinations [86]. The medication combination can then aid to avoid the formation of resistant mutations and restore antibiotic activity against resistant organisms. The activity of test extracts was significantly improved in the presence of reserpine, an efflux pump inhibitor. The anti-staphylococcal activity of mango extracts ranged from 2 to 64 µg/mL in the presence of reserpine against 256 to 2048 µg/mL in the absence of the inhibitor. This suggests the role of efflux pumps expressed by studied bacteria. Indeed, it's known that reserpine reverses NorA-mediated resistance in *S. aureus* [87]. The combination assay revealed noteworthy potentiation activity between the selected conventional antibiotics and *M. indica* bark extract with AMF ranging from 2 to 128-fold (Table 3). These suggest the presence of antibiotic-resistance reversal agents in the test extract and therefore could be recommended as potential adjuvant therapy in the management of MDR *S. aureus* infections. Moreover, the percentage of potentiation was obtained on more than 70% in all cases, suggesting the possible presence of efflux pump inhibitors in the extracts [88]. These effects would be caused by the simultaneous action of the extract's active ingredient(s) and the antibiotic at distinct locations. Previous reports highlighted the remarkable ability of food plants to improve the activity of commonly used antibiotics [89-96]. The current study, therefore, contributes to the field with additional data on antibiotic-resistance modifying properties of edible plants. Phytochemicals act via several mechanisms targeting major structural components and functions in bacteria. The present study revealed the concentration-dependent inhibition of *S. aureus* growth at 0.5×MIC, MIC, and 2×MIC (Figure 1). The latent phase has been extended to up to 6 h following exposure to the extract, possibly due to the inhibition of key bacterial enzymes used to degrade nutrients necessary for their growth. The kinetic curve also validated the bacteriostatic action (MBC/MIC = 8) of the leaf extract against S. aureus MRSA4, since it showed no complete killing of the bacterium. The leaf extract also showed a concentration-dependent significant reduction of the acidification of the bacterial solution at 0.5×MIC, MIC, and 2×MIC in H^+-ATPase-mediated proton pumps. This implies that the proton pump has been inhibited, preventing the bacteria from producing energy for development [57].

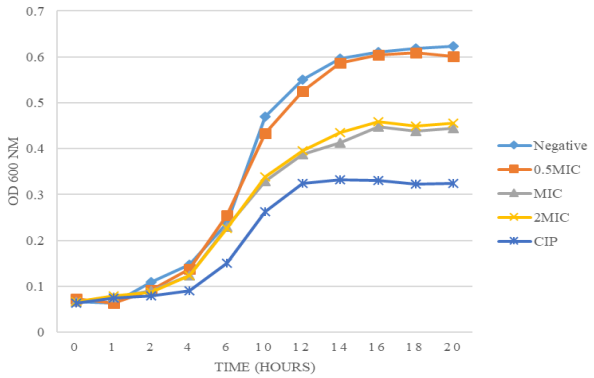

Figure 1. Effects of *Mangifera indica* leaf methanol extract on the kinetic growth of *S. aureus* MRSA4.

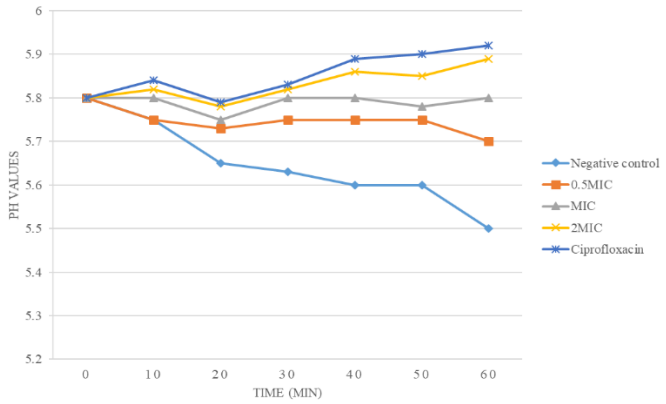

Figure 2. Ability of *Mangifera indica* leaf methanol extract to inhibit the H^+-ATPase-mediated proton pumps of *S. aureus* MRSA4.

Table 1. Anti-staphylococcal activity (MIC and MBC in µg/mL) of *Mangifera indica* leaf and bark methanol extracts.

Bacterial strains/isolates	*Mangifera indica*						Ciprofloxacin		
	Leaves			Barks					
	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R
MRSA3	1024	1024	1	1024	1024	1	32	64	2
MRSA4	256	2048	8	1024	2048	2	1	32	32
MRSA6	512	2048	4	512	1024	2	32	64	2
MRSA 8	1024	2048	2	256	1024	4	32	64	2
MRSA 11	256	2048	8	512	1024	2	32	32	1
MRSA 12	1024	2048	2	1024	2048	2	16	32	2
ATCC25923	512	2048	4	1024	1024	1	16	32	2
ST20	512	2048	4	512	1024	2	16	32	2
ST30	1024	2048	2	1024	2048	2	16	32	2
ST39	1024	>2048	nd	1024	>2048	nd	32	64	2
ST52	512	1024	2	1024	1024	1	32	64	2
ST76	1024	1024	1	1024	2048	2	32	64	2
ST96	1024	>2048	nd	1024	1024	1	1	32	32
ST132	2048	>2048	nd	2048	2048	1	16	32	2
ST135	512	512	1	512	512	1	16	32	2
ST218	1024	1024	1	1024	1024	1	16	32	2
ST674	512	2048	4	512	>2048	nd	8	32	4

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

Table 2. The influence of the addition of reserpine in the anti-staphylococcal activity of *M. indica* barks

MIC: minimal inhibitory concentration (in µg/mL); RES: Reserpine; +RES: MIC in the presence of reserpine (in µg/mL); R: MIC/ +RES ratio.

Bacterial strains/isolates	*M. indica* barks			Ciprofloxacin		
	+RES	MIC	R	+RES	MIC	R
MRSA 3	64	1024	**16**	0.25	32	**128**
MRSA8	256	1024	**4**	0.5	32	**64**
MRSA 11	64	256	**4**	<0.25	32	**>128**
ST 218	256	1024	**4**	<0.25	32	**>128**
ATCC 25923	16	512	**32**	<0.25	32	**>128**

Table 3. Effects of the association of *M. indica* back extract at MIC/2 and MIC/4 with standard antibiotics against selected multidrug resistant *S. aureus* strains

Bacterial strains	MIC (µg/mL)	*M. indica* methanol bark extract, MIC (µg/mL), and AMF (in brackets)	
	0	MIC/2	MIC/4
Chloramphenicol			
MRSA 4	64	4(**16**)	4(**16**)
MRSA 8	64	4(**16**)	4(**16**)
MRSA 11	64	8**(8)**	4(**16**)
ST 20	128	8(**16**)	4(**32**)
ST 39	128	8(**16**)	4(**32**)
ST 135	64	8**(8)**	8**(8)**
ST 218	32	8(**4**)	8(**4**)
Doxycycline			
MRSA 4	8	1(**8**)	4(**2**)
MRSA 8	16	4(**4**)	4(**4**)
MRSA 11	32	1(**32**)	16(**2**)
ST 20	32	0.25(**128**)	0.25(**128**)
ST 39	16	0.25(**4**)	0.5(**32**)
ST 135	8	0.25(**32**)	0.25(**32**)
ST 218	8	0.5(**16**)	2(**4**)
Tetracycline			
MRSA 4	16	0.25(6**4**)	0.25(6**4**)
MRSA 8	8	2(**4**)	2(**4**)
MRSA 11	4	0.5(**8**)	2(**2**)
ST 20	8	0.25(**32**)	0.5 (**16**)
ST 39	8	0.5 (**16**)	0.25(**32**)
ST 135	8	0.25(**32**)	0.25(**32**)
ST 218	4	0.25(**16**)	0.25(**16**)
Levofloxacin			
MRSA 4	16	2(**8**)	2(**8**)
MRSA 8	32	8(**4**)	8(**4**)
MRSA 11	32	1(**32**)	1(**32**)
ST 20	16	8(**2**)	8(**2**)
ST 39	32	2(**16**)	2(**16**)
ST 135	16	2(**8**)	4(**4**)
ST 218	16	0.5(**32**)	0.5(**32**)

MIC: minimal inhibitory concentration (in µg/mL); AMF: Antibiotic-resistance modulating factor.

Table 3. *continued and end.*

Bacterial strains	MIC (µg/mL)	*M. indica* methanol bark extract. MIC (µg/mL). and AMF (in brackets)	
	0	**MIC/2**	**MIC/4**
Ciprofloxacin			
MRSA 4	8	1(**8**)	8(1)
MRSA 8	32	2(**16**)	4(**8**)
MRSA 11	8	2(**4**)	4(**8**)
ST 20	4	0.25(**16**)	0.25(**16**)
ST 39	4	0.25(**16**)	0.25(**16**)
ST 135	16	0.25(**64**)	0.25(**64**)
ST 218	8	0.25(**32**)	0.25(**32**)
Ampicillin			
MRSA 4	64	8(**8**)	16(**4**)
MRSA 8	128	16(**8**)	32(**4**)
MRSA 11	256	8(**32**)	32(**8**)
ST 20	128	8(**16**)	4(**32**)
ST 39	128	8(**16**)	4(**32**)
ST 135	128	2(**64**)	2(**64**)
ST 218	32	2(**16**)	2(**16**)
Penicillin			
MRSA 4	64	16(**4**)	16(**4**)
MRSA 8	256	4(**64**)	4(**64**)
MRSA 11	256	256(1)	256(1)
ST 20	128	8(**32**)	16(**8**)
ST 39	32	8(**4**)	16(**2**)
ST 135	8	4(**2**)	4(**2**)
ST 218	32	4(**8**)	4(**8**)
Ceftriaxone			
MRSA 4	32	4(**8**)	4(**8**)
MRSA 8	128	128(1)	128(1)
MRSA 11	4	2(**2**)	4(1)
ST 20	16	8(**2**)	4(**4**)
ST 39	16	4(**4**)	8(**2**)
ST 135	16	4(**4**)	4(**4**)
ST 218	32	4(**8**)	4(**8**)

MIC: minimal inhibitory concentration (in µg/mL); AMF: Antibiotic-resistance modulating factor.

Conclusion

The present study revealed the remarkable activity of *M. indica* leaf and bark extracts against MDR strains and clinical isolates of *S. aureus*, including MRSA. In general, the effects were bactericidal in most cases and could, therefore, inform the development of potent phytopharmaceuticals to fight *S. aureus* infections. Interestingly, *M. indica* could also be exploited as an adjuvant to antibiotic therapy as evidenced by its noteworthy potentiation property obtained once in association with standard antibiotics. Further exploration of the exact mechanisms of the combined agents should be considered for future investigations.

Abbreviations

AMF, antibiotic-resistance modulating factor; DMSO, dimethylsulfoxide, HNC, Cameroon national herbarium; INT, para-Iodonitrotetrazolium chloride; MDR, multidrug-resistant; MBC, minimal bactericidal concentrations; MHA, Mueller Hinton Agar; MHB, Mueller Hinton Broth; MIC, minimum inhibitory concentrations.

Authors' Contribution

EB, MYV, KJRN, MJF, and PN carried out the study; AJS analyzed data and wrote the manuscript; ATM and VK supervised the study; All authors read and approved the final version of the manuscript.

Acknowledgments

The authors are grateful to the Cameroon National Herbarium for identifying the plant material.

Conflict of interest

The authors declare no conflict of interest.

Article history:

Received: 12 May 2023
Received in revised form: 17 July 2023
Accepted: 24 July 2023
Available online: 24 July 2023

References

1. Aljeldah MM. 2022. Antimicrobial Resistance and Its Spread Is a Global Threat. *Antibiotics (Basel).* 11(8):1082.
2. Fongang H, Mbaveng AT, Kuete V. 2023. Chapter One - Global burden of bacterial infections and drug resistance. *Advances in Botanical Research 106*: 1-20. https://doi.org/10.1016/bs.abr.2022.08.001.
3. Seukep AJ, Mbuntcha HG, Kuete V, Chu Y, Fan E, Guo M-Q. 2022. What Approaches to Thwart Bacterial Efflux Pumps-Mediated Resistance? *Antibiotics.* 11(10):1287.
4. Santajit S, Indrawattana N. 2016. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *BioMed Res Iint.* 2016:2475067.

5. Kuete V, Ngameni B, Mbaveng AT, Ngadjui B, Meyer JJ, Lall N. 2010. Evaluation of flavonoids from *Dorstenia barteri* for their antimycobacterial, antigonorrheal and anti-reverse transcriptase activities. *Acta Trop.* 116(1):100-104.
6. Kuete V, Tangmouo JG, Marion Meyer JJ, Lall N. 2009. Diospyrone, crassiflorone and plumbagin: three antimycobacterial and antigonorrhoeal naphthoquinones from two *Diospyros* spp. *Int J Antimicrob Ag.* 34(4):322-325.
7. Nguemeving JR, Azebaze AG, Kuete V, Eric Carly NN, Beng VP, Meyer M, Blond A, Bodo B, Nkengfack AE. 2006. Laurentixanthones A and B, antimicrobial xanthones from *Vismia laurentii*. *Phytochemistry.* 67(13):1341-1346.
8. Mbaveng AT, Sandjo LP, Tankeo SB, Ndifor AR, Pantaleon A, Nagdjui BT, Kuete V. 2015. Antibacterial activity of nineteen selected natural products against multi-drug resistant Gram-negative phenotypes. *Springerplus.* 4:823.
9. Kuete V, Betrandteponno R, Mbaveng AT, Tapondjou LA, Meyer JJ, Barboni L, Lall N. 2012. Antibacterial activities of the extracts, fractions and compounds from *Dioscorea bulbifera*. *BMC Complement Altern Med.* 12:228.
10. Nono EC, Mkounga P, Kuete V, Marat K, Hultin PG, Nkengfack AE. 2010. Pycnanthulignenes A-D, antimicrobial cyclolignene derivatives from the roots of *Pycnanthus angolensis*. *J Nat Prod.* 73(2):213-216.
11. Kuete V, Sandjo LP. 2012. Isobavachalcone: an overview. *Chin J Integr Med.* 18(7):543-547.
12. Kuete V, Wansi JD, Mbaveng AT, Kana Sop MM, Tadjong AT, Beng VP, Etoa FX, Wandji J, Meyer JJM, Lall N. 2008. Antimicrobial activity of the methanolic extract and compounds from *Teclea afzelii* (Rutaceae). *S Afr J Bot.* 74(4):572-576.
13. Kuete V, Wiench B, Hegazy ME, Mohamed TA, Fankam AG, Shahat AA, Efferth T. 2012. Antibacterial activity and cytotoxicity of selected Egyptian medicinal plants. *Planta Med.* 78(2):193-199.
14. Komguem J, Meli AL, Manfouo RN, Lontsi D, Ngounou FN, Kuete V, Kamdem HW, Tane P, Ngadjui BT, Sondengam BL *et al*. 2005. Xanthones from Garcinia smeathmannii (Oliver) and their antimicrobial activity. *Phytochemistry.* 66(14):1713-1717.
15. Ngameni B, Kuete V, Simo IK, Mbaveng AT, Awoussong PK, Patnam R, Roy R, Ngadjui BT. 2009. Antibacterial and antifungal activities of the crude extract and compounds from *Dorstenia turbinata* (Moraceae). *S Afr J Bot.* 75(2):256-261.
16. Kuete V, Tangmouo JG, Penlap Beng V, Ngounou FN, Lontsi D. 2006. Antimicrobial activity of the methanolic extract from the stem bark of Tridesmostemon omphalocarpoides (Sapotaceae). *J Ethnopharmacol.* 104(1-2):5-11.
17. Tchinda CF, Voukeng KI, Beng VP, Kuete V. 2016. Antibacterial activities of the methanol extracts of *Albizia adianthifolia, Alchornea laxiflora, Laportea ovalifolia* and three other Cameroonian plants against multi-drug resistant Gram-negative bacteria *Saudi J Biol Sci.* 24:950-955.
18. Omosa LK, Midiwo JO, Mbaveng AT, Tankeo SB, Seukep JA, Voukeng IK, Dzotam JK, Isemeki J, Derese S, Omolle RA, Efferth T, Kuete V. 2016. Antibacterial activity and structure-activity relationships of a panel of 48 compounds from kenyan plants against multidrug resistant phenotypes. *SpringerPlus.* 5:901.
19. Dzotam JK, Touani FK, Kuete V. 2016. Antibacterial activities of the methanol extracts of *Canarium schweinfurthii* and four other Cameroonian dietary plants against multi-drug resistant Gram-negative bacteria. *Saudi J Biol Sci.* 23:565-570.
20. Kuete V. 2013. Medicinal Plant Research in Africa In: *Pharmacology and Chemistry.* Edited by Kuete V, 1 edn. Oxford: Elsevier.
21. Ngounou FN, Manfouo RN, Tapondjou LA, Lontsi D, Kuete V, Penlap V, Etoa FX, Dubois MAL, Sondengam BL. 2005. Antimicrobial diterpenoid alkaloids from *Erythrophleum suaveolens* (guill. & perr.) brenan. *Bull Chem Soc Ethiop.* 19(2):221-226.
22. Kuete V, Tabopda TK, Ngameni B, Nana F, Tshikalange TE, Ngadjui BT. 2010. Antimycobacterial, antibacterial and antifungal activities of *Terminalia superba* (Combretaceae). *S Afr J Bot.* 76(1):125-131.
23. Tankeo SB, Damen F, Sandjo LP, Celik I, Tane P, Kuete V. 2016. Antibacterial activities of the methanol extracts, fractions and compounds from *Harungana madagascariensis* Lam. ex Poir. (Hypericaceae). *J Ethnopharmacol.* 190:100-105.
24. Kuete V. 2023. Chapter Twelve - Ethnopharmacology, phytochemistry and pharmacology of potent antibacterial medicinal plants from Africa. *Advances in Botanical Research* 107:353-660. https://doi.org/10.1016/bs.abr.2022.08.022.
25. Kuete V. 2010. Potential of Cameroonian plants and derived products against microbial infections: a review. *Planta Med.* 76(14):1479-1491.
26. Kuete V, Efferth T. 2010. Cameroonian medicinal plants: pharmacology and derived natural products. *Front Pharmacol.* 1:123.
27. Voukeng IK, Beng VP, Kuete V. 2016. Antibacterial activity of six medicinal Cameroonian plants against Gram-positive and Gram-negative multidrug resistant phenotypes. *BMC Complement Altern Med.* 16(1):388.
28. Dzotam JK, Simo IK, Bitchagno G, Celik I, Sandjo LP, Tane P, Kuete V. 2018. *In vitro* antibacterial and antibiotic modifying activity of crude extract, fractions and 3',4',7-trihydroxyflavone from *Myristica fragrans* Houtt against MDR Gram-negative enteric bacteria. *BMC Complement Altern Med.* 18(1):15.
29. Dzoyem JP, Tchuenguem RT, Kuiate JR, Teke GN, Kechia FA, Kuete V. 2014. *In vitro* and *in vivo* antifungal activities of selected Cameroonian dietary spices. *BMC Complement Altern Med.* 14:58.
30. Nguenang GS, Mbaveng AT, Fankam AG, Manekeng HT, Nayim P, Wamba BEN, Kuete V. 2018. *Tristemma hirtum* and five other Cameroonian edible plants with weak or no antibacterial effects modulate the activities of antibiotics against gram-negative multidrug-resistant phenotypes. *ScientificWorldJournal.* 2018:7651482.
31. Moungoue Ngwaneu LS, Mbaveng AT, Nayim P, Wamba BEN, Youmbi LM, Bonsou IN, Ashu F, Kuete V. 2022. Antibacterial and antibiotic potentiation activity of *Coffea arabica* and six other Cameroonian edible plants against multidrug-resistant phenotypes. *Invest Med Chem Pharmacol.* 5(2):68.
32. Parvez G. 2016. Pharmacological activities of Mango (*Mangifera indica*): A Review. *J Pharmacogn Phytochem.* 5(3):1-7.
33. Andreu GL, Delgado R, Velho JA, Curti C, Vercesi AE. 2005. Mangiferin, a natural occurring glucosyl xanthone, increases susceptibility of rat liver mitochondria to calcium-induced permeability transition. *Arch Biochem Biophys.* 439(2):184-193.
34. Mahattanatawee K, Manthey JA, Luzio G, Talcott ST, Goodner K, Baldwin EA. 2006. Total antioxidant activity and fiber content of select Florida-grown tropical fruits. *J Agric Food Chem.* 54(19):7355-7363.
35. Bidla G, Titanji P, Joko B, Ghazali GE, Bolad A, Berzins K. 2004. Antiplasmodial activity of seven plants used in African folk medicine. *Indian J Pharmacol.* 36(4):245–246.
36. Vega-Vega V, Silva-Espinoza BA, Cruz-Valenzuela MR, Bernal-Mercado AT, González-Aguilar GA, Ruiz-Cruz S, Leyva E, Siddiqui WA, Ayala-Zavala JF. 2013. Antimicrobial and antioxidant properties of byproduct extracts of mango fruit. *DOAJ (DOAJ: Directory of Open Access Journals).* https://doi.org/10.5073/jabfq.2013.5086.5028.
37. Sahrawat A, Pal S, Shahi S. 2013. Antibacterial activity of *Mangifera indica* (mango) leaves against drug resistant bacterial strains. *Int J Adv Res.* 1(6):82–86.
38. Dzotam JK, Kuete V. 2017. Antibacterial and antibiotic-modifying activity of methanol extracts from six cameroonian food plants against multidrug-resistant enteric bacteria. *BioMed Res Int.* 2017:1583510.
39. Mirza B, Croley CR, Ahmad M, Pumarol J, Das N, Sethi G, Bishayee A. 2021. Mango (*Mangifera indica* L.): a magnificent plant with cancer preventive and anticancer therapeutic potential. *Crit Rev Food Sci Nutr.* 61(13):2125-2151.
40. Wamba BEN, Mbaveng AT, Nayim P, Dzotam JK, Ngalani OJT, Kuete V. 2018. Antistaphylococcal and antibiotic resistance modulatory activities of thirteen cameroonian edible plants against resistant phenotypes. *Int J Microbiol.* 2018:1920198.
41. Ekamgue B, Mbaveng AT, Kuete V. 2023. Anti-staphylococcal and antibiotic-potentiating activities of botanicals from nine Cameroonian food plants towards multidrug-resistant phenotypes. *Invest Med Chem Pharmacol.* 6(1):75.
42. Tiotsop RS, Kuete V, Mbaveng AT. 2023. Botanicals from ten selected Cameroonian edible plants displayed Anti-pseudomonas effects and potentiated the activities of antibiotics against multidrug-resistant phenotypes over-expressing MexAB-OprM efflux pumps. *Invest Med Chem Pharmacol.* 6(1):74.
43. Seukep JA, Sandjo LP, Ngadjui BT, Kuete V. 2016. Antibacterial and antibiotic-resistance modifying activity of the extracts and compounds from *Nauclea pobeguinii* against Gram-negative multi-drug resistant phenotypes. *BMC Complement Altern Med.* 16:193.
44. Seukep JA, Ngadjui B, Kuete V. 2015. Antibacterial activities of *Fagara macrophylla, Canarium schweinfurthii, Myrianthus arboreus, Dischistocalyx grandifolius* and *Tragia benthamii* against multi-drug resistant Gram-negative bacteria. *Springerplus.* 4:567.
45. Tiotsop RS, Mbaveng AT, Seukep AJ, Matieta VY, Nayim P, Wamba BEN, Guefack MF, Kuete V. 2023. *Psidium guajava* (Myrtaceae) re-sensitizes multidrug-resistant Pseudomonas aeruginosa over-expressing MexAB-OprM efflux pumps to commonly prescribed antibiotics. *Invest Med Chem Pharm.* 6(2):80.
46. Matieta VY, Seukep AJ, Kuete JRN, Megaptche JF, Guefack MGF, Nayim P, Mbaveng AT, Kuete V. 2023. Unveiling the antibacterial potential and antibiotic-resistance breaker activity of *Syzygium jambos* (Myrtaceae) towards critical-class priority pathogen Klebsiella isolates. *Invest Med Chem Pharm.* 6(2):82.
47. Kuete V, Alibert-Franco S, Eyong KO, Ngameni B, Folefoc GN, Nguemeving JR, Tangmouo JG, Fotso GW, Komguem J, Ouahouo BMW *et al*. 2011. Antibacterial activity of some natural products against bacteria expressing a multidrug-resistant phenotype. *Int J Antimicrob Agents.* 37(2):156-161.
48. Kuete V, Ngameni B, Tangmouo JG, Bolla JM, Alibert-Franco S, Ngadjui BT, Pages JM. 2010. Efflux pumps are involved in the defense of Gram-negative bacteria against the natural products isobavachalcone and diospyrone. *Antimicrob Agents Chemother.* 54(5):1749-1752.
49. Manekeng HT, Mbaveng AT, Nguenang GS, Seukep JA, Wamba BEN, Nayim P, Yinkfu NR, Fankam AG, Kuete V. 2018. Anti-staphylococcal and antibiotic-potentiating activities of seven Cameroonian edible plants against resistant phenotypes. *Investig Med Chem Pharmacol.* 1:7.
50. Eloff JN. 1998. A sensitive and quick microplate method to determine the minimal inhibitory concentration of plant extracts for bacteria. *Planta Med.* 64(8):711-713.
51. Fouotsa H, Mbaveng AT, Mbazoa CD, Nkengfack AE, Farzana S, Iqbal CM, Marion Meyer JJ, Lall N, Kuete V. 2013. Antibacterial constituents of three Cameroonian medicinal plants: *Garcinia nobilis*, *Oricia suaveolens* and *Balsamocitrus camerunensis*. *BMC Complement Altern Med.* 13(1):81.
52. Demgne OMF, Damen F, Fankam AG, Guefack MF, Wamba BEN, Nayim P, Mbaveng AT, Bitchagno GTM, Tapondjou LA, Penlap VB *et al*: 2021. Botanicals and phytochemicals from the bark of *Hypericum roeperianum* (Hypericaceae) had strong antibacterial activity and showed synergistic effects with antibiotics against multidrug-resistant bacteria expressing active efflux pumps. *J Ethnopharmacol.* 277:114257.
53. Tankeo SB, Lacmata ST, Noumedem JA, Dzoyem JP, Kuiate JR, Kuete V. 2014. Antibacterial and antibiotic-potentiation activities of some Cameroonian food plants against multi-drug resistant Gram-negative bacteria. *Chin J Integr Med.* 20(7):546-554.
54. Fankam AG, Kuiate JR, Kuete V. 2015. 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 Complement Altern Med.* 15:206.
55. Fankam AG, Kuiate JR, Kuete V. 2017. Antibacterial and antibiotic resistance modulatory activities of leaves and bark extracts of Recinodindron heudelotii (Euphorbiaceae) against multidrug-resistant Gram-negative bacteria. *BMC Complement Altern Med.* 17(1):168.

56. Kovač J, Gavarić N, Bucar F, Smole Možina S. 2014. Antimicrobial and resistance modulatory activity of Alpinia katsumadai seed phenolic extract, essential oil and post-distillation extract. *Food Technol Biotechnol.* 52(2):248-254.
57. Seukep AJ, Fan M, Sarker SD, Kuete V, Guo MQ. 2020. *Plukenetia huayllabambana* fruits: analysis of bioactive compounds, antibacterial activity and relative action mechanisms. *Plants (Basel).* 9(9): 1111.
58. Demgne OMF, Mbougnia JFT, Seukep AJ, Mbaveng AT, Tene M, Nayim P, Wamba BEN, Guefack MGF, Beng VP, Tane P *et al*. 2021. Antibacterial phytocomplexes and compounds from *Psychotria sycophylla* (Rubiaceae) against drug-resistant bacteria. *Adv Trad Med. doi:* 10.1007/s13596-13021-00608-13590.
59. Mbaveng AT, Fotso GW, Ngnintedo D, Kuete V, Ngadjui BT, Keumedjio F, Andrae-Marobela K, Efferth T. 2018. Cytotoxicity of epunctanone and four other phytochemicals isolated from the medicinal plants *Garcinia epunctata* and *Ptycholobium contortum* towards multi-factorial drug resistant cancer cells. *Phytomedicine* 48:112-119.
60. Kuete V, Fankam AG, Wiench B, Efferth T. 2013. Cytotoxicity and modes of action of the methanol extracts of six Cameroonian medicinal plants against multidrug-mesistant tumor cells. *Evid Based Complement Alternat Med.* 2013:285903.
61. Kuete V, Sandjo LP, Djeussi DE, Zeino M, Kwamou GM, Ngadjui B, Efferth T. 2014. Cytotoxic flavonoids and isoflavonoids from *Erythrina sigmoidea* towards multi-factorial drug resistant cancer cells. *Invest New Drugs.* 32:1053–1062.
62. Dzoyem JP, Nkuete AH, Kuete V, Tala MF, Wabo HK, Guru SK, Rajput VS, Sharma A, Tane P, Khan IA *et al.* 2012. Cytotoxicity and antimicrobial activity of the methanol extract and compounds from *Polygonum limbatum*. *Planta Med.* 78(8):787-792.
63. Kuete V, Ngameni B, Wiench B, Krusche B, Horwedel C, Ngadjui BT, Efferth T. 2011. Cytotoxicity and mode of action of four naturally occuring flavonoids from the genus *Dorstenia*: gancaonin Q, 4-hydroxylonchocarpin, 6-prenylapigenin, and 6,8-diprenyleriodictyol. *Planta Med.* 77(18):1984-1989.
64. Kuete V, Nkuete AHL, Mbaveng AT, Wiench B, Wabo HK, Tane P, Efferth T. 2014. Cytotoxicity and modes of action of 4'-hydroxy-2',6'-dimethoxychalcone and other flavonoids toward drug-sensitive and multidrug-resistant cancer cell lines. *Phytomedicine* 21(12):1651-1657.
65. Kuete V, Wiench B, Alsaid MS, Alyahya MA, Fankam AG, Shahat AA, Efferth T. 2013. Cytotoxicity, mode of action and antibacterial activities of selected Saudi Arabian medicinal plants. *BMC Complement Altern Med.* 13:354.
66. Mbaveng AT, Bitchagno GTM, Kuete V, Tane P, Efferth T. 2019. Cytotoxicity of ungeremine towards multi-factorial drug resistant cancer cells and induction of apoptosis, ferroptosis, necroptosis and autophagy. *Phytomedicine* 60:152832.
67. Mbaveng AT, Zhao Q, Kuete V. 2014. 20 - Harmful and protective effects of phenolic compounds from african medicinal plants. In: *Toxicological Survey of African Medicinal Plants.* edn. Edited by Kuete V: Elsevier. pp. 577-609.
68. Kuete V, Dzotam JK, Voukeng IK, Fankam AG, Efferth T. 2016. Cytotoxicity of methanol extracts of *Annona muricata, Passiflora edulis* and nine other Cameroonian medicinal plants towards multi-factorial drug-resistant cancer cell lines. *Springerplus.* 5(1):1666.
69. Kuete V, Mbaveng AT, Sandjo LP, Zeino M, Efferth T. 2017. Cytotoxicity and mode of action of a naturally occurring naphthoquinone, 2-acetyl-7-methoxynaphtho[2,3-b]furan-4,9-quinone towards multi-factorial drug-resistant cancer cells. *Phytomedicine.* 33:62-68.
70. Kuete V, Sandjo LP, Kwamou GM, Wiench B, Nkengfack AE, Efferth T. 2014. Activity of three cytotoxic isoflavonoids from Erythrina excelsa and *Erythrina senegalensis* (neobavaisoflavone, sigmoidin H and isoneorautenol) toward multi-factorial drug resistant cancer cells. *Phytomedicine* 21(5):682-688.
71. Kuete V. 2014. 21 - Health Effects of Alkaloids from African Medicinal Plants. In: *Toxicological Survey of African Medicinal Plants.* edn. Edited by Kuete V: Elsevier. pp. 611-633.
72. Kuete V, Sandjo LP, Mbaveng AT, Seukep JA, Ngadjui BT, Efferth T. 2015. Cytotoxicity of selected Cameroonian medicinal plants and *Nauclea pobeguinii* towards multi-factorial drug-resistant cancer cells. *BMC Complement Altern Med.* 15:309.
73. Poumale HMP, Hamm R, Zang Y, Shiono Y, Kuete V. 2013. 8 - Coumarins and Related Compounds from the Medicinal Plants of Africa. In: *Medicinal Plant Research in Africa.* edn. Edited by Kuete V. Oxford: Elsevier. pp. 261-300.
74. Omosa LK, Midiwo JO, Kuete V. 2017. Chapter 19 - Curcuma longa. In: *Medicinal Spices and Vegetables from Africa.* edn. Edited by Kuete V: Academic Press. pp. 425-435.
75. Mbaveng AT, Kuete V, Efferth T. 2017. Potential of Central, Eastern and Western Africa medicinal plants for cancer therapy: spotlight on resistant cells and molecular targets. *Front Pharmacol.* 8:343.
76. Seukep AJ, Mbuntcha HG, Zeuko'o EM, Woquan LS, Nembu NE, Bomba FT, Watching D, Kuete V. 2023. Chapter Five - Established antibacterial drugs from plants. *Advances in Botanical Research.* 106:81-149. https://doi.org/10.1016/bs.abr.2022.08.005.
77. Organization. WH. 2017. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. https://apps.who.int/iris/handle/10665/311820.
78. Tamokou JDD, Mbaveng AT, Kuete V. 2017. Chapter 8 - Antimicrobial Activities of African Medicinal Spices and Vegetables. In: *Medicinal Spices and Vegetables from Africa.* edn.: Academic Press. pp. 207-237.
79. Kuete V. 2023. Chapter Six - Potential of African medicinal plants against Enterobacteria: Classification of plants antibacterial agents. *Advances in Botanical Research 106:* 151-335. https://doi.org/10.1016/bs.abr.2022.08.006.
80. Tankeo SB, Kuete V. 2023. Chapter Seven - African plants acting on *Pseudomonas aeruginosa*: Cut-off points for the antipseudomonal agents from plants. *Advances in Botanical Research 106:* 337-412. https://doi.org/10.1016/bs.abr.2022.08.007.
81. Tchinda CF, Kuete V. 2023. Chapter Nine - Potential of African flora to combat tuberculosis and drug resistance of Mycobacteria: Rationale classification of antimycobacterial agents from a natural source. Advances in Botanical *Research 106:* 523-598. https://doi.org/10.1016/bs.abr.2022.08.009.
82. Wamba BEN, Mbaveng AT, Kuete V. 2023. Chapter Eight - Fighting Gram-positive bacteria with African medicinal plants: Cut-off values for the classification of the activity of natural products. Advances in Botanical *Research 106*: 413-522. https://doi.org/10.1016/bs.abr.2022.08.008.
83. Davis J. 2018. Pharmacologic principles. In Equine Internal Medicine (pp. 79–137). *Elsevier.* https://doi.org/10.1016/b1978-1010-1323-44329-44326.00002-44324.
84. Singh R, Singh SK, Maharia RS, Garg AN. 2015. Identification of new phytoconstituents and antimicrobial activity in stem bark of *Mangifera indica* (L.). *J Pharm Biomed Anal.* 105:150-155.
85. Chirayath RB, A AV, Jayakumar R, Biswas R, Vijayachandran LS. 2019. Development of *Mangifera indica* leaf extract incorporated carbopol hydrogel and its antibacterial efficacy against *Staphylococcus aureus*. *Colloids Surf B Biointerfaces.* 178:377-384.
86. Bohnert JA, Kern WV. 2005. Selected arylpiperazines are capable of reversing multidrug resistance in *Escherichia coli* overexpressing RND efflux pumps. *Antimicrob Agents Chemother.* 49(2):849-852.
87. Gibbons S, Oluwatuyi M, Kaatz GW. 2003. A novel inhibitor of multidrug efflux pumps in *Staphylococcus aureus*. *J Antimicrob Chemother.* 51(1):13-17.
88. Lorenzi V, Muselli A, Bernardini AF, Berti L, Pages JM, Amaral L, Bolla JM. 2009. Geraniol restores antibiotic activities against multidrug-resistant isolates from Gram-negative species. *Antimicrob Agents Chemother.* 53(5):2209-2211.
89. Fankam AG, Kuete V, Voukeng IK, Kuiate JR, Pages JM. 2011. Antibacterial activities of selected Cameroonian spices and their synergistic effects with antibiotics against multidrug-resistant phenotypes. *BMC Complement Altern Med.* 11:104.
90. Djeussi DE, Noumedem JA, Seukep JA, Fankam AG, Voukeng IK, Tankeo SB, Nkuete AH, Kuete V. 2013. Antibacterial activities of selected edible plants extracts against multidrug-resistant Gram-negative bacteria. *BMC Complement Altern Med.* 13(1):164.
91. Tekwu EM, Askun T, Kuete V, Nkengfack AE, Nyasse B, Etoa FX, Beng VP. 2012. Antibacterial activity of selected Cameroonian dietary spices ethno-medically used against strains of *Mycobacterium tuberculosis*. *J Ethnopharmacol.* 142(2):374-382.
92. Voukeng IK, Kuete V, Dzoyem JP, Fankam AG, Noumedem JA, Kuiate JR, Pages JM. 2012. Antibacterial and antibiotic-potentiation activities of the methanol extract of some Cameroonian spices against Gram-negative multi-drug resistant phenotypes. *BMC Res Notes.* 5:299.
93. Seukep JA, Fankam AG, Djeussi DE, Voukeng IK, Tankeo SB, Noumdem JA, Kuete AH, Kuete V. 2013. Antibacterial activities of the methanol extracts of seven Cameroonian dietary plants against bacteria expressing MDR phenotypes. *Springerplus.* 2:363.
94. Touani FK, Seukep AJ, Djeussi DE, Fankam AG, Noumedem JA, Kuete V. 2014. Antibiotic-potentiation activities of four Cameroonian dietary plants against multidrug-resistant Gram-negative bacteria expressing efflux pumps. *BMC Complement Altern Med.* 14:258.
95. Nayim P, Mbaveng AT, Sudhir K, Wamba BEN, Sanjukta M, Kuete V. 2023. Phytochemistry and pharmacology of Imperata cylindrica: A comprehensive review. *Invest Med Chem Pharmacol.* 6(1):00076.
96. Matieta VY, Kuete V, Mbaveng AT. 2023. Anti-Klebsiella and antibiotic-potentiation activities of the methanol extracts of seven Cameroonian dietary plants against multidrug-resistant phenotypes over-expressing AcrAB-TolC efflux pumps. *Invest Med Chem Pharmacol.* 6(1):73.