Investigational
Medicinal Chemistry & Pharmacology

Research Article Open Access

Antibacterial activity and antibiotic-potentiating effects of *Termnalia laxiflora* and *Azadirachta indica* against multidrug-resistant *Staphylococcus aureus*

Larissa Mpude[1], Eric Cadet[1], Derick J. Assonfack[1], Ancela W. B. Yendze[1], Jenifer R. N. Kuete[2], Valaire Y. Matieta[1], Junior F. Megaptche[1], Michael F. Kengne[1], Idrios N. Bonsou[1], Armelle T. Mbaveng[1]*, and Victor Kuete[1]**

Abstract

Background: *S. aureus* is a multidrug-resistant (MDR) bacterium that poses a significant public health threat globally. In response, plants have emerged as promising alternatives in combatting infections caused by this pathogen. This study aims to evaluate the efficacy of two medicinal plants against MDR Gram-positive *Staphylococcus aureus.*

Methods: The antibacterial activity of various plant extracts was assessed both individually and in combination with conventional antibiotics using the microdilution assay. Additionally, qualitative phytochemical screening was conducted following established experimental protocols.

Results: The extracts from the evaluated plants demonstrated antibacterial properties, with Minimum Inhibitory Concentrations (MICs) ranging from 32 to 1024 µg/mL. The methanolic extract from the leaves of *Terminalia laxiflora* exhibited strong activity against the *S. aureus* ATCC 25923 strain, achieving a MIC of 32 µg/mL. Likewise, the extract from the fruits of *Azadirachta indica* showed excellent activity against both the S. *aureus* MRSA A9 isolate and the ATCC 25923 strain, also with a MIC of 32 µg/mL. The different extracts, at concentrations of MIC/2 and MIC/4, demonstrated an antibiotic-enhancing effect, with Activity Enhancement Factors (AEF) ranging from 2 to 128. Extracts from the leaves of *T. laxiflora* and the fruits of *A. indica* enhanced the effectiveness of antibiotics against at least 62.5% of the tested isolates. The antibiotics that exhibited improved efficacy included cefixime, ceftriaxone, ciprofloxacin, doxycycline, levofloxacin, penicillin, and tetracycline. Qualitative phytochemical screening revealed the presence of alkaloids, phenols, and flavonoids in the leaves of *T. laxiflora*, while phenols and flavonoids were identified in the fruits of *A. indica*.

Conclusion: Extracts from *T. laxiflora* and *A. indica* contain antibacterial compounds that hold potential for addressing infections caused by MDR *S. aureus*.

Keywords: Antibacterial; *Terminalia laxiflora*; multidrug resistance; *Azadirachta indica.*

*Correspondence: *Tel.: +237 676542386; E-mail: armbatsa@yahoo.fr; ORCID: https://orcid.org/0000-0003-4178-4967 (Armelle T. Mbaveng); ** Tel.: +237 677355927; E-mail: kuetevictor@yahoo.fr; ORCID: http://orcid.org/0000-0002-1070-1236 (Victor Kuete);*

[1]Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon; [2]Department of Chemistry, Faculty of Science, University of Dschang, Dschang, Cameroon

Other authors E-mails:
Email: larissampude5@yahoo.com (Larissa Mpude); Email: ericcadet19@gmail.com (Eric Cadet) ; Email: derickassonfack7@gmail.com (Derick J. Assonfack); Email: whitneyancela13@gmail.com (Ancela W. B. Yendze); Email: jeniferkuete@gmail.com; ORCID: http://orcid.org/0009-0009-1101-6044 (Jenifer R. N. Kuete); Email: yvmatieta@yahoo.com (Valaire Y. Matieta); Email: megapfabrice@gmail.com (Junior F. Megaptche); Email: fmkengne@yahoo.com (Michael F. Kengne); Email: bonichrist89@yahoo.com (Idrios N. Bonsou) ;

Citation on this article: Mpude L, Cadet E, Assonfack DJ, Yendze AWB, Kuete JRN, Matieta VY, Megaptche JF, Kengne MF, Bonsou IN, Mbaveng AT, Kuete V. Antibacterial activity and antibiotic-potentiating effects of Termnalia laxiflora and Azadirachta indica against multidrug-resistant Staphylococcus aureus. Investigational Medicinal Chemistry and Pharmacology (2025) 8(2):111; Doi: https://dx.doi.org/10.31183/imcp.2025.00111

Background

The advent of antibiotics in clinical practice brought a significant transformation in the management of bacterial infections [1]. Nonetheless, their misuse resulted in the emergence of bacterial resistance, which presents a significant global health threat [2]. In 2014, bacterial resistance accounted for approximately 700,000 deaths, while in 2019, this figure rose to 1.27 million worldwide, highlighting the alarming growth of this trend [3,39]. If no measures are implemented by 2050, bacterial resistance could peak, leading to 10 million fatalities annually, thus becoming the second leading cause of death globally after cardiovascular diseases [4]. Bacterial resistance to antibiotics is indeed a multifaceted issue characterized by various biochemical mechanisms, including enzymatic inactivation, alteration of antibiotic targets, decrease in membrane permeability to antibiotics, efflux pumps, and biofilm formation [5]. Bacteria are deemed multidrug resistant (MDR) as they withstand at least three antibiotics from different families. The World Health Organization identified most of these bacteria as high-priority resistant pathogens, including MDR *Staphylococcus aureus* [40]. In 2018, this bacterium was implicated in 100,000 deaths worldwide [8]. This pathogen requires in-depth attention, particularly within vulnerable populations such as children and the elderly. The multi-resistance exhibited by *S. aureus* hampers effective treatment of infections, underscoring its considerable health impact [40]. In response to this worldwide health crisis, various alternatives, including the research and development of new antibacterial substances, need to be considered. Plant extracts have been demonstrated to be the source of phytochemicals, which present promising antibacterial potential. The effectiveness of botanicals against MDR pathogens alone or in association with conventional antibacterial agents has been previously reported [10-11]. Most of these plants are found in the African flora [6,9,12,17,36]. *Terminalia laxiflora* Engl. & Diels (Combretaceae) is a tree traditionally utilized in the form of macerations, ointments, decoctions, liniments, fumigations, and infusions for treating back pains, coughs, malaria, skin ailments, eye diseases, hemostatic hemorrhoids, rheumatism, and inflammations. Extracts from the stem wood and bark of *T. laxiflora* were evaluated against Gram-positive bacteria, particularly those in the *Staphylococcus* genus, using the micro-dilution assay [35]. The present work has also focused on *Azadirachta indica* A. Juss. (Meliaceae), which is a tree growing up to 30 m high and 2.5 m in girth, with an attractive evergreen broadleaf. Often referred to as *neem*, *A. indica* is used in folk medicine for addressing numerous ailments. Their leaves are used in the form of decoctions or poultices in the treatment of malaria, warts, boils, eczema, smallpox, ulcers, and chicken pox. The neem oil is applied for addressing indolent ulcers, ringworm, and scrofula. Due to their antiseptic potential, the twigs of this species are used as a toothbrush in preventing periodontal disease [29]. Its pharmacological attributes, including anti-inflammatory, nematicidal, anti-leishmanial, and antimicrobial effects, have been reported [13]. Its antibacterial activity has been assessed using the disk diffusion method on agar medium and the macro-dilution technique against *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum* [14]. However, the antibacterial activity of the methanol extracts from the leaves of *T. laxiflora* and the fruits of *A. indica*, either alone or in combination with usual antibiotics against MDR *S. aureus* has not been a focus of previous research. This study aims to explore these dimensions.

Methods

Plant material and extraction

The plant material was harvested in the Tandjilé-Est region of Chad, specifically in the town of Laï. The collection included the leaves of *T. laxiflora* and the fruits of *A. indica*, which were assigned the identification numbers 7896/SRF/Cam and 19223/SRF/Cam at the Cameroon National Herbarium (HNC) by botanist Mr. Tchatchouang Ngansop Eric. The collected specimens were dried in a shaded area, then crushed and macerated with constant stirring in a 1:3 (m/v) ratio using methanol for 48 hours. The resulting macerates were filtered through Whatman paper No. 1. The filtered solutions were concentrated using a rotary evaporator at 65°C and dried in an oven at 45°C to remove any residual extraction solvent. The crude extracts from the different samples were collected and stored at 4°C for future use.

Chemicals and culture media

In this study, various chemicals were used, including para-iodonitrotetrazolium chloride (INT) with a purity of ≥ 97%, which acts as an indicator for bacterial growth. The antibiotics employed consisted of *β*-lactams such as ampicillin (AMP), imipenem (IMI), cefixime (CFX), penicillin (PEN), and ceftriaxone (CTX). Additionally, the study included quinolones like ciprofloxacin (CIP) and levofloxacin (LEV), as well as tetracyclines such as tetracycline (TET) and doxycycline (DOX). Mueller Hinton Agar (MHA) and Mueller Hinton Broth (MHB) were used as culture media for the experiments. Mannitol Salt Agar (MSA) was utilized to verify the purity of *S. aureus* isolates. The strain, along with the purified isolates, was subsequently cultured on MHA, while MHB was employed for micro-dilution, extracts, and antibiotic preparation. All chemicals used in this study were purchased from Sigma Aldrich (Saint Quentin Fallavier, France).

Studied bacteria

The study evaluated 15 isolates of S. aureus and a reference strain. Table 1 illustrates their resistance profiles. The characteristics of these isolates, along with the reference strain, were documented in previous studies [26-27].

Determination of minimal inhibitory and bactericidal concentrations

Minimum Inhibitory Concentrations (MICs) and Minimum Bactericidal Concentrations (MBCs) were assessed using the liquid micro-dilution technique, which required 96-well microplates as previously documented [37], with slight modifications [38]. The reference antibiotic, imipenem, and extracts from various plant species were initially prepared at concentrations of 512 and 8192 µg/mL, respectively. These were dissolved in DMSO before to combining with MHB to achieve the required volumes. The bacterial inoculum was prepared according to McFarland's 0.5 standard scale, which corresponds to a bacterial concentration of 1.5×10^{8} CFU/mL. Following an incubation period of 18 to 24 hours at 37°C, MICs and MBCs were assessed by incorporating the para-iodonitrotetrazolium chloride (INT) as a colorimetric indicator. The MIC was defined as the lowest concentration of the extract that successfully inhibits all bacterial growth after 18 to 24 hours of incubation, while the MBC was the minimum concentration eliminating the tested bacterial species after 48 hours of incubation at 37°C [13-14]. The positive control included imipenem and MHB,

whereas the negative control comprised 2.5% DMSO, MHB, and the bacterial inoculum. In contrast, the neutral control consisted solely of MHB.

Evaluation of the antibiotic-potentiating effects of extracts

The potentiating effect of extracts in combination with antibiotics was assessed following the previously outlined procedure. A preliminary assessment was conducted to identify sub-inhibitory concentrations for the extract-antibiotic combinations. Extracts were prepared at concentrations of MIC/2, MIC/4, MIC/8, and MIC/16 and tested against the *S. aureus* DO 74SA isolate (data not shown), which was the most resistant isolate found in the sensitivity testing. For further experiments on the potentiating effects of the various extracts on antibiotics, the MIC/2 and MIC/4 concentrations were chosen. The Activity Enhancement Factor (AEF), which is the ratio of the MIC of the antibiotic alone to the MIC of the antibiotic combined with the plant extract, was employed to evaluate the potentiating effect of the extracts on the antibiotics tested. Extracts were considered to have a potentiating effect when the AEF was greater than or equal to 2 [15].

Botanicals phytochemical screening

The qualitative phytochemical screening was conducted using established methodologies for alkaloids, flavonoids (Shinoda test), phenols, saponins, triterpenes (Liebermann-Burchard test), and anthocyanins [16].

Antibacterial data interpretation

The established classification scale for antibacterial activity of botanicals against Gram-positive bacteria was used in this study. Based on this classification criteria, the antibacterial potential of extracts is considered outstanding when MIC ≤ 8 µg/mL, excellent when 8<MIC ≤ 40 µg/mL, very good when 40<MIC ≤ 128 µg/mL, good when 128<MIC ≤ 320 µg/mL, average when 320 <MIC ≤ 625 µg/mL, weak when 625 <MIC ≤ 1024 µg/mL, and deemed not active when MIC > 1024 µg/mL [18].

Results

Antibacterial activity

The data presented in Table 2 indicated that the methanol extracts from the leaves of *T. laxiflora* and the fruits of *A. indica* exhibit antibacterial activities. Botanical from *T. laxiflora* exhibited an inhibition spectrum of 62.5% against the strain and all the tested bacterial isolates, with MIC values ranging from 32 to 1024 µg/mL. This extract demonstrated excellent activity, with a MIC value of 32 µg/mL against the *S. aureus* ATCC 25923 strain, very good activity, presenting a MIC value of 128 µg/mL against the *S. aureus* MRSA A9 isolate, and good activity against the *S. aureus* MRSA A11, DO 31SA, and DO 58SA isolates, recording a MIC of 256 µg/mL. The same plant extract showed an average activity (MIC value of 512 µg/mL) against the *S. aureus* MRSA A6, DO 21SA isolates, while demonstrating a weak activity (MIC value of 1024 µg/mL) against the *S. aureus* MRSA A4, DO 49SA, and DO 94SA isolates. Regarding the methanol extract from the fruits of *A. indica*, an antibacterial activity with an inhibition spectrum of 68,75% against the strain/isolates was observed. This extract exhibited excellent activity, with a MIC value of 32 µg/mL against the *S. aureus* MRSA A9 isolate and the *S. aureus* ATCC 25923 strain. It also demonstrated very good activity, achieving MIC values of 64, 128, and 128 µg/mL against the *S. aureus* DO 49SA, MRSA A4, and MRSA A11 isolates, respectively. This extract further displayed good (MIC value of 256 µg/mL) activity against the *S. aureus* DO 31SA, DO 58SA, and DO 96SA isolates, and an average activity, with a MIC value of 512 µg/mL against the *S. aureus* MSSA A1 and *S. aureus* MRSA A12 isolates. However, it exhibited a weak activity against the *S. aureus* DO 09SA isolate, recording a MIC value of 1024 µg/mL. Both extracts demonstrated bactericidal effects (BMC/MIC≤ 4), with an inhibition spectrum of 62,5% for *T. laxiflora* and 50% for *A. indica*.

Antibiotic-modulating effects of extract from the leaves of T. laxiflora and from the fruits of A. indica

Table 3 indicates the potentiating effect of the botanical from the leaves of *T. laxiflora* at sub-inhibitory concentrations (MIC/2 and MIC/4). This extract enhanced the activity of antibiotics, with Activity Enhancement Factor (AEF) ranging from 2 to 128. The activity of ciprofloxacin, levofloxacin, and doxycycline was enhanced by 4-fold against the *S. aureus* MSSA A1 isolate. Penicillin and tetracycline demonstrated at least a 32-fold increase in activity against the *S. aureus* MSSAA4 and *S. aureus* MSSAA11 isolates when combined with this extract prepared at MIC/2 and MIC/4. The same extract demonstrated synergistic effects at MIC/2 against 62.5% of all strains when combined with levofloxacin. Furthermore, synergistic effects were observed against 50% of the tested isolates at MIC/2 and MIC/4 for tetracycline and cefixime, whereas a modulation in activity of penicillin and doxycycline was recorded at the same concentrations against 37.5% of the tested isolates. Additionally, the activity of ciprofloxacin, ceftriaxone, and imipenem was enhanced at MIC/2 and MIC/4 against 25% of the same bacterial isolates.

Table 4 highlights the enhancing effects of the extract from the fruits of *A. indica*, which elevated the effectiveness of conventional antibiotics, achieving AEF levels from 2 to 128. The botanical from the fruits of *A. indica* increased the activity of levofloxacin by 8-fold at MIC/2 and MIC/4 against the *S. aureus* MSSAA4 isolate and by 4-fold against the *S. aureus* DO57SA isolate. Penicillin, ceftriaxone, tetracycline, cefixime, and doxycycline, when tested alongside this extract, showed up to 4 times greater antibacterial efficacy against the *S. aureus* DO96SA, *S. aureus* MSSA A1, *S. aureus* MSSAA11, *S. aureus* DO96SA, *S. aureus* MSSA A1, and DO57SA isolates. This extract improved the activity of antibiotics against 25 to 62.5% at MIC/2 and 12.5 to 50% at MIC/4 against the various bacterial isolates. The extract also enhanced the activity of levofloxacin and doxycycline against 62.5% of bacterial isolates at MIC/2 and against 50% at MIC/4. Furthermore, the extract improved the effectiveness of tetracycline, ceftriaxone, and cefixime against 50% and 37.5% of various isolates at MIC/2 and MIC/4, respectively. Additionally, the activity of ciprofloxacin was amplified when combined with the extract at MIC/2 and MIC/4 against 37.5% of the tested isolates. Similarly, imipenem experienced the same enhancement in association with the extract at MIC/2 and against 25% of the *S. aureus* isolates at MIC/4. Moreover, the extract amplified the activity of penicillin against 25% of bacterial isolates at MIC/2 and at MIC/4 against 12.5%.

Phytochemical screening

The methanol extract from the leaves of *T. laxiflora* revealed the presence of alkaloids, phenols, and flavonoids, while botanicals

from the fruits of *A. indica* showed phenols and flavonoids as recorded in Table 1.

Discussion

Even though effective antibacterial substances have been discovered, bacterial infections continue to feature amongst the first leading cause of mortality globally [7,34]. The growing issue of bacterial resistance to antibiotics is fast becoming one of the significant challenges of this century. There is an urgent need to develop effective strategies to combat this concerning trend. Numerous studies have reported plants from the African flora to exhibit promising antibacterial effects, both alone and in combination with conventional antibiotics, against MDR strains [19,20,36]. To this end, the present study assessed the antibacterial activity and explored the potentiating effect of extracts from the leaves of *T. laxiflora* and from the fruits of *A. indica* on usual antibiotics against MDR *S. aureus.* In accordance with the classification scale for antibacterial activities of plant extracts against MDR Gram-positive bacteria, including *S. aureus,* an extract is classified as having excellent activity when 8 < MIC ≤ 40 µg/mL, very good activity when 40 < MIC≤128 µg/mL, and good activity when 128 < MIC ≤ 320 µg/mL [18]. The findings indicate that the methanol extract from the leaves of *T. laxiflora* was active against 62.5% of the tested *S. aureus* isolates and strain, with MIC values ranging from 32 to 1024 µg/mL. This extract showed an excellent activity against the *S. aureus* ATCC 2592 strain, achieving a MIC value of 32 µg/mL, a very good activity towards the *S. aureus* MRSA A9 isolate presenting a MIC value of 128 µg/mL, and a good activity against the *S. aureus* MRSA A11, DO 31SA, and DO 58SA isolates each with a MIC value of 256 µg/mL. Likewise, botanical from the fruits of *A. indica* was effective against 68.75% of the tested *S. aureus* strain and isolates, with MIC values ranging from 32 to 1024 µg/mL. This extract demonstrated an excellent activity against the *S. aureus* MRSA A9 isolate and ATCC 25923 stain, achieving a MIC of 32 µg/mL. The same extract presented a very good activity against the *S. aureus* DO 49SA, MRSA A4, and MRSA A11 isolates, with MIC values ranging from 64 to 128 µg/mL. A good antibacterial activity from this extract was observed against the *S. aureus* DO 49SA, MRSA A4, and MRSA A11 isolates, presenting a MIC value of 256 µg/mL.

These results underscore the effectiveness of botanicals from the leaves of *T. laxiflora* and those from the fruits of *A. indica* demonstrating antibacterial capabilities at very low concentrations (≤256 µg/mL) against the MDR *S. aureus*. The antibacterial effects of the various extracts are attributed to their alkaloid, phenol, and flavonoid content (*T. laxiflora*) and alkaloids and flavonoids (*A. indica*), which may interact with the studied bacterial species through various mechanisms [42-45]. However, the present studies were not conducted *in vivo* to obtain conclusive data. These results are not like those obtained from the previously documented report. Recent research by Boulis et al. (2025) in Egypt reported the antibacterial properties of the hydromethanolic extract of *T. laxiflora* leaves against *S. aureus*, utilizing the macro-dilution method, yielding a MIC value of 16 mg/mL [21]. Additionally, N'do and collaborators in Burkina Faso demonstrated the effectiveness of the ethanol extracts against the *S. aureus* ATCC43800 strain, with a MIC value of 3.125 mg/mL [22]. Nonetheless, the methanol extract from species within the genus *Terminalia* exhibited outstanding activity against *S. aureus*, with MIC values ranging from 3 to 14 µg/mL which is like those obtained in the present study [23]. The antibacterial effect of the methanol extract from the fruits of *A. indica* aligns with findings from Akinduti and colleagues, who showed via the macro-dilution method that the aqueous extract from the leaves of *A. indica* collected in Ota, Nigeria, exhibited anti-*Staphylococcus* activity, with a MIC value of 100 mg/mL [24]. The remarkable antibacterial activity of botanical from the leaves of *T. laxiflora* observed in this study, along with previous research, can likely be attributed to variations in extraction solvents and pedoclimatic conditions which might affect the qualitative phytochemical composition of the extracts. Moreover, the methanol extract of *T. laxiflora* in our study contains alkaloids, unlike the other extracts. Regarding the *A. indica* extract, the differences in antibacterial activity between our findings and those of previous studies may be attributed not only to the variety of extraction solvents used but also to the distinct harvesting locations [30-33].

Given the challenge of bacterial resistance to antibiotics, investigating new antibacterial compounds derived from plants, alongside the modulation of the antibacterial activity of antibiotics whose effectiveness has diminished, serves as an alternative strategy to address bacterial resistance [46]. Numerous reports documented the potential of botanicals to potentiate at sub-inhibitory concentrations the activity of usual antibiotics [47-51]. In this study, the methanol extracts from the leaves of *T. laxiflora* and from the fruits of *A. indica* was combined with conventional antibiotics (Table 3 and Table 4). The leaves extract from *T. laxiflora* and the fruit extract from *A. indica* at sub-inhibitory concentrations (MIC/2 and MIC/4), enhanced the effectiveness of various antibiotics against the *S. aureus* isolates, with Activity Enhancement Factors (AEF) ranging from 2 to 128. Specifically, botanical from *T. laxiflora* at sub-inhibitory concentrations in association with ciprofloxacin, levofloxacin, and doxycycline showed a potentiating factor of 4 against the *S. aureus* MSSA A1 isolate. Penicillin and tetracycline exhibited at least a 32-fold increase in activity against the *S. aureus* MSSAA4 and *S. aureus* MSSAA11 isolates when combined with this extract prepared at MIC/2 and MIC/4. The extract from this species modulates the activity of these antibiotics by 25 to 62.5% against the tested isolates. In the same manner, the methanol extract from the fruits of *A. indica*, increase the activity of levofloxacin by 8-fold at MIC/2 and MIC/4 against the *S. aureus* MSSAA4 isolate and by 4-fold increase against the *S. aureus* DO57SA isolate. Penicillin, tetracycline, ceftriaxone, cefixime, and doxycycline, when tested alongside this extract, showed up to 4 times greater antibacterial efficacy against the *S. aureus* DO96SA, MSSA A1, MSSAA11, DO96SA, and DO57SA isolates. Extract from the fruits of *A. indica* increased the activity of the antibiotics by 12.5 to 62.5% against the tested isolates. Although the number of antibiotic families utilized was limited, the results from these combinations indicate a significant restoration of antibacterial activity for several antibiotics that had previously shown reduced effectiveness against the various tested *S. aureus* isolates. The potentiating effects attributed to the different extracts are related to the presence of bioactive compounds such as phenolic compounds, which have demonstrated synergistic effects when associated with nalidixic acid, ciprofloxacin, norfloxacin, levofloxacin, oxacillin, tetracycline, and chloramphenicol against the *S. aureus* ATCC 6538 strain [41]. Mabhiza et al. (2016) indicated in their research that alkaloids can disrupt certain bacterial resistance mechanisms, such as active efflux, thereby allowing antibiotics to effectively reach and target their intended sites [25]. The antibacterial properties observed in this research further support the significance and medicinal benefits of African medicinal plants [52-74]. These data affirm the potential of African botanicals and phytochemicals as sources of drugs to address various human ailments [75-91].

Table 1. Characteristics of bacteria strain and isolates tested.

Bacteria strains	Features	References
ATCC 25923	Reference strain	
S.aureus MRSA A1	Clinical isolate: MET^s; NIS^r, CHL^r	[26, 28]
S.aureus MRSA A4	Clinical isolate: $OFXA^r$, FLX^r, KAN^r, CYP^r, CHL^r, GEN^r, NIS^r, AMP^r	[26, 28]
S.aureus MRSA A6	Clinical isolate: $OFXA^r$, KAN^r, CYP^r, CHL^r, GEN^r, NIS^r, AMP^r	[26, 28]
S.aureus MRSA A9	Clinical isolate: $OFXA^r$, FLX^r, TET^r, ERM^r, CYP^r, IM/CS^r, CHL^r, GEN^r, NIS^r, AMP^r	[26, 28]
S.aureus MRSA A11	Clinical isolate: $OFXA^r$, KAN^r, ERM^r, CYP^r, IM/CS^r, CHL^r, NIS^r, AMP^r	[26, 28]
S.aureus MRSA A12	Clinical isolate : $OFXA^r$, FLX^r, KAN^r, ERM^r, IM/CS^r, CHL^r, GEN^r, NIS^r, AMP^r	[26, 28]
DO 21SA	Clinical isolate MET^s, AMX^r, CAZ^r, FOX^r, OXA^r, VAN^r	[27]
DO 31SA	Clinical isolate MET^s, IMP^r, FOX^r, AMC^r, CXM^r, COT^r, ERY^r, TET^r, OXA^r, VAN^r	[27]
DO 49SA	Clinical isolate MET^s, CAZ^r, FOX^r, AMC^r, CXM^r, COT^r, ERY^r, AMK, CYP^r, OFX^r, TET^r, OXA^r, VAN^r, NIT^r	[27]
DO 57SA	Clinical isolate: MET^s, IMP^r, AMX^r, FOX^r, CXM^r, ERY^r, $CY\dot{P}$, OFX^r, VAN^r	[27]
DO 58SA	Clinical isolate: MET^s, AMX^r, CAZ^r, CXM^r, ERY^r, TET^r, OXA^r, VAN^r	[27]
DO 74SA	Clinical isolate: MET^s, AMX^r, CAZ^r, FOX^r, CXM^r, COT^r, ERY^r, AMK^r, GEN^r, FUS^r, TET^r	[27]
DO 94SA	Clinical isolate: MET^s, AMX^r, CAZ^r, FOX^r, AMC^r, CXM^r, COT^r, ERY^r, CYP^r, OFX^r, FUS^r, TET^r, OXA^r, VAN^r, NIT^r	[27]
DO 96SA	Clinical isolate: MET^s, AMX^r, CAZ^r, FOX^r, AMC^r, CXM^r, COT^r, ERY^r, CYP^r, OFX^r, FUS^r, TET^r, OXA^r, VAN^r, NIT^r	[27]
DO 09SA	Clinical isolate: AMX^r, ERY^r, VAN^r, $NI\dot{T}^r$	[27]

$OFXA^r$ OR OFX^r, KAN^r, IM/CS^r, CHL^r, GEN^r, IMP^r, FLX^r, ERM^r OR ERY^r, AMP^r, AMK^r, NIS^r, AMX^r, CAZ^r, FOX^r, AMC^r, CXM^r, COT^r, CYP^r, FUS^r, TET^r, OXA^r, VAN^r, NIT^r resistance to Ofloxacin, Kanamycin, Imipenem/Cilastatin sodium, Chloramphenicol, Gentamicin, Imipenem, Flomoxef, Erythromycin, Ampicillin, Amikacin, Nisin, Amoxicillin, Ceftazidime, Cefoxitin, Amoxicillin-clavulanic acid, Cefuroxime, Trimethoprim-sulfamethoxazole, Ciprofloxacin, Fusidic acid, Tetracycline, Oxacillin, Vancomycin, Nitrofurantoin respectively. MET^S: sensible to Methicillin.

Table 2. Minimum inhibitory concentration and minimum bactericidal concentration of plants extracts.

Strain and isolates	*Plant extracts*						Antibiotic		
	T. laxiflora			*A. indica*			Imipenem		
	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R
S. aureus MSSA A1	>2048			512	512	1	8	nd	nd
S. aureus MRSA A4	1024	2048	2	128	512	4	128	512	4
S. aureus MRSA A6	512	2048	4	2048	2048	1	16	512	32
S. aureus MRSA A9	128	128	1	32	2048	64	128	512	4
S. aureus MRSA A11	256	1024	4	128	1024	8	>128	512	4
S. aureus MRSA A12	>2048	nd	nd	512	512	1	128	256	2
ATCC 25923	32	256	4	32	256	8	<1/2	32	64
DO 21SA	512	1024	2	>2048	nd	nd	64	256	4
DO 31SA	256	1024	4	256	1024	4	16	nd	nd
DO 49SA	1024	1024	1	64	128	2	64	nd	nd
DO 57SA	>2048	nd	nd	>2048	nd	nd	2	128	64
DO 58SA	256	256	1	256	256	1	32	32	1
DO 74SA	>2048	nd	nd	>2048	nd	nd	2	64	32
DO 94SA	1024	1024	1	>2048	2048	1	16	nd	nd
DO 96SA	>2048	nd	nd	256	2048	8	2	64	32
DO 09SA	>2048	nd	nd	1024	1024	1	2	nd	nd

MIC: Minimum inhibitory concentration, MBC: Minimum bactericidal concentration, nd: not determined, R: Ratio of MBC/MIC

Table 3. Results of the association test between usual antibiotics and the extract from the leaves of *T. laxiflora* against bacteria isolates.

ATB	Extracts	MIC of antibiotics in the presence of extracts from the leaves of *T. laxiflora* at sub-inhibitory concentrations and AEF							PBP
		S. aureus							
		MSSA A1	MSSAA4	MSSAA11	MSSAA12	DO96SA	DO09SA	DO57SA	
CIP	0	4	1	1	1	<1/2	<1/2	<1/2	
	MIC/2	<1/2**(8)**	2**(0.5)**	<1/2**(2)**	<1**(1)**	<1/2**(1)**	<1/2**(1)**	<1/2**(1)**	25
	MIC/4	<1/2**(8)**	16**(0.06)**	<1/2**(2)**	<1**(1)**	<1/2**(1)**	<1/2**(1)**	<1/2**(1)**	25
LEV	0	2	4	1	1	<1/2	1	2	-
	MIC/2	<1/2**(4)**	2**(2)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	<1/2**(2)**	2**(1)**	62.5
	MIC/4	<1/2**(4)**	2**(2)**	2**(0.5)**	<1/2**(2)**	<1/2**(1)**	1**(1)**	2**(1)**	37.5
PEN	0	128**()**	256	1024	64	128	128	1024	-
	MIC/2	128**(1)**	<8**(32)**	<8**(128)**	512**(0.125)**	<8**(16)**	1024**(0.125)**	1024**(1)**	37.5
	MIC/4	256**(0.5)**	<8**(32)**	<8**(128)**	512**(0.125)**	32**(4)**	1024**(0.125)**	1024**(1)**	37.5
TET	0	2	64	64	1	<1/2	1	1	-
	MIC/2	128**(0.016)**	32**(2)**	<1/2**(128)**	64**(0.016)**	<1/2**(1)**	<1/2**(2)**	<1/2**(2)**	50
	MIC/4	128**(0.016)**	64**(1)**	<1/2**(128)**	64**(0.016)**	<1/2**(1)**	<1/2**(2)**	<1/2**(2)**	50
CTX	0	32	16	64	32	<8	<8	16	-
	MIC/2	32**(1)**	<8**(2)**	64**(1)**	<8**(4)**	<8**(1)**	<8**(1)**	16**(1)**	25
	MIC/4	32**(1)**	<8**(2)**	64**(1)**	<8**(4)**	<8**(1)**	32**(0.25)**	16**(1)**	25
CFX	0	64	256	32	16	32	32	<8	
	MIC/2	128**(0.5)**	512**(0.5)**	<8**(4)**	<8**(4)**	<8**(4)**	<8**(4)**	<8**(1)**	50
	MIC/4	128**(0.5)**	512**(0.5)**	<8**(4)**	<8**(4)**	16**(2)**	<8**(4)**	<8**(1)**	50
DOX	0	2	1	1	1	<1/2	4	4	-
	MIC/2	<1/2**(4)**	16**(0.07)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	4**(1)**	8**(0.5)**	37.5
	MIC/4	<1/2**(4)**	32**(0.04)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	8**(0.5)**	16**(0.25)**	37.5
IMI	0	8	128	>128	128	2	2	2	-
	MIC/2	16**(0.5)**	128**(1)**	>128**(1)**	128**(1)**	<1**(2)**	<1**(2)**	4**(0.5)**	25
	MIC/4	16**(0.5)**	128**(1)**	>128**(1)**	128**(1)**	<1**(2)**	2**(1)**	8**(0.25)**	25

MIC: Minimal inhibitory concentration; (): activity modulation factor; ATB: Antibiotics, PBS: Percentage of bacteria where Potentiation is observed.

Table 4. Results of the association test between common antibiotics and the extract from the fruits of *A. indica* against bacteria strains.

ATB	Extracts	MIC of antibiotics in the presence of extract from the fruits of *A. indica* at sub-inhibitory concentrations and AEF							PBP
		S. aureus							
		MSSA A1	MSSAA4	MSSAA11	MSSAA12	DO96SA	DO09SA	DO57SA	
CIP	0	4	1	1	1	<1/2	<1/2	<1/2	
	MIC/2	<1/2**(8)**	16**(0.07)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	<1/2**(1)**	<1/2**(1)**	37.5
	MIC/4	2**(2)**	32**(0.04)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	<1/2**(1)**	<1/2**(1)**	37.5
LEV	0	2	4	1	1	<1/2	1	2	
	MIC/2	2**(1)**	<1/2**(8)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	<1/2**(2)**	<1/2**(4)**	62.5
	MIC/4	2**(1)**	<1/2**(8)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	1**(1)**	<1/2**(4)**	50
PEN	0	128	256	1024	64	128	128	1024	
	MIC/2	256**(0.5)**	128**(2)**	1024**(1)**	64**(1)**	32**(4)**	512**(0.25)**	<8**(128)**	25
	MIC/4	256**(0.5)**	256**(1)**	1024**(1)**	128**(0.5)**	32**(4)**	512**(0.25)**	16**(64)**	12.5
TET	0	2	64	64	1	<1/2	1	1	
	MIC/2	<1/2**(4)**	64**(1)**	64**(1)**	<1/2**(2)**	<1/2**(1)**	<1/2**(2)**	<1/2**(2)**	50
	MIC/4	<1/2**(4)**	64**(1)**	64**(1)**	<1/2**(2)**	<1/2**(1)**	1**(1)**	<1/2**(2)**	37.5
CTX	0	32	16	64	32	<8	<8	16	
	MIC/2	32**(1)**	<8**(2)**	16**(4)**	16**(2)**	<8**(1)**	<8**(1)**	<8**(2)**	50
	MIC/4	32**(1)**	16**(1)**	16**(4)**	16**(2)**	<8**(1)**	<8**(1)**	<8**(2)**	37.5
CFX	0	64	256	32	16	32	32	<8	
	MIC/2	64**(1)**	128**(2)**	128**(0.25)**	<8**(2)**	<8**(4)**	16**(2)**	<8**(1)**	50
	MIC/4	64**(1)**	256**(1)**	128**(0.25)**	<8**(2)**	<8**(4)**	16**(2)**	<8**(1)**	37.5
DOX	0	2	1	1	1	<1/2	4	4	
	MIC/2	<1/2**(4)**	2**(0.5)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	<1/2**(8)**	1**(4)**	62.5
	MIC/4	<1/2**(4)**	2**(0.5)**	<1/2**(2)**	<1/2**(2)**	<1/2**(1)**	4**(1)**	1**(4)**	50
IMI	0	8	128	>128	128	2	2	2	
	MIC/2	8**(1)**	128**(1)**	>128**(1)**	128**(1)**	<1**(2)**	<1**(2)**	<1**(2)**	37.5
	MIC/4	8**(1)**	128**(1)**	>128**(1)**	128**(1)**	<1**(2)**	2**(1)**	<1**(2)**	25

MIC: Minimal inhibitory concentration; (): activity modulation factor; ATB: Antibiotics, PBS: Percentage of Bacteria where Potentiation is observed.

Table 5. Phytochemical screening of methanol extracts from the roots of *T. laxiflora* and the leaves of *A. indica.*

Secondary metabolites	*T. laxiflora* (leaves)	*A. indica* (fruits)
Alkaloids	+	-
Phenols	+	+
Flavonoids	+	+
Terpenoids	-	-
Saponins	-	-
Anthocyanins	-	-

+: Present, -: Absent

Conclusion

The current research highlighted the antibacterial potential of botanicals derived from the leaves of *T. laxiflora* and from the fruits of *A. indica*. The results indicated that both extracts are rich in phytochemicals with considerable efficacy in combating infections caused by MDR *Staphylococcus aureus.* The purification of these phytochemicals together with the assessment of their safety will be the focus of our next study.

Abbreviations

AEF: Activity Enhancement Factor
ATCC: American-Type Culture Collection
CFU: Colony Forming Unit
CFX: cefixime
CIP: ciprofloxacin
CTX: ceftriaxone
DMSO: Dimethyl sulfoxide
DOX: Doxycycline
HNC: National Herbarium of Cameroon
IMI: Imipenem
INT: Para-Iodonitrotetrazolium chloride
LEV: levofloxacin
MDR: multidrug-resistant
PEN: penicillin
TET: tetracycline
WHO: World Health Organization

Authors' Contribution

DJA, LM, EC, AWBY, JRNK, VYM, MFK, JFM, and INB carried out the study; 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.

Conflict of interest

The authors declare no conflict of interest

Article history:

Received: 08 August 2025
Received in revised form: 06 October 2025
Accepted: 12 October 2025
Available online: 12 October 2025

References

1. Lee RA, Centor RM, Humphrey LL, Jokela JA, Andrews R, Qaseem A, Scientific Medical Policy Committee of the American College of Physicians. 2021. Appropriate use of short-course antibiotics in common infections: best practice advice from the American College of Physicians. *Ann Intern Med.* 174(6): 822-827.
2. Kilari V, Oroszi T. 2024. The Misuse of Antibiotics and the Rise of Bacterial Resistance: A Global Concern. *Pharmacol Pharm*. 15: 508-523.
3. O'Neill, J. 2016. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. *Wellcome Trust and HM Government.* https://www.cabidigitallibrary.org/doi/full/10.5555/20173071720.
4. de Kraker ME, Stewardson AJ, Harbarth S. 2016. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med. 13*(11): e1002184.
5. Belay WY, Getachew M, Tegegne BA, Teffera ZH, Dagne A, Zeleke TK, Abebe RB, Gedif AA, Fenta A, Yirdaw G, Tilahun A, Aschale Y. 2024. Mechanism of antibacterial resistance, strategies and next-generation antimicrobials to contain antimicrobial resistance: a review. *Front Pharmacol.* 15: 1444781.
6. Oyedemi SO, Oyedemi BO, Falowo AB, Fayemi PO, Coopoosamy RM. 2016. Antibacterial and ciprofloxacin modulating activity of Ptaeroxylon obliquum (Thunb.) Radlk leaf used by the Xhosa people of South Africa for the treatment of wound infections. *Biotechnol Biotechnol Equip. 30*(5): 1006-1015.
7. Mohr KI. 2016. History of antibiotics research. *How to overcome the antibiotic crisis: facts, challenges, technologies and future perspectives*, 237-272.
8. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, Tasak N. 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The lancet. 399*(10325): 629-655.
9. Van Vuuren SF. 2008. Antimicrobial activity of South African medicinal plants. *J Ethnopharmacol. 119*(3): 462-472.
10. Yendze AW, Mpude L, Cadet E, Assonfack DJ, Matieta VY, Kuete JRN, Kuete V. 2024. Antibacterial and antibiotic-potentiation activities of methanol extracts from *Blighia sapida* KD Koenig (Sapindaceae) against Gram-negative multidrug-resistant bacteria overexpressing efflux pumps. *Invest Med Chem Pharmacol.* 7(3):99.
11. Seukep AJ, Mbu BF, Mbuntcha HG, Matieta VY, Ngounou E, Kouam AF, Pokam BDT. 2025. Enhancing tetracycline, ceftazidime, and amoxicillin efficacy with hydroethanolic extracts of *Mammea africana* (Calophyllaceae) and *Baillonella toxisperma* (Sapotaceae) against clinically relevant drug-resistant enteric bacteria. *Pharmacol Res* 8: 100311.
12. Lapo R, Ingambire C, Moussa A. 2025. Effets de *Azadirachta indica* dans la lutte contre le stress thermique chez le poulet de chair au Sénégal. *Revue africaine de santé et de productions animales*, *2*. https://doi.org/10.46298/raspa.15196
13. 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.
14. Ngwaneu LSM, Mbaveng AT, Nayim P, Wamba BE, Youmbi LM, Bonsou IN, 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.
15. Coutinho HD, Vasconcellos A, Freire-Pessoa HL, Gadelha CA, Gadelha TS, Almeida-Filho GG. 2010. Natural products from the termite Nasutitermes corniger lower aminoglycoside minimum inhibitory concentrations. *Pharmacogn Mag.* 6:1-4.
16. Harbone JB. 1973. Phytochemical methods: A guide to modern techniques of plant analysis. London, Chapman and Hall Ltd, p.116.
17. Kuete V. 2013. Medicinal Plant Research in Africa: Pharmacology and Chemistry In: *Pharmacology and Chemistry.* Edited by Kuete V, 1 edn. Oxford: Elsevier.
18. Wamba BE, Mbaveng AT, & Kuete V. 2023. 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.
19. Kuete V. 2023. Potential of African medicinal plants against Enterobacteria: Classification of plants antibacterial agents. *Advances in Botanical Research* 106: 151-335.
20. Tamokou JDD, Mbaveng AT, Kuete V. 2017. Antimicrobial activities of African medicinal spices and vegetables. In *Medicinal spices and vegetables from Africa* (pp. 207-237). Academic Press.
21. Boulis AG, Melek FR, Ghaly NS, Sabry OM, Abdelwahed NA, El Zalabani SM. 2025. Antioxidant and Antimicrobial Activities of *Terminalia laxiflora* Engl. and *Terminalia myriocarpa* Van Heurck & Müll. Arg. Leaves in Relation to Their GC-MS and UPLC-ESI-MS Metabolite Profiling. *Egypt J Chem. 68*(4): 205-221.
22. N'do JYP, Paré D, Bondé L, Hilou A. 2024. Comparative phytochemical profile and biological activity of three Terminalia species as alternative antimicrobial therapies. *Heliyon*. 10(21): e40159.
23. Mbwambo ZH, Moshi MJ, Masimba PJ, Kapingu MC, Nondo RS. 2007. Antimicrobial activity and brine shrimp toxicity of extracts of Terminalia brownii roots and stem. *BMC Complement Altern Med. 7*(1): 9
24. Akinduti PA, Emoh-Robinson V, Obamoh-Triumphant HF, Obafemi YD, Banjo TT. 2022. Antibacterial activities of plant leaf extracts against multi-antibiotic resistant *Staphylococcus aureus* associated with skin and soft tissue infections *BMC Complement Altern Med. 22*(1): 47.
25. Mabhiza D, Chitemerere T, Mukanganyama S. 2016. Antibacterial Properties of Alkaloid Extracts from *Callistemon citrinus* and *Vernonia adoensis* against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *Int J Med Chem.* 2016: 6304163.
26. Paudel A, Hamamoto H, Kobayashi Y, Yokoshima S, Fukuyama T, Sekimizu K. 2012. Identification of novel deoxyribofuranosyl indole antimicrobial agents. J Antibiot. *65*(2): 53-57.
27. Kengne MF, Mbaveng AT, Kuete V. 2024. Antibiotic resistance profile of *Staphylococcus aureus* in cancer patients at Laquintinie hospital in Douala, littoral region, Cameroon. *BioMed Res Int.* 2024(1): 5859068.
28. Dzoyem JP, Hamamoto H, Ngameni B, Ngadjui BT, Sekimizu K. 2013. Antimicrobial action mechanism of flavonoids from *Dorstenia species*. *Drug Discov Ther.* 7(2): 66-72
29. National Research Council (US) Panel on Neem. 1992. Neem: A Tree For Solving Global Problems. National Academies Press (US). https://doi.org/10.17226/1924
30. Thouri A, Chahdoura H, El Arem A, Omri Hichri A, Ben Hassin R, Achour L. 2017. Effect of solvents extraction on phytochemical components and biological activities

of Tunisian date seeds (var. Korkobbi and Arechti). *BMC Complement Altern Med.* 17(1): 248.
31. Munuo MS, Martin MJ, Shechambo LF, Gervas I. 2025. Effect of solvent extraction on phytochemical profile and quantification of bioactive compounds in *Ocimum suave* (wild). *J Current Opinion Crop Sci.* 6(1): 27-41.
32. Moomin A, Russell WR, Knott RM, Scobbie L, Mensah KB, Adu-Gyamfi PKT, Duthie SJ. 2023. Season, storage and extraction method impact on the phytochemical profile of *Terminalia ivorensis*. *BMC plant biology*, *23*(1): 162.
33. Kabubii ZN, Mbaria JM, Mathiu MP, Wanjohi JM, Nyaboga EN. 2023. Evaluation of seasonal variation, effect of extraction solvent on phytochemicals and antioxidant activity on *Rosmarinus officinalis* grown in different agro-ecological zones of Kiambu County, Kenya. *CABI Agric Biosci.* 4(1): 1.
34. Naghavi M, Mestrovic T, Gray A, Hayoon AG, Swetschinski LR, Aguilar GR, Murray CJ. 2024. Global burden associated with 85 pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Infect Dis.* 24(8): 868-895.
35. Salih EYA, Kanninen M, Sipi M, Luukkanen O, Hiltunen R, Vuorela H, Fyhrquist P. 2017. Tannins, flavonoids and stilbenes in extracts of African savanna woodland trees *Terminalia brownii*, *Terminalia laxiflora* and *Anogeissus leiocarpus* showing promising antibacterial potential. *S Afr J Bot.* 108: 370-386.
36. Badawe G, Fankam AG, Nayim P, Wamba BE, Mbaveng AT, Kuete V. 2018. Antistaphylococcal activity and antibiotic-modulating effect of *Olax subscorpioidea, Piper guineense, Scorodophloeus zenkeri, Fagara leprieurii*, and *Monodora myristica* against resistant phenotypes. *Invest Med Chem Pharmacol. 1*(2): 17.
37. Eloff JN. 1998. A sensitive and quick microplate method to determine the minimal inhibitory concentration of plant extracts for bacteria. *Planta Med.* 64: 711-713.
38. Kuete V, Mbaveng AT, Tsaffack M, Beng VP, Etoa FX, Nkengfack AE, Meyer JJ, Lall N. 2008). Antitumor, antioxidant and antimicrobial activities of *Bersama engleriana* (Melianthaceae). *J Ethnopharmacol.* 115(3): 494–501
39. World Health Organization. (2023). Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance#:~:text=Credits ,Antimicrobial%20resistance,-21%20November%202023 (access on the 15th June 2025).
40. World Health Organization. 2024. Bacterial priority pathogens list, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1. (access on the 15th June 2025).
41. Sanhueza L, Melo R, Montero R, Maisey K, Mendoza L, Wilkens M. 2017. Synergistic interactions between phenolic compounds identified in grape pomace extract with antibiotics of different classes against *Staphylococcus aureus* and *Escherichia coli. PloS one*. 12(2): e0172273.
42. Ulanowska K, Tkaczyk A, Konopa G, Wegrzyn G. 2006. Differential antibacterial activity of genistein arising from global inhibition of DNA, RNA and protein synthesis in some bacterial strains. *Arch Microbiol.* 184: 271-278.
43. Salaheen S, Peng M, Joo J, Teramoto H, Biswas D. 2017. Eradication and sensitization of methicillin resistant *Staphylococcus aureus* with bioactive extracts of Berry pomace. *Front Microbiol*. 8: 253.
44. Beuria TK, Santra MK, Panda D. 2005. Sanguinarine blocks cytokinesis in bacteria by inhibiting FtsZ assembly and bundling. Biochemistry.44: 16584−16593.
45. Giri P, Kumar GS. 2010. Molecular recognition of poly(A) targeting by protoberberine alkaloids: in vitro biophysical studies and biological perspectives. *Mol Biosyst.* 6: 81-88.
46. Vaou N, Stavropoulou E, Voidarou CC, Tsakris Z, Rozos G, Tsigalou C, Bezirtzoglou E. 2022. Interactions between Medical Plant-Derived Bioactive Compounds: Focus on Antimicrobial Combination Effects. Antibiotics (Basel, Switzerland): 11(8): 1014.https://doi.org/10.3390/antibiotics11081014
47. Cadet E, Assonfack DJ, Yendze AW, Mpude L, Matieta VY, Kuete JRN, Mbaveng AT, Kuete V. 2024. Antibacterial activity and antibiotic-potentiating effects of methanol extracts from *Ocimum basilicum* and *Sarcocephalus latifolius* against multidrug-resistant Gram-negative bacteria overexpressing efflux pumps. *Invest Med Chem Pharmacol.* 16: 17.
48. Mpude L, Yendze AW, Assonfack DJ, Cadet E, Matieta VY, Megaptche JF, Kuete V. 2024. Antibacterial activity of *Sarcocephalus latifolius* and *Acacia sieberiana*, and the effect of their association with antibiotics against multidrug-resistant Staphylococcus aureus. *Invest Med Chem Pharmacol.* 7(2): 96.
49. Assonfack DJ, Cadet E, Mpude L, Yendze AW, Matieta VY, Kuete JR, Bonsou IN, Megaptche JF, Kengne MF, Mbaveng AT, Kuete V. (2024). Botanicals from the flowers of *Vernonia calvoana* and the leaves of *Senna spectabilis* showed anti-Klebsiella activity and potentiated the activity of antibiotics against multidrug-resistant phenotypes overexpressing efflux pumps. *Invest Med Chem Pharmacol. 7*(3): 101.
50. Assonfack DJ, Mpude L, Cadet E, Yendze AWW, Matieta VY, Kuete, JR, Mbaveng A, Kuete V. Unveiling the anti-Klebsiella activity of methanol extracts from Hallea ciliata leaves and barks against multidrug-resistant strains overexpressing AcrAB-TolC efflux pumps. *Invest Med Chem Pharmacol.* 7 *(3): 98*.
51. Fankam AG, Kuete V. 2023. Phytochemistry and antibacterial potential of the genus Allanblackia. *Advances in Botanical Research* 107: 1-36.
52. Kuete V. 2014. Health effects of alkaloids from African medicinal plants. In *Toxicological survey of African medicinal plants* (pp. 611-633). Elsevier.
53. Kuete V. 2010. Potential of Cameroonian plants and derived products against microbial infections: a review. *Planta Med.* 76: 1479-1491.
54. Kuete JR, Kuete V. 2023. Harvesting and processing medicinal plants for antibacterial testing. *Advances in Botanical Research* 106: 47-60.
55. Kuete V, Efferth T. 2010. Cameroonian medicinal plants: pharmacology and derived natural products. *Front Pharmacol.* 1: 123.
56. Kuete V, Karaosmanoğlu O, Sivas H. 2017. Anticancer activities of African medicinal spices and vegetables. In *Medicinal spices and vegetables from Africa* (pp. 271-297). Academic Press.
57. Kuete V. 2017. Other health benefits of African medicinal spices and vegetables. In *Medicinal spices and vegetables from Africa* (pp. 329-349). Academic Press.
58. Kuete V. 2024. The best African plant-derived antibacterial products for clinical perspectives: The state-of-the-art. *Invest Med Chem Pharmacol. 7*(2): 94.
59. Kuete V. 2017. African medicinal spices and vegetables and their potential in the management of metabolic syndrome. In *Medicinal Spices and Vegetables from Africa* (pp. 315-327). Academic Press.
60. Kuete V, Wiench B, Hegazy MEF, Mohamed TA, Fankam AG, Shahat AA, Efferth, T. 2012. Antibacterial activity and cytotoxicity of selected Egyptian medicinal plants. *Planta Med.* 78: 193-199.
61. Taïwe GS, Kuete V. 2014. Neurotoxicity and neuroprotective effects of African medicinal plants. *Toxicological Survey of African Medicinal Plants*, 423-444.
62. Mbaveng AT, Wamba BE, Bitchagno GT, Tankeo SB, Çelik İ, Atontsa BC, Efferth T. 2021. Bioactivity of fractions and constituents of *Piper capense* fruits towards a broad panel of cancer cells. *J Ethnopharmacol.* 271, 113884.
63. Djeussi DE, Noumedem JA, Seukep JA, Fankam AG, Voukeng IK, Tankeo SB, Kuete V. 2013. Antibacterial activities of selected edible plants extracts against multidrug-resistant Gram-negative bacteria. *BMC Complementary Alternative Med*. 13(1): 164.
64. Tshikalange TE, Modishane DC, Tabit FT. 2017. Antimicrobial, antioxidant, and cytotoxicity properties of selected wild edible fruits of traditional medicinal plants. *J Herbs Spices Med P.* 23(1): 68-76.
65. Madureira AM, Ramalhete C, Mulhovo S, Duarte A, Ferreira, MJU. 2012. Antibacterial activity of some African medicinal plants used traditionally against infectious diseases. *Pharmaceut Biol.* 50(4): 481-489.
66. Mathabe MC, Nikolova RV, Lall N, Nyazema NZ. 2006. Antibacterial activities of medicinal plants used for the treatment of diarrhoea in Limpopo Province, South Africa. *J Ethnopharmacol.* 105(1-2): 286-293.
67. Cock IE, Van Vuuren SF. (2015). South African food and medicinal plant extracts as potential antimicrobial food agents. *J Food Sci Technol.* 52(11): 6879-6899.
68. Maregesi SM, Pieters L, Ngassapa OD, Apers S, Vingerhoets R, Cos P, Vlietinck AJ. 2008. Screening of some Tanzanian medicinal plants from Bunda district for antibacterial, antifungal and antiviral activities. *J Ethnopharmacol.* 119(1): 58-66.
69. Van Vuuren SF. 2008. Antimicrobial activity of South African medicinal plants. *J Ethnopharmacol.* 119(3): 462-472.
70. 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.* 104:5-11.
71. Seukep JA, Fankam AG, Djeussi DE, Voukeng IK, Tankeo SB, Noumdem JA, Kuete V. 2013. Antibacterial activities of the methanol extracts of seven Cameroonian dietary plants against bacteria expressing MDR phenotypes. *Springerplus*, 2(1): 363.
72. 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 Complementary Alternative Med*. 11(1): 104.
73. Kuete V. 2023. African Flora to Fight Bacterial Resistance, Part II*: The Best Source of Herbal Drugs and Pharmaceuticals* (Vol. 107). Elsevier.
74. Tlhapi D, Malebo N, Manduna IT, Lautenschläger T, Mawunu M. 2024. A review of medicinal plants used in the management of microbial infections in Angola. *Plants. 13*(21): 2991.
75. Kuete V, Mbaveng AT, Zeino M, Fozing CD, Ngameni B, Kapche GD, Ngadjui BT, Efferth T. 2015. Cytotoxicity of three naturally occurring flavonoid derived compounds (artocarpesin, cycloartocarpesin and isobavachalcone) towards multi-factorial drug-resistant cancer cells. *Phytomedicine.* 22(12):1096-1102.
76. Sandjo LP, Kuete V, Tchangna RS, Efferth T, Ngadjui BT. 2014. Cytotoxic benzophenanthridine and furoquinoline alkaloids from *Zanthoxylum buesgenii* (Rutaceae). *Chem Cent J.* 8(1):61.
77. Mbaveng AT, Hamm R, Kuete V. 2014. 19 - Harmful and protective effects of terpenoids from african medicinal plants. In: *Toxicological Survey of African Medicinal Plants.* edn. Edited by Kuete V: Elsevier. 557-576.
78. 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.
79. Kuete V, Fokou FW, Karaosmanoğlu O, Beng VP, Sivas H. 2017. Cytotoxicity of the methanol extracts of *Elephantopus mollis, Kalanchoe crenata* and 4 other Cameroonian medicinal plants towards human carcinoma cells. *BMC Complement Altern Med.* 17(1):280.
80. 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.
81. Kuete V. 2017. Chapter 28 - Thymus vulgaris. In: *Medicinal Spices and Vegetables from Africa.* edn. Edited by Kuete V: Academic Press. 599-609.
82. Kuete V, Sandjo L, Seukep J, Maen Z, Ngadjui B, Efferth T. 2015. Cytotoxic compounds from the fruits of *Uapaca togoensis* towards multi-factorial drug-resistant cancer cells. *Planta Med.* 81(1):32-38.
83. Fongang H, Mbaveng AT, Kuete V. 2023. Chapter One - Global burden of bacterial infections and drug resistance. *Adv Bot Res.* 106:1-20.
84. Nayim P, Mbaveng AT, Wamba BEN, Fankam AG, Dzotam JK, Kuete V. 2018. Antibacterial and antibiotic-potentiating activities of thirteen Cameroonian edible

plants against gram-negative resistant phenotypes. *ScientificWorldJournal.* 2018:4020294.

85. 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.
86. 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.
87. Kuete V, Ango PY, Yeboah SO, Mbaveng AT, Mapitse R, Kapche GD, Ngadjui BT, Efferth T. 2014. Cytotoxicity of four *Aframomum* species (*A. arundinaceum, A. alboviolaceum, A. kayserianum and A. polyanthum*) towards multi-factorial drug resistant cancer cell lines. *BMC Complement Altern Med.* 14:340.
88. 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. *Invest Med Chem Pharmacol.* 1:7.
89. Mbaveng AT, Manekeng HT, Nguenang GS, Dzotam JK, Kuete V, Efferth T. 2018. Cytotoxicity of 18 Cameroonian medicinal plants against drug sensitive and multi-factorial drug resistant cancer cells. *J Ethnopharmacol.* 222:21-33.
90. Tankeo SB, Tane P, Kuete V. 2015. *In vitro* antibacterial and antibiotic-potentiation activities of the methanol extracts from *Beilschmiedia acuta, Clausena anisata, Newbouldia laevis* and *Polyscias fulva* against multidrug-resistant Gram-negative bacteria. *BMC Complement Altern Med.* 15(1):412.
91. Adem FA, Mbaveng AT, Kuete V, Heydenreich M, Ndakala A, Irungu B, Yenesew A, Efferth T. 2019. Cytotoxicity of isoflavones and biflavonoids from *Ormocarpum kirkii* towards multi-factorial drug resistant cancer. *Phytomedicine.* 58:152853.