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Phytochemical analysis and antibiotic-modulating activity of *Cocos nucifera*, *Glycine max* and *Musa sapientum* methanol extracts against multidrug resistant Gram-negative bacteria

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Abstract

Background: The rapid emergence of multidrug resistant (MDR) bacteria is occurring worldwide, endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives. Antibiotic-resistant infections are already widespread in the Sub-Saharan Africa and across the globe. To extend the search for new and more efficient antimicrobial drugs from natural sources, this work has been carried out to study the phytochemical composition and the antibacterial activities of some Cameroonian dietary plants (*Cocos nucifera*, *Glycine max* and *Musa sapientum*) against several MDR Gram-negative strains including *Escherichia coli*, *Enterobacter aerogenes*, *Providencia stuartii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* species expressing efflux pumps.

Methods: Phytochemical screening of plant extracts was performed using qualitative standard methods and the antimicrobial assays of these extracts alone and in combination with antibiotics were done using serial 96-wells microplate dilution essays.

Results: Each plant extract contained at least three mean classes of secondary metabolites. *Glycine max*, epicarps, leaves and bark of *C. nucifera* as well as mesocarps of *M. sapientum* contained each alkaloids, polyphenols, flavonoids, and triterpenes. Moreover, steroids were also found in *G. max*, steroids and saponins in epicarps and saponins in bark of *C. nucifera*. Meanwhile epicarps from *M. sapientum* contained only polyphenols, flavonoids and saponins. Antibacterial assays showed that different parts of *C. nucifera* were more active than other extracts. Their minimal inhibitory concentrations (MICs) varied from 128 to 2048 µg/mL. The bark part presented the highest antibacterial potential inhibiting the growth of 90% of strains with significant activity (100≤MIC≤512 µg/mL) against 50% of them (three *E. coli*, four *E. aerogenes* and three *K. pneumoniae*). It showed bactericidal effects (MBC/MIC≤4) on 45% of the same bacterial species. It was followed by epicarps and leaves parts which exhibited an inhibitory power against 75% and 60% of bacteria with significant activity on 40% and 20% of them respectively. They also showed bactericidal effects on *E. coli* ATCC8739 for epicarps extract and *E. coli* ATCC8739 and *P. stuartii* NEA16 for leaves extract. Extracts from *G. max* were less active and those from mesocarps and epicarps of *M. sapientum* did not showed any activity on all studied bacteria. Bark and epicarps extracts of *C. nucifera* potentiated the activities of all used antibiotics against at least 70% of bacteria while leaves extract exhibited this effect improving the activities of 67% of antibiotics with improvement activity factors (IAF) ranging from 2 to 256 suggesting that they contain bioactive compounds which could be considered as efflux pumps inhibitors. Extracts from *G. max*, epicarps and mesocarps of *M. sapientum* enhanced the inhibitory potential of 56%, 34% and 23% of antibiotics respectively against at least 70% of studied bacteria. These increases of activities also characterize synergistic effects between antibiotics and bioactive compounds of plants.

Conclusion: The findings of this work suggest that infections by resistant bacteria can be treated using different parts of *C. nucifera* as an alternative to commonly used antibiotics.

Keywords: Edible plants; antibiotics; infectious diseases; MDR bacteria; efflux pumps.

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Background

For more than 60 years, antimicrobial agents have been used to control bacterial infections in humans, animals, and plants. Nowadays, antimicrobial agents are among the most frequently used therapeutics in humans and veterinary medicine. In the early days of antimicrobial chemotherapy, antimicrobial resistance was not considered as an important problem, since the numbers of resistant strains were low and many new highly effective antimicrobial agents of different classes were detected [1,2]. The increased selective pressure imposed by the wide-spread use of antimicrobial agents since the 1950s has distinctly accelerated the development and the spread of bacterial resistance to existing drugs. Antibiotics were first prescribed to treat serious infections in the 1940s. Antibiotics discovery, modes of action and mechanisms of resistance have been productive research topics in academia and until recently, in the pharmaceutical industry [3,4]. Moreover, antibiotics have revolutionized medicine in many respect, and countless lives have been saved. Their discovery was a turning point in human history. Regrettably, the use of these wonder drugs has been accompanied by the rapid appearance of resistant strains. Unfortunately, resistance has eventually been seen to nearly all antibiotics that have been developed [5]. The antibiotic resistance crisis has been attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements. A wide range of biological and physiological mechanisms may be responsible for bacterial resistance including enzymatic inactivation by either disintegration or chemical modification of antibiotics, reduced intracellular accumulation by decreased influx and/or increased efflux of antibiotics and finally the modification of the cellular target sites [6,7,8].

Today, there has been an increasing concern to find alternative antibiotics substitutes for the treatment of infectious diseases, particularly those from various natural sources including plants that are easy to obtain and have considerably few side effects, to replace synthetic antibiotics used against bacterial infections. These antibiotics substitutes derived from plants sources can highly decrease the growth of resistant microbes by preventing infectious diseases caused by them. The medicinal value of plants has assumed important dimension in the few decades owing mainly to the discovery that extracts from plants contain not only minerals and primary metabolites but also a diverse array of secondary metabolites with antimicrobial potential [9,10]. There are approximately 250.000 to 500.000 species of plants with pharmacological interests on this planet and a good number of them have been investigated and reported for their antimicrobial potential. Moreover, some of these plants improved the activities of usual antibiotics among which some are edible plants [11-16].

To date, there has been little information on studies of *Cocos nucifera*, *Glycine max* and *Musa sapientum* dietary plants related to their pharmacological usage [17,18,19]. Therefore, this study was conducted to investigate the phytochemical composition and the antibacterial activity of the above three plants as well as their capacity to improve the activities of some commonly used antibiotics on several MDR Gram-negative strains.

Methods

Plant's collection and their extraction

Parts of three Cameroonian dietary plants including epicarps, leaves and bark of *Cocos nucifera*, beans of *Glycine max* and mesocarps and epicarps of *Musa sapientum* were used. They were collected in Bamboutos and Menoua Divisions, West Region of Cameroon, between September and October 2019. They were then identified at the National Herbarium (Yaoundé, Cameroon) where voucher specimens were deposited. Some information concerning the traditional use and previous biological activities as well as extractive yields of these plants are summarized in Table 1.

Plants were freshly collected and washed with clean water. They were then dried safe from sun and crushed to give powders that were soaked in the methanol solvent in the proportions 1:3 m/v for 48h. The preparation was stirred three times per days after which it was filtered using Wattman N°1 filter paper. The obtained filtrate was concentrated under reduced pressure (at 65°C) in a rotary evaporator to give the corresponding crude extracts which were dried at room temperature for complete evaporation of methanol. These crude extracts were kept at 4°C until further uses. Extractive yields (Table 1) of each sample were obtained by calculating the (crude extract weight /powder weight) x100.

Microbial samples and culture media

Microorganisms used were multidrug resistant (MDR) Gram-negative bacteria phenotypes involved in microbial infections and expressing efflux pumps. These bacteria which were constituted of reference strains and clinical isolates included *Escherichia coli, Enterobacter aerogenes, Klebsiella pneumoniae, Providencia stuartii* and *Pseudomonas aeruginosa* strains. They were provided from American Type Culture Collection (ATCC) and laboratory of UMR-MD1 of the University of Mediterranean, Marseille, France. Table 2 shows the studied bacteria with their features. Bacterial colonies were cultivated and activated in the Mueller Hinton Agar (MHA) medium while the Mueller Hinton Broth (MHB) was used for determination of minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) as well as bacterial storage at 4°C.

Chemicals

Nine different classes of conventional antibiotics including Azithromycin (AZT), Ciprofloxacin (CIP), Doxycycline (DOX), Erythromycin (ERY), Flucloxacillin (FLC), Gentamycin (GEN), Ofloxacin (OFL), Oxacillin (OXA) and Thiamphenicol (THI) were used. They were prepared in MHB. Dimethylsulfoxide (DMSO) for extracts and antibiotics dissolution and *p*-Iodonitrotetrazolium chloride (INT) was used for colorimetric detection of living bacteria. All these chemicals provided from Sigma-Aldrich (St. Quentin Fallavier, France).

Phytochemical essays

Phytochemical screening of used plant extracts was carried out to detect the different main classes of secondary metabolites contained in these plants that could be responsible for their antimicrobial or pharmacological activities. These qualitative essays were done using colorimetric methods as described by [20].

Antibacterial assays

The antibacterial activities of plant extracts and used antibiotics were performed by determining the minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) using broth microdilution methods described by [21] and 22].

Determination of minimal inhibitory concentrations

In a sterile 96-wells microplate initially containing 100 µL of MHB culture medium, 100 µL of extracts dissolved in DMSO 2.5 % was added to first wells and then serially distributed to other wells. Then 100 µL of bacterial suspension ($2x10^6$ UFC/mL) were added to all wells to afford 200 µL. DMSO 2.5 % and Ciprofloxacin, the reference antibiotic, were respectively used as negative and positive controls. Plates were then covered and incubated at 37°C for 18 hrs after which 40 µL of INT 0.2 % were introduced and plates were re-incubated at 37°C for 30 min. The INT (yellow colour) is reduced by viable bacteria to yield pink colour. The MIC was defined as the lowest concentration that prevented the change of this colour and which resulted in the complete inhibition of bacterial growth. Each assay was done in triplicate and two independent times. Plant extract was considered to have strong activity if MIC<100 µg/mL, significant activity if 100≤MIC≤512 µg/mL, moderate activity if 512<MIC≤2048 µg/mL and weak activity if MIC>2048 µg/mL [23].

Determination of minimal bactericidal concentrations

In a sterile new 96-wells microplate containing 150 µL of MHB culture medium, 50 µL from the previous wells content that did not received INT and that correspond to MICs values were added. Plate was covered and incubated at 37°C for 48 hrs after which 40 µL of INT 0.2 % were introduced. MBCs of each sample were determined as described in case of MICs determination. Each assay was performed in triplicate and two independent times. Plant extract or antibiotic was considered to bactericidal effect if MBC/MIC≤4 and bacteriostatic effect if MBC/MIC>4 [22,23].

Determination of MICs of the combination extract-antibiotics

Plants extracts were combined to conventional antibiotics commonly used in nosocomial infections treatment to evaluate the antibiotic-potentiation effects of bioactive compounds contained in these plants. Serial liquid microdilution method was also used [22]. One hundred microliter of MHB were introduced in a sterile 96-wells microplate followed by 100 µL of antibiotic solution (256 µg/mL final concentration) in first wells. After serial dilution, 50 µL of extract solution followed by 50 µL of bacterial inoculum ($4x10^6$ UFC/ml) were then added. Microplate was then covered and incubated at 37°C for 18 hrs. After this incubation time, 40 µL of INT 0.2 % were introduced and the MICs of antibiotics alone and those of antibiotic-extract combinations were determined as described above. Preliminary tests were carried out on *Pseudomonas aeruginosa* PA124 strain which was the most resistant bacteria and extracts were tested at MIC/2, MIC/4, MIC/8 and MIC/16 (results are summarized in Table 1 of supplementary file). From the obtained results, two concentrations of extracts (MIC/2 and MIC/4) were choice to be tested on the other studied bacteria. The effects of combination were evaluated by calculating the improvement activity factors (IAF) of each combination using the following formulation: MIC of antibiotic alone / MIC of combination (Tables 5-10). Each assay was also performed in triplicate and two independent times. Extract and antibiotic were considered to have synergistic, indifference or antagonistic effects if IAF≥2, IAF=1 or IAF≤0.5 respectively [24].

Results

Phytochemical analysis

Phytochemical screening of plant extracts showed selective distribution of main classes of secondary metabolites in these plants. Each plant extract contained at least three phytochemicals. All metabolites (alkaloids, polyphenols, flavonoids, triterpenes, steroids and saponins) were found in epicarps of *Cocos nucifera*. Bark and leaves of this plant extracts contained five and four metabolites respectively. Steroids were absent in bark extract while steroids and saponins were absent in leaves extract. These two metabolites were also absent in mesocarps part of *Musa sapientum* meanwhile epicarps part of this plant contained only three metabolites which are saponins, polyphenols and flavonoids. All these bioactive compounds were found in *Glycine max* extracts except saponins (Table 3).

Antibacterial activity of plant extracts alone

Table 4 shows antibacterial activities of different tested extracts. Six extracts were used and four of them selectively presented an inhibitory effect against studied bacterial strains. Extract from different parts of *Cocos nucifera* were most active. Bark extract of this plant inhibited the growth of 90% of bacteria with MIC ranging from 128 to 2048 µg/ml and with significant activity (100≤MIC≤512 µg/mL) against 50% of bacteria. Moreover, it showed bactericidal effects (MBC/MIC≤4) against 45% of bacteria: four *Escherichia coli* strains (ATCC8739, AG100A, $AG100A_{Tet}$ and AG102), two *Klebsiella pneumoniae* strains (Kp55 and Kp63), *Providencia stuartii* NEA16 and two *Enterobacter aerogenes* strains (ATCC13048 and EA294) and bacteriostatic affects MBC/MIC>4 against other strains. Epicarps extract of the same plant presented an antibacterial potential against 75% of strains also with MIC ranging 128 to 2048 µg/ml and with significant activity against 40% of bacterial strains. It showed bactericidal effects against two strains which are *E. coli* (ATCC8739) and *Providencia stuartii* NEA16. They were followed by leaves part of this plant which exhibited inhibitory activity against 60% of bacteria with significative activity only on two *E. coli* strains (ATCC8739 and AG102) and showed bactericidal effects also against two strains including *E. coli* (ATCC8739) and *P. stuartii* NEA16. These three extracts were most active especially on *E. coli* strains (MIC=128-256 µg/mL) and less active on *Pseudomonas aeruginosa* strains. In the other hand, extracts from *Glycine max* were moderately active (512<MIC≤2048 µg/mL) against 25% of studied bacteria and did not showed any bactericidal effects. However, mesocarps and epicarps extracts from *Musa sapientum* did not presented any antibacterial activity on all studied strains as well as DMSO 2.5% used as negative control. Ciprofloxacin used as positive control inhibited the growth of all studied bacterial with bactericidal effects against 55% of strains. Its antibacterial potential was comparable to that of *C. nucifera* bark extract.

Antibacterial activity of antibiotic-extract combination

Tested plant extracts were associated to commonly used antibiotics to evaluate the effects of their combination against some

of studied bacteria. Preliminary essays were carried out on *P. aeruginosa* PA124 and synergistic effects were mostly obtained at MIC/2 and MIC/4 of extracts (see Table 5). These two concentrations were then selected for testing on the other bacteria as shown in Tables 5-10. *Glycine max* extract at all concentrations potentiated the activity of 56% (5/9) of antibiotics against at least 70% of bacteria with improvement activity factors (IAF) ranging from 2 to 64. These antibiotics are Oxacillin, Ciprofloxacin, Doxocyclin, Ofloxacin and Flucloxacillin. It also improved the activity of Gentamicin and Azithromycin on 60% of studied bacteria strains. The activities of Thiamphenicol and Erythromycin were less improved and they decreased on some bacteria as *E. coli* ATCC8739, *P. stuartii* and *K. pneumoniae* strains (Table 6). Leaves extract of *Cocos nucifera* also enhanced the activity of 67% (6/9) of antibiotics against at least 70% of bacteria and with IAF values ranging from 2 to 256. It highly increased the antibacterial potential of Oxacillin, Gentamicin, Ciprofloxacin and Ofloxacin against almost all bacteria. Only the activity of Flucloxacillin was less improved. In presence of this extract, some bacteria including *E. aerogenes* CM64, *K. pneumoniae* ATCC1129, *P. stuartii* (NAE16 and ATCC2991) become more susceptible toward used antibiotics as IAF≥8. However, MICs values of this extract combined with Thiamphenicol and Azithromycin increased against *P. aeruginosa* PA01 strain (Table 7). In contrary to leaves, bark and epicarps parts of this plant potentiated more the activities of antibiotics with IAF values of 16-256 in many cases. In presence of these two extracts, the inhibitory potential of all antibiotics (100%) increased against at least 70% of bacteria at all used concentrations in case of bark and at MIC/2 in case of epicarps. On the one hand, the bark extract highly improved the activities of Oxacillin, Thiamphenicol, Erythromycin and Gentamicin as IAF≥16 were obtained against the majority of bacteria. *E. coli* AG102, *E. aerogenes* (ATCC13048 and CM64), *K. pneumoniae* ATCC11296 and *P. stuartii* ATCC29916 were more susceptible towards the combination of this extract with antibiotics. However, few antagonistic effects (IAF≤0.5) were obtained only on *K. pneumoniae* Kp55 strain (Table 8). On the other hand, epicarps extract highly enhanced the activity of many antibiotics including Oxacillin, Gentamicin, Ciprofloxacin and Doxocyclin against the majority of bacteria making them more susceptible. These bacteria were *E. aerogenes* CM64, *K. pneumoniae* (ATCC11296 and Kp55) and *P. aeruginosa* PA01. No antagonistic effects were observed between this extract and all antibiotics (Table 9). Extracts from *Musa sapientum* which showed no antibacterial activity against all studied strains have less improved the inhibitory power of several antibiotics. Mesocarps part of this plant potentiated the activity of 34% of antibiotics (Oxacillin, Thiamphenicol and Ciprofloxacin) against almost 70% of bacteria (Table 10) meanwhile epicarps part displayed this effect only of 23% of antibiotics (Oxacillin and Doxocyclin) (Table 11). In the presence of each of these extracts, some few bacterial were highly susceptible vis-à-vis selected antibiotics and some antagonistic effects were also obtained mainly with Erythromycin, Azithromycin and Ofloxacin in case of mesocarps and with Erythromycin, Thiamphenicol and Ciprofloxacin in case of epicarps. Usually, *P. aeruginosa* strains were less susceptible or more resistant vis-à-vis all combination and many cases of indifferent effects (IAF=1) were observed.

Discussion

Antibacterial activities of plant extracts alone

Resistance is the ability of a bacteria against the antagonizing effect on an antibacterial agent upon reproduction prevention or bactericidal. Microbial resistance to classic antibiotics and its rapid progression have raised concern in the treatment of infectious diseases. Recently, many studies have been directed towards finding promising solutions to overcome these problems [25]. In the present work, the antibacterial activity of the edible plants extracts against examined microorganisms was assessed by determining the MIC values of each extract. Results indicated that extracts from *Cocos nucifera* were most active. Extract from bark part of this plant showed the highest inhibitory potential with significant activity against the half of studied bacteria and epicarps and leaves parts displayed this effect respectively on 40% and 10% of bacteria. Endocarp of *C. nucifera* using methanolic and aqueous extracts were reported to have strong antibacterial activity against *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Micrococcus luteus* strains. Also, husk extracts of this plant showed inhibitory effects of some Gram-positive and Gram-negative bacteria including some used in this study [26,27]. Leaves extract of *C. nucifera* was found to exhibit antibacterial activity on some strains among which *Salmonella typhi*, *E. coli*, *Acetobacter* spp, *Bacillus cereus* and *shigella dysenteriae*. Furthermore, coconut shells or its oils were reported to possess antibacterial, antifungal and antiviral properties [10,28]. In another study, the mesocarp part extracts of *C. nucifera* fruit have demonstrated high antimicrobial activity against *E. coli* and *S. typhi* [29]. Some studies also demonstrated the antibacterial action of bark and root extracts of *C. nucifera* against microbes involved in urinary tract infections among which those used in the present work like *P. aeruginosa*, *E. coli* and *K. pneumoniae*. Apart from their biological activities, various parts of *C. nucifera* are more exploited in traditional pharmacopoeia to treat infections caused by pathogens [30,31,32]. This can also explain the bactericidal effects of all tested parts of this plant against selected studied bacteria. To the best of our knowledge, the antimicrobial activity of epicarp part of this plant was not previously investigated. This activity would be reported herein for the first time. Tested crude extract from *Glycine max* moderately inhibited the growth of five studied bacteria including two *E. coli*, two *K. pneumoniae* and one *P. stuartii* strains. It was not active against *P. aeruginosa* and this result corroborates that obtained by [18] which showed a weak inhibition of this bacterial strain by methanolic extract of soybean (*G. max*). The seed extracts of this plant have been reported to possess antibacterial activity against some Gram-positive and Gram-negative strains including *Staphylococcus aureus*, *Bacillus cereus*, *K. pneumoniae* and *P. aeruginosa*. Ethanolic extracts were more active than the other extracts [33,34]. In another study carried out on two varieties of methanolic extracts of *G. max* seeds, there was absence or very weak inhibition of *P. aeruginosa* growth and moderated inhibition of *K. pneumoniae* growth. These results are also similar to those obtained in the present work [35]. The epicarp and mesocarp extracts of *Musa sapientum* plant used in the present study did not show any activity against all studied bacteria. In contrary to these results, methanolic extracts from seeds of this plant were reported to exhibit moderate and weak activities on some sensitive bacterial flora. Moreover, previous studies on methanolic extracts from leaves of *M. sapientum* demonstrated their antibacterial and antioxidant properties [36,37,38]. The absence of activity of the other parts of this plant used in this work could be since studied bacteria are more resistant. Also, biological activity of a plant

extract can be affected by structural variations of its bioactive compounds, such as stereochemistry [39].

Phytochemical of plants extracts

Face with respect of this serious problem of microbial resistance, therapeutic and pharmacological factories tried to use from novel sources for antimicrobial agents to produce strong antibiotic drugs. The medicinal values of plants are attributed to the presence of some chemical substances which produce a definite physiological action on the human body. These chemical substances are called phytochemicals. These bioactive compounds are responsible for antimicrobial activity of plant extracts *in vitro*. Some common examples of phytochemicals are flavonoids, alkaloids, saponins, glycosides, sterols, tannins, phenols and terpenes [40,41]. In the present work, each tested plant extract contained at least three secondary metabolisms. Recorded data revealed the high antioxidant and antimicrobial content of *G. max*. soybean seeds which are rich in proteins, isoflavones and phytoestrogens. While genistein, a soy isoflavone, has also been reported to possess anti-cancerous, anti-inflammatory, antioxidant and anti-osteoporosis effects and is considered as a potential compound for metabolic disorders' treatment. Numerous other bioactive compounds such as phenolic acids, flavonoids, phytosterols, anthocyanins, sphingolipids and saponins were previously detected in *G. max* [34,35,42,43]. Some of these constituents (polyphenols, flavonoids and steroids) were also detected in seeds extract of this plant used in the present study. Phytochemical screening of methanolic extracts from leaves of *M. sapientum* in the literature [38] indicated the presence of various types of phytochemical active compounds including alkaloids, phenols, flavonoids, saponins, steroids and tannins that were also found in mesocarp and epicarp of this plant in the present work. Despite the presence of these bioactive components in these tested extracts, the absence and weak activities of *M. sapientum* and *G. max* respectively could be due to the low quantity of these phytochemicals or to the fact that they could have antagonistic effects acting on the same site of bacterial cell. Concerning *C. nucifera* plant, epicarps contained all analysed phytochemicals whereas only steroids were absent in bark on the one hand and steroids and saponins were absent in leaves on the other hand. Some uses of the plant were partially confirmed by previous studies demonstrating the presence of flavonoids, phenols, tannins, leucoanthocyanidins, triterpenes, steroids, saponins and alkaloids in ethanolic extract of coconut fibre (mesocarp). Other compounds identified in leaf epicuticular wax were lupeol methylether, skimmiwallin and isoskimmiwallin. Moreover, various isolated compounds from different parts of the coconut fruit were reported to exhibit different activities [44,45]. The fact that bark and epicarp extracts were most active than leaves extract in the present work could be justified by the presence of steroids in these leaves that could negatively influence their antibacterial potential inhibiting the activity of other bioactive compounds.

Synergistic effects of the combination of antibiotics and extracts

This work was then extended to evaluating the antibacterial effects of combinations of conventional antibiotics belonging different classes and edible plant extracts against several multidrug resistant strains. Many strategies for avoiding, inhibiting, or bypassing resistance mechanisms in pathogens have been attempted. A related tactic involves treatment with combinations of inhibitory compounds that have different modes of action. This combinational approach has been used in the past to overcome resistance and has also been applied with success in the treatment of diseases such as cancer and HIV infection [4]. Therefore, the antimicrobial activity may be enhanced by synergistic effect of natural product and antimicrobial drugs. Phytotherapy has many potentially significant advantages associated with the synergistic interactions in combatting microbial resistance like increased efficiency, reduction of undesirable effects, increase in the stability or bioavailable of the free agents and obtaining an adequate therapeutic effect with relatively of small doses, when compared with a synthetic medication [46,47]. Numerous previous studies proving the improvement of the antimicrobial activity of commonly used antibiotics by medicinal as well as edible plants extracts have been reported [14,50-52]. Synergistic effects or interactions of two or more antimicrobial agents could be mediated through some generally accepted mechanisms including inhibition of protective enzymes, combination of membrane active agents, sequential inhibition of common biochemical pathways and the use of membranotropic agents to enhance the diffusion of other antimicrobials [47,51]. In the present work, many cases of synergism between all tested plant extracts and antibiotics were obtained as the MICs of the combinations were less than those of antibiotics alone and IAF values ≥2. In this case, these effects could be due to the fixation of bioactive compounds of plant and antibiotic at different sites of the bacterial cell as the structures and the mechanisms of action of these compounds are unknown. It has been reported the synergistic effect between *C. nucifera* extract and methicillin and indifferent effect between vancomycin and this extract against methicillin-resistant *S. aureus* isolate [39]. Meanwhile, studies concerning the combinations of *G. max* and *M. sapientum* as well as their isolated compounds with antibiotics have not been reported. Moreover, it is clearly accepted that a substance can be considered as an efflux pumps inhibitor (EPI) when it highly enhances (IAF≥8) the antibacterial activity of almost 70% of effluxed antibiotics against 70% of strains. The efflux pumps inhibition allows to maintain higher the intracellular concentration of removal antibiotic and restores its antibacterial activity [52]. Results obtained herein indicate that extracts from all part of *C. nucifera* (Tables 7-9) could contain bioactive compounds displaying the role of EPI. Several natural products from plants acting as EPIs have been reported. Examples include reserpine, an alkaloid isolated from *Rauwolfia vomitoria* that has been shown to restore the activity of fluoroquinolones and tetracycline in multidrug resistant *S. aureus* isolates and in *Bacillus subtilis* strain inhibiting the *Bmr* EPs; Also, two isopimaranes isolated from *Lycopus europaeus* improved the antibacterial potential of tetracycline and erythromycin in methicillin-resistant *S. aureus* inhibiting the *TetK* and *MsrA* Eps [53-55]. However, some few antagonistic effects obtained in this work could result to the competitive inhibitions between phytochemicals and antibiotics in the same target sites of cell and indifferent effects observed indicate that the inhibitory effect of extract has not changed against concerned bacteria and could not thus influence the antibacterial activity of antibiotic.

Table 1. Plants extracts, their extractive yields, traditional use, and biological activities

Plants samples	Family	Part of plant used and extractive yields (%)	Traditional usage	Biological activities	Identified or isolated bioactive compounds
Glycine max	Fabaceae	Seeds : 6.03	It is used in the treatment of types of cancers such as prostate, mammary breast and uterus; it also treat osteoporosis, inflammations and cardiovascular diseases [18,56]	Ethanolic extracts of seeds and leaves active against *Ec, Sa, Ca* and *An*; it has antioxidant, immunomodulatory, antiviral, antidiabetic, antihypertensive, anti-obesity and antimicrobial activities [43,57]	Isoflavones, amino acids, saponins, tannins, phytosterols, phenolic compounds, flavonoids, fats, proteins, carbohydrates [34,58]
Cocos nucifera	Arecaceae	Epicarps : 20.84 Bark : 18.85 Leaves : 9.92	Treats diarrhea, arthritis, urogenital tract infection, fever and malaria. Hot water extract of husk is used in the treatment of dysmenorrhea, cancers, fractures and sprains. Seeds oil are applied topically for scabies and ringworms infections. Leaves are used to treat Alzheimer's disease; Bark aqueous extract and tea are used to treat amenorrhea and venereal diseases [17,26,32,45]	Aqueous and ethyl acetate extracts active against *Ec, Ca, Sa, Ka, Pa, Bp*. It also has antiviral, anti-inflammatory, antineoplastic, antioxidant, anticancer, antiarthritic, anthelmintic, analgesic, antioxidant, diuretic, antihypertensive, aphrodisiac, antiseptic and antidotal activities [26,27,39,45]	Saponins, lignin, alkaloids, phenols, tannins, steroids, leucoanthocyanidins, flavonoids, triterpenes. Compounds such as methylether, skimmiwallin and isoskimmiwallin iso lated from leaves [27,32,45,59]
Musa sapientum	Musaceae	Mesocarps : 41.12 Epicarps : 9.40	Fruits, leaves, root, peels and stalks parts are used to treat inflammation, dysentery, worms, diarrhea, snakebite, hyperglycaemia, diabetes, ulcers [19,60]	Different parts display antioxidant, anti-tumoral, antimutagenic, anthelmintic, antibacterial, antiulcerogenic activities; aqueous and methanolic extracts active against *Ec, Sa, Bs, Kp, Pa, St, Mm, Sd, Sp, Ea, Ca, Ma* [37,60]	Alkaloids, steroids, tannins, flavonoids, campesterol, saponins, stigmasterol, β-sitosterol, 3-O-galactoside, cardiac glycosides, 3-O-glucoside 3-O-rhamnosyl-glucoside [38,61,62]

Ec : Escherichia coli *Sa : Staphylococcus aureus* *Ca : Candida albicans* *An : Aspergillus niger* *Ka : Klebsiella aerogenes* *Pa : Pseudomonas aeruginosa* *Bs: Bacillus subtilis* *Bp: Bacillus pumilus* *St : Salmonella typhi* *Mm : Morganella morganii* *Sd : Shigella dysenteriae* *Ea : Enterobacter aerogenes* *Ma : Moraxella catarrhalis* Mesocarps part of *Musa sapientum* had the higher extractive yield (41.12%)

Table 2. Studied bacterial and their main features

Species	Types	Characteristics	References
Escherichia coli	ATCC8739	Reference strain	[63]
	AG100A	*E. coli* K-12 expressing △acrAB: KAN^r	[64]
	AG102	△acrAB mutant AG100, owing acrF gene markedly over expressed TET^r	[65]
	$AG100A_{Tet}$	△acrAB mutant AG100, with over-expressing *acrF* gene; TET^r	[66]
	W3110	Wild type *E. coli* K-12	[67]
	MC4100	Wild type *E. coli* expressed ABC pumps KAN^r	
Enterobacter aerogenes	ATCC13048	Reference strain	[63]
	EA27	Clinical MDR isolate exhibiting energy-dependent norfloxacin and chloramphenicol efflux with KAN^r, AMP^r, NAL^r, STR^r, TET^r	[68,69]
	EA289	KAN sensitive derivative of EA27	[68]
	EA294	EA289 expressing acrA: KAN^r	
	EA298	EA289 expressing *tolC* : KAN^r	[68,70]
Klebsiella pneumoniae	ATCC11296	Reference strain	[63]
	Kp55	Clinical MDR isolate, TET^r, AMP^r, ATM^r, CEF^r	[71]
	Kp63	Clinical MDR isolate, TET^r, CHL^r, AMP^r, ATM^r	
Providencia stuartii	NEA16	Clinical MDR isolate, AcrAB-TolC	[63]
	PS299645	Clinical MDR isolate, AcrAB-TolC associated to types OMPF and OMPC porins	
Pseudomonas aeruginosa	PA 01	Reference strain	[63]
	PA 124	Clinical MDR isolate, expressing *MexAB-OprM*	[64]

KAN^r, TET^r, AMP^r, NAL^r, STR^r, ATM^r, CEF^r, CHL^r : resistant (r) to kanamycin, tetracycline, ampicillin, nalidixic acid, streptomycin, aztreonam, cefepime, chloramphenicol, respectively; MDR : Multidrug-resistant ; AcrAB-TolC, AcrAB and TolC are efflux pumps.

Table 3. Phytochemical composition of different plant extracts

Phytochemicals	Plant extracts and composition					
	Glycine max	*Cocos nucifera*			*Musa sapientum*	
		epicarps	leaves	barks	mesocarps	epicarps
Alkaloids	+	+	+	+	+	-
Polyphenols	+	+	+	+	+	+
Flavonoids	+	+	+	+	+	+
Triterpenes	+	+	+	+	+	-
Steroids	+	+	-	-	-	-
Saponins	-	+	-	+	-	+

(-): absence of phytochemicals (+): presence of phytochemicals

Table 4. Minimal inhibitory and bactericidal concentrations of plant extracts and ciprofloxacin

Bacterial strains	Plant extracts (µg/mL)												Ciprofloxacin		
	Glycine max Seeds			*Cocos nucifera*											
				leaves			barks			epicarps					
	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R	MIC	MBC	R
Escherichia coli															
ATCC8739	1024	-	>2	256	1024	4	128	512	4	128	512	4	0.5	1	2
AG100A	2048	-	>1	-	nt	nd	512	512	1	-	nt	nd	4	32	8
AG102	-	nt	nd	128	2048	16	128	512	4	128	2048	16	2	8	4
MC4100	-	nt	nd	2048	-	>1	2048	-	>1	256	2048	8	4	8	2
$AG100A_{Tet}$	-	nt	nd	-	nt	nd	1024	2048	2	256	2048	8	8	32	4
W3110	-	nt	nd	-	nt	nd	1024	-	>2	1024	-	>2	2	2	1
Enterobacter aerogenes															
ATCC13048	-	nt	nd	-	nt	nd	512	2048	4	256	2048	8	1	8	8
EA289	-	nt	nd	-	nt	nd	-	nt	nd	-	nt	nd	2	16	8
EA294	-	nt	nd	2048	-	>1	512	2048	4	512	-	>4	2	8	4
EA27	-	nt	nd	2048	-	>1	2048	-	>1	2048	-	>1	4	64	16
EA298	-	nt	nd	2048	-	>1	512	-	>4	256	-	>8	2	4	2
CM64	-	nt	nd	2048	-	>1	512	-	>4	-	nt	nd	4	32	8
Klebsiella pneumoniae															
ATCC11296	1024	-	>2	2048	-	>1	512	-	>4	-	nt	nd	8	64	8
Kp55	2048	-	>1	-	nt	nd	512	2048	4	512	-	>4	8	16	2
Kp63	-	nt	nd	2048	-	>1	512	1024	2	1024	-	>2	16	128	8
Providencia stuartii															
ATCC29916	-	nt	nd	1024	-	>2	-	nt	nd	2048	-	>1	16	64	4
NEA16	-	nt	nd	1024	1024	1	1024	1024	1	1024	1024	1	16	128	8
PS2636	1024	-	>2	2048	-	>1	1024	-	>2	2048	-	>1	2	8	4
Pseudomonas aeruginosa															
PA01	-	nt	nd	-	nt	nd	1024	-	>2	1024	-	>2	8	32	4
PA124	-	nt	nd	-	nt	nd	2048	-	>1	-	nt	nd	32	256	8
PSBS (%)	25			60			90			75			100		

The two parts of *Musa sapientum* (Mesocarps and epicarps) did not showed any antibacterial activity till 2048 µg/ml DMSO 2.5% used as negative control does not showed inhibitory effect against all bacteria [72-78] MIC : minimal inhibitory concentration MBC : minimal bactericidal concentration R : MBC / MIC ratio (a sample is considered as bacteriostatic or bactericidal when this ratio is >4 or ≤4 respectively) (-) : MIC or MBC > 2048 µg/mL nt : not tested nd : not determined (as no MIC and MBC values were not observed till 2048 µg/mL) PSBS : percentage of susceptible bacteria to substances Extract was considered to have strong activity if MIC<100 µg/mL, significant activity if 100≤MIC≤512 µg/mL, moderate activity if 512<MIC≤2048 µg/mL and weak activity if MIC>2048 µg/mL

Table 5. Minimal inhibitory concentrations of antibiotics combined with plant extracts against PA124

Plant extracts	MICs of antibiotics	Antibiotics									PBS (%)
		OXA	THI	ERY	GEN	CIP	DOX	AZI	OFL	FLU	
	0	32	32	2	4	32	16	64	1	32	
Glycine max (Seeds)	MIC/2	16(2)	32(1)	1(2)	0.25(16)	2(16)	2(8)	2(32)	1(1)	4(8)	77.77
	MIC/4	16(2)	32(1)	2(1)	0.25(16)	8(4)	2(8)	2(32)	1(1)	4(8)	66.66
	MIC/8	32(1)	32(1)	2(1)	0.5(8)	32(1)	2(8)	16(4)	1(1)	8(4)	44.44
	MIC/16	32(1)	32(1)	2(1)	2(2)	32(1)	8(2)	32(2)	1(1)	16(2)	44.44
Cocos nucifera (epicarps)	MIC/2	16(2)	4(8)	1(2)	4(1)	8(4)	8(2)	64(1)	0.5(2)	32(1)	66.66
	MIC/4	16(2)	8(4)	1(2)	4(1)	8(4)	8(2)	64(1)	1(1)	32(1)	55.55
	MIC/8	32(1)	8(4)	2(1)	4(1)	32(1)	16(1)	64(1)	1(1)	32(1)	11.11
	MIC/16	32(1)	16(2)	2(1)	4(1)	32(1)	16(1)	64(1)	1(1)	32(1)	11.11
Cocos nucifera (leaves)	MIC/2	1(32)	4(8)	2(1)	4(1)	16(2)	0.5(32)	64(1)	1(1)	16(2)	55.55
	MIC/4	8(4)	8(4)	2(1)	4(1)	16(2)	0.5(32)	64(1)	1(1)	32(1)	44.44
	MIC/8	16(2)	32(1)	2(1)	4(1)	32(1)	2(8)	64(1)	1(1)	32(1)	22.22
	MIC/16	32(1)	32(1)	2(1)	4(1)	32(1)	2(8)	64(1)	1(1)	32(1)	11.11
Cocos nucifera (barks)	MIC/2	32(1)	4(8)	2(1)	4(1)	16(2)	0.25(64)	1(64)	0.5(4)	4(8)	66.66
	MIC/4	32(1)	16(2)	2(1)	4(1)	16(2)	0.25(64)	2(32)	0.5(2)	16(2)	66.66
	MIC/8	32(1)	16(2)	2(1)	4(1)	32(1)	1(16)	8(8)	1(1)	4(8)	44.44
	MIC/16	32(1)	32(1)	2(1)	4(1)	32(1)	1(16)	32(2)	1(1)	16(2)	33.33
Musa sapientum (mesocarps)	MIC/2	2(16)	32(1)	2(1)	8(0.5)	64(0.5)	0.25(64)	2(32)	0.5(2)	2(16)	55.55
	MIC/4	16(2)	32(1)	2(1)	8(0.5)	64(0.5)	1(16)	8(4)	0.5(2)	2(16)	55.55
	MIC/8	32(1)	32(1)	2(1)	4(1)	64(0.5)	2(8)	2(32)	0,5(2)	16(2)	44.44
	MIC/16	32(1)	32(1)	2(1)	4(1)	64(0.5)	2(8)	2(32)	0,5(2)	32(1)	33.33
Musa sapientum (epicarps)	MIC/2	8(4)	16(2)	2(1)	4(1)	64(0.5)	2(8)	64(1)	0.5(2)	4(8)	55.55
	MIC/4	8(4)	16(2)	2(1)	4(1)	64(0.5)	2(8)	64(1)	1(1)	16(2)	44.44
	MIC/8	32(1)	32(1)	2(1)	4(1)	64(0.5)	4(4)	64(1)	1(1)	16(2)	33.33
	MIC/16	32(1)	32(1)	2(1)	4(1)	64(0.5)	8(2)	64(1)	1(1)	32(1)	11.11

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination Most synergistic cases were obtained at MIC/2 and MIC/4 of plant extracts MICs: minimal inhibitory concentrations PBS : percentage of bacterial susceptibility 0: MICs values of antibiotics tested alone OXA: Oxacillin THI: Thiamphenicol ERY: Erythromycin GEN: Gentamicin CIP: Ciprofloxacin DOX: Doxycycline AZI: Azithromycin OFL: Ofloxacin FLU: Flucloxacillin The MIC of extract sample is those showed in Table 4

Table 6. Minimal inhibitory concentrations of antibiotics combined with *Glycine max* extract

Antibiotics	MICs of plant extract	Bacterial strains and concentrations of antibiotics										PBS (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		ATCC8739	AG102	ATCC13048	CM64	ATCC11296	KP55	ATCC29916	NAE16	PA01	PA124	
Oxacillin	0	32	32	64	64	64	8	64	64	64	32	
	MIC/2	8(4)	16(2)	16(4)	8(8)	32(2)	4(2)	8(8)	32(2)	32(2)	16(2)	**100**
	MIC/4	16(2)	32(1)	16(4)	8(8)	32(2)	4(2)	32(2)	32(2)	32(2)	16(2)	**90**
Thiamphenicol	0	2	2	4	4	32	16	16	8	2	32	
	MIC/2	4(0.5)	1(2)	4(1)	4(1)	32(1)	32(0.5)	64(0.25)	1(8)	2(1)	32(1)	20
	MIC/4	4(0.5)	1(2)	4(1)	4(1)	32(1)	32(0.5)	64(0.25)	1(8)	2(1)	32(1)	20
Erythromycin	0	1	2	16	16	16	8	16	16	16	2	
	MIC/2	2(0.5)	1(2)	16(1)	8(2)	32(0.5)	16(0.5)	2(8)	0.5(32)	32(0.5)	1(2)	50
	MIC/4	2(0.5)	1(2)	16(1)	8(2)	32(0.5)	16(0.5)	2(8)	0.5(32)	32(0.5)	2(1)	40
Gentamicin	0	2	1	16	8	16	8	16	8	16	4	
	MIC/2	0.5(4)	0.25(4)	0.25(64)	2(4)	16(1)	8(1)	8(2)	16(0.5)	16(1)	0.25(16)	60
	MIC/4	0.5(4)	0.25(4)	16(1)	2(4)	16(1)	8(1)	8(2)	16(0.5)	16(1)	0.25(16)	50
Ciprofloxacin	0	1	2	1	4	8	8	16	16	8	32	
	MIC/2	0.5(2)	2(1)	0.25(4)	4(1)	1(8)	4(2)	8(2)	8(2)	1(8)	2(16)	**80**
	MIC/4	0.5(2)	2(1)	0.5(2)	4(1)	2(4)	4(2)	16(1)	8(2)	4(2)	8(4)	**70**
Doxycycline	0	2	8	2	2	4	8	2	16	4	16	
	MIC/2	0.5(4)	2(4)	0.25(8)	1(2)	4(1)	2(4)	1(2)	16(1)	1(4)	2(8)	**80**
	MIC/4	0.5(4)	2(4)	0.5(4)	1(2)	4(1)	2(4)	1(2)	16(1)	2(2)	2(8)	**80**
Azithromycin	0	4	16	16	16	4	4	4	16	4	64	
	MIC/2	2(2)	16(1)	4(4)	16(1)	0.5(8)	4(1)	1(4)	16(1)	0.5(8)	2(32)	60
	MIC/4	2(2)	16(1)	4(4)	16(1)	2(2)	4(1)	2(2)	16(1)	2(2)	2(32)	60
Ofloxacin	0	2	2	2	16	4	2	2	16	4	1	
	MIC/2	0.5(4)	0.5(4)	0.5(4)	16(1)	2(2)	0.25(8)	0.25(8)	16(1)	2(2)	1(1)	**70**
	MIC/4	0.5(4)	0.5(4)	0.5(4)	16(1)	2(2)	(1)	0.5(4)	16(1)	2(2)	1(1)	60
Flucloxacillin	0	16	2	32	4	32	8	2	32	4	32	
	MIC/2	4(4)	0.5(4)	16(2)	4(1)	8(4)	4(2)	0.5(4)	32(1)	1(4)	4(8)	**80**
	MIC/4	4(4)	0.5(4)	16(2)	4(1)	8(4)	4(2)	0.5(4)	32(1)	1(4)	4(8)	**80**

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination 0: MICs values of antibiotics tested alone PBS : percentage of bacterial susceptibility *E. coli: Escherichia coli* *E. aerogenes: Enterobacter aerogenes* *K. pneumoniae: Klebsiella pneumoniae* *P. aeruginosa: Pseudomonas aeruginosa* *P. stuartii: Providencia stuartii* The MIC values of each plant extract is those showed in Table 4.

Table 7. Minimal inhibitory concentrations of antibiotics combined with leaves extract of *Cocos nucifera*

Antibiotics	MICs of plant extract	Bacterial strains and concentrations of antibiotics										PBS (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		ATCC8739	AG102	ATCC13048	CM64	ATCC11296	KP55	ATCC29916	NAE16	PA01	PA124	
Oxacillin	0	32	32	64	64	64	8	64	64	64	32	
	MIC/2	8(4)	8(4)	32(2)	0.25(256)	16(4)	0.5(16)	32(2)	16(4)	16(4)	16(2)	**100**
	MIC/4	8(4)	16(2)	32(2)	0.25(256)	16(4)	0.5(16)	32(2)	16(4)	16(4)	16(2)	**100**
Thiamphenicol	0	2	2	4	4	32	16	16	8	2	32	
	MIC/2	0.125(8)	0.125(16)	0.25(16)	0.125(32)	16(2)	4(4)	16(1)	16(0.5)	4(0.5)	4(8)	**70**
	MIC/4	1(1)	0.25(8)	0.25(16)	0.25(16)	16(2)	8(2)	16(1)	16(0.5)	4(0.5)	8(4)	60
Erythromycin	0	1	2	16	16	16	8	16	16	16	2	
	MIC/2	1(1)	0.25(8)	2(8)	2(8)	8(2)	2(4)	0.5(32)	0.25(64)	8(2)	1(2)	**90**
	MIC/4	1(1)	0.25(8)	2(8)	2(8)	8(2)	8(1)	0.5(32)	1(16)	8(2)	1(2)	**80**
Gentamicin	0	2	1	16	8	16	8	16	8	16	4	
	MIC/2	0.25(8)	0.125(8)	0.25(64)	0.5(16)	8(2)	1(8)	2(8)	4(2)	8(2)	4(1)	**100**
	MIC/4	0.25(8)	0.25(4)	0.25(64)	0.5(16)	16(1)	1(8)	2(8)	4(2)	8(2)	4(1)	**80**
Ciprofloxacin	0	1	2	1	4	8	8	16	16	8	32	
	MIC/2	0.25(4)	1(2)	0.25(4)	0.125(32)	0.5(16)	0.5(16)	0.5(32)	1(16)	1(8)	8(4)	**100**
	MIC/4	0.25(4)	1(2)	0.25(4)	0.25(16)	0.5(16)	0.5(16)	2(8)	1(16)	1(8)	8(4)	**100**
Doxycycline	0	2	8	2	2	4	8	2	16	4	16	
	MIC/2	0.5(4)	8(1)	2(1)	0.25(8)	0.5(8)	16(0.5)	2(1)	1(16)	0.25(16)	8(2)	60
	MIC/4	1(2)	8(1)	2(1)	0.25(8)	1(4)	16(0.5)	2(1)	1(16)	0.25(16)	8(2)	60
Azithromycin	0	4	16	16	16	4	4	4	16	4	64	
	MIC/2	8(0.5)	1(16)	4(4)	8(2)	0.25(16)	4(1)	0.5(8)	8(2)	8(0.5)	64(1)	60
	MIC/4	8(0.5)	1(16)	8(2)	8(2)	0.25(16)	4(1)	0.5(8)	1(16)	8(0.5)	64(1)	60
Ofloxacin	0	2	2	2	16	4	2	2	16	4	1	
	MIC/2	1(2)	0.25(8)	1(2)	8(2)	0.25(32)	1(2)	0.25(8)	4(4)	2(2)	0.5(2)	**100**
	MIC/4	1(2)	0.5(4)	1(2)	8(2)	0.25(32)	1(2)	0.25(8)	1(16)	2(2)	1(1)	**90**
Flucloxacillin	0	16	2	32	4	32	8	2	32	4	32	
	MIC/2	16(1)	4(0.5)	4(8)	0.5(8)	0.25(128)	8(1)	0.125(16)	32(1)	2(2)	32(1)	50
	MIC/4	16(1)	4(0.5)	4(8)	0.5(8)	1(32)	8(1)	0.25(8)	32(1)	4(1)	32(1)	40

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination 0: MICs values of antibiotics tested alone PBS : percentage of bacterial susceptibility *E. coli: Escherichia coli* *E. aerogenes: Enterobacter aerogenes* *K. pneumoniae: Klebsiella pneumoniae* *P. aeruginosa: Pseudomonas aeruginosa* *P. stuartii: Providencia stuartii* The MIC values of each plant extract is those showed in Table 4

Table 8. Minimal inhibitory concentrations of antibiotics combined with bark extract of *Cocos nucifera*

Antibiotics	MICs of plant extract	Bacterial strains and concentrations of antibiotics										PBS (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		ATCC8739	AG102	ATCC13048	CM64	ATCC11296	KP55	ATCC29916	NAE16	PA01	PA124	
Oxacillin	0	32	32	64	64	64	8	64	64	64	32	
	MIC/2	0.5(64)	0.125(256)	0.25(256)	0.25(256)	0.25(256)	8(1)	0.25(256)	8(8)	0.25(256)	1(32)	**90**
	MIC/4	1(32)	0.25(128)	0.25(256)	0.25(256)	8(8)	8(1)	0.25(256)	16(4)	1(64)	8(4)	**90**
Thiamphenicol	0	2	2	4	4	32	16	16	8	2	32	
	MIC/2	0.125(16)	0.125(16)	0.25(16)	0.25(16)	0.125(256)	32(0.5)	0.25(64)	0.5(16)	0.25(8)	4(8)	**100**
	MIC/4	1(2)	0.5(4)	0.25(16)	2(2)	0.5(64)	32(0.5)	2(8)	2(4)	0.25(8)	8(4)	**90**
Erythromycin	0	1	2	16	16	16	8	16	16	16	2	
	MIC/2	0.5(2)	0.125(16)	0.125(128)	0.125(128)	0.25(4)	16(0.5)	2(8)	0.25(64)	2(8)	2(1)	**80**
	MIC/4	0.5(2)	0.25(8)	0.25(64)	1(16)	0.25(4)	16(0.5)	4(4)	2(8)	2(8)	2(1)	**80**
Gentamicin	0	2	1	16	8	16	8	16	8	16	4	
	MIC/2	0.125(16)	0.25(4)	0.125(32)	0.125(64)	0.5(2)	2(8)	0.125(128)	0.125(64)	0.25(64)	4(1)	**90**
	MIC/4	0.25(8)	0.25(4)	0.25(32)	0.25(32)	1(1)	2(8)	0.25(64)	2(4)	0.25(64)	4(1)	**80**
Ciprofloxacin	0	1	2	1	4	8	8	16	16	8	32	
	MIC/2	1(4)	2(2)	0.5(2)	0.125(32)	0.25(32)	2(4)	0.25(64)	0.25(64)	0.25(32)	16(2)	**100**
	MIC/4	1(4)	2(2)	1(1)	0.25(16)	2(4)	1(8)	2(8)	2(8)	1(8)	16(2)	**90**
Doxycycline	0	2	8	2	2	4	8	2	16	4	16	
	MIC/2	0.25(8)	2(4)	0.5(4)	0.125(16)	0.25(64)	2(4)	1(2)	16(1)	0.5(8)	0.5(32)	**90**
	MIC/4	0.5(4)	16(0.5)	0.5(4)	0.5(4)	0.25(64)	4(2)	1(2)	16(1)	0.5(8)	0.5(32)	**80**
Azithromycin	0	4	16	16	16	4	4	4	16	4	64	
	MIC/2	2(2)	8(2)	2(8)	2(8)	0.25(16)	4(1)	2(2)	16(1)	2(2)	64(1)	**70**
	MIC/4	2(2)	8(2)	2(8)	4(4)	1(4)	4(1)	2(2)	16(1)	2(2)	64(1)	**70**
Ofloxacin	0	2	2	2	16	4	2	2	16	4	1	
	MIC/2	1(2)	0.25(8)	0.25(8)	2(8)	0.5(16)	1(2)	0.5(4)	8(2)	4(1)	1(1)	**80**
	MIC/4	1(2)	0.25(8)	0.25(8)	2(8)	1(8)	8(0.5)	0.5(4)	8(2)	4(1)	1(1)	**70**
Flucloxacillin	0	16	2	32	4	32	8	2	32	4	32	
	MIC/2	16(1)	0.5(4)	8(4)	0.125(32)	0.25(128)	8(1)	0.25(8)	32(1)	0.5(8)	16(2)	**70**
	MIC/4	16(1)	2(1)	8(4)	0.25(16)	4(8)	8(1)	0.25(8)	32(1)	0.5(8)	16(2)	60

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination 0: MICs values of antibiotics tested alone PBS : percentage of bacterial susceptibility *E. coli: Escherichia coli* *E. aerogenes: Enterobacter aerogenes* *K. pneumoniae: Klebsiella pneumoniae* *P. aeruginosa: Pseudomonas aeruginosa* *P. stuartii: Providencia stuartii* The MIC values of each plant extract is those showed in Table 4.

Table 9. Minimal inhibitory concentrations of antibiotics combined with epicarp extract of *Cocos nucifera*

Antibiotics	MICs of plant extract	Bacterial strains and concentrations of antibiotics										PBS (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		ATCC8739	AG102	ATCC13048	CM64	ATCC11296	KP55	ATCC29916	NAE16	PA01	PA124	
Oxacillin	0	32	32	64	64	64	8	64	64	64	32	
	MIC/2	0.25(128)	0.125(256)	4(16)	0.25(256)	0.25(256)	0.25(32)	32(2)	16(4)	64(1)	32(1)	**80**
	MIC/4	0.25(128)	0.25(128)	16(4)	0.25(256)	4(16)	4(2)	32(2)	32(2)	64(1)	32(1)	**80**
Thiamphenicol	0	2	2	4	4	32	16	16	8	2	32	
	MIC/2	1(2)	0.5(4)	4(1)	4(1)	0.25(128)	0.25(8)	16(1)	4(2)	0.25(8)	4(8)	**70**
	MIC/4	1(2)	0.5(4)	4(1)	4(1)	2(16)	0.25(8)	16(1)	8(1)	1(2)	16(2)	60
Erythromycin	0	1	2	16	16	16	8	16	16	16	2	
	MIC/2	1(1)	0.25(8)	8(2)	8(2)	0.25(64)	2(4)	0.25(64)	0.25(64)	16(1)	2(1)	**70**
	MIC/4	1(1)	1(2)	16(1)	8(2)	0.25(64)	2(4)	1(16)	1(16)	16(1)	2(1)	60
Gentamicin	0	2	1	16	8	16	8	16	8	16	4	
	MIC/2	0.5(4)	0.25(4)	0.25(64)	0.125(64)	0.25(64)	0.25(32)	8(2)	2(4)	0.25(64)	4(1)	**90**
	MIC/4	1(2)	1(1)	2(8)	0.25(32)	0.25(44)	0.5(16)	16(1)	8(1)	0.25(64)	4(1)	60
Ciprofloxacin	0	1	2	1	4	8	8	16	16	8	32	
	MIC/2	0.125(8)	0.5(4)	0.125(8)	0.125(32)	0.125(64)	0.125(64)	0.25(64)	2(8)	0.25(32)	16(2)	**100**
	MIC/4	0.125(8)	0.5(4)	0.25(4)	0.25(16)	0.25(32)	0.25(32)	0.25(64)	16(1)	0.25(32)	16(2)	**100**
Doxycycline	0	2	8	2	2	4	8	2	16	4	16	
	MIC/2	1(2)	0.25(32)	2(1)	0.125(16)	0.125(32)	0.25(32)	2(1)	16(1)	0.25(16)	0.25(64)	**70**
	MIC/4	2(1)	2(4)	2(1)	2(8)	0.25(16)	2(4)	2(1)	16(1)	0.5(8)	0.25(64)	60
Azithromycin	0	4	16	16	16	4	4	4	16	4	64	
	MIC/2	0.5(8)	0.5(32)	1(16)	8(2)	1(4)	4(1)	0.125(32)	16(1)	0.25(16)	1(64)	**80**
	MIC/4	0.5(8)	0.5(32)	2(8)	16(1)	2(2)	4(1)	0.25(16)	16(1)	1(4)	2(32)	**70**
Ofloxacin	0	2	2	2	16	4	2	2	16	4	1	
	MIC/2	2(1)	0.5(4)	0.5(4)	2(8)	0.25(16)	2(1)	0.25(8)	8(2)	4(1)	0.5(4)	**70**
	MIC/4	2(1)	0.5(4)	0.5(4)	16(1)	0.25(16)	2(1)	0.25(8)	8(2)	4(1)	0.5(2)	60
Flucloxacillin	0	16	2	32	4	32	8	2	32	4	32	
	MIC/2	4(4)	0.25(8)	32(1)	0.5(8)	0.25(128)	0.5(16)	0.25(8)	32(1)	0.25(16)	4(8)	**80**
	MIC/4	16(1)	0.25(8)	32(1)	0.5(8)	4(8)	0.5(16)	0.25(8)	32(1)	0.25(16)	16(2)	**70**

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination 0: MICs values of antibiotics tested alone PBS : percentage of bacterial susceptibility *E. coli: Escherichia coli* *E. aerogenes: Enterobacter aerogenes* *K. pneumoniae: Klebsiella pneumoniae* *P. aeruginosa: Pseudomonas aeruginosa* *P. stuartii: Providencia stuartii* The MIC values of each plant extract is those showed in Table 4.

Table 10. Minimal inhibitory concentrations of antibiotics combined with mesocarp extract of *Musa sapientum*

Antibiotics	MICs of plant extract	Bacterial strains and concentrations of antibiotics										PBS (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		ATCC8739	AG102	ATCC13048	CM64	ATCC11296	KP55	ATCC29916	NAE16	PA01	PA124	
Oxacillin	0	32	32	64	64	64	8	64	64	64	32	
	MIC/2	0.125(256)	1(32)	32(2)	32(2)	32(2)	0.25(32)	64(1)	0.25(256)	64(1)	2(16)	**80**
	MIC/4	0.25(128)	1(32)	32(2)	32(2)	32(2)	4(2)	64(1)	4(16)	64(1)	16(2)	**70**
Thiamphenicol	0	2	2	4	4	32	16	16	8	2	32	
	MIC/2	0.25(8)	1(2)	0.25(16)	0.25(16)	0.25(128)	0.25(8)	4(4)	4(4)	2(1)	32(1)	**80**
	MIC/4	0.25(8)	1(2)	1(4)	0.25(16)	1(32)	0.25(8)	4(4)	8(1)	2(1)	32(1)	**70**
Erythromycin	0	1	2	16	16	16	8	16	16	16	2	
	MIC/2	0.5(2)	1(2)	8(2)	16(1)	2(8)	16(0.5)	16(0.5)	1(16)	8(0.5)	2(1)	50
	MIC/4	0.5(2)	1(2)	16(1)	16(1)	8(2)	16(0.5)	16(0.5)	4(4)	8(0.5)	2(1)	40
Gentamicin	0	2	1	16	8	16	8	16	8	16	4	
	MIC/2	0.125(16)	1(1)	0.25(32)	0.25(32)	0.5(32)	0.5(32)	16(1)	16(0.5)	16(1)	2(2)	60
	MIC/4	0.5(4)	1(1)	0.25(32)	0.25(32)	4(4)	1(16)	16(1)	16(0.5)	16(1)	4(1)	50
Ciprofloxacin	0	1	2	1	4	8	8	16	16	8	32	
	MIC/2	0.125(8)	0.25(8)	0.25(4)	0.125(32)	8(1)	0.25(32)	2(8)	16(1)	4(2)	32(1)	**70**
	MIC/4	0.25(4)	0.25(8)	0.25(4)	0.25(16)	8(1)	0.25(32)	2(8)	16(1)	4(2)	32(1)	**70**
Doxycycline	0	2	8	2	2	4	8	2	16	4	16	
	MIC/2	2(1)	0.5(16)	2(1)	2(1)	4(1)	0.5(16)	1(2)	4(4)	4(1)	0.25(64)	50
	MIC/4	2(1)	0.5(16)	2(1)	2(1)	4(1)	0.5(16)	1(2)	4(4)	4(1)	1(16)	50
Azithromycin	0	4	16	16	16	4	4	4	16	4	64	
	MIC/2	4(1)	4(4)	1(16)	32(0.5)	4(1)	8(0.5)	1(4)	16(1)	2(2)	2(32)	50
	MIC/4	4(1)	8(2)	2(8)	32(0.5)	4(1)	8(0.5)	2(2)	16(1)	2(2)	8(4)	40
Ofloxacin	0	2	2	2	16	4	2	2	16	4	1	
	MIC/2	0.5(4)	0.25(8)	4(0.5)	32(0.5)	8(0.5)	0.25(8)	0.25(8)	8(2)	4(1)	0.5(2)	60
	MIC/4	0.5(4)	0.25(8)	4(0.5)	32(0.5)	8(0.5)	0.25(8)	0.25(8)	8(2)	4(1)	0.5(2)	60
Flucloxacillin	0	16	2	32	4	32	8	2	32	4	32	
	MIC/2	8(2)	2(1)	32(1)	4(1)	32(1)	4(2)	4(0.5)	32(1)	4(1)	2(16)	30
	MIC/4	8(2)	2(1)	32(1)	4(1)	32(1)	4(2)	4(0.5)	32(1)	4(1)	2(16)	30

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination 0: MICs values of antibiotics tested alone PBS : percentage of bacterial susceptibility *E. coli: Escherichia coli* *E. aerogenes: Enterobacter aerogenes* *K. pneumoniae: Klebsiella pneumoniae* *P. aeruginosa: Pseudomonas aeruginosa* *P. stuartii: Providencia stuartii* The MIC values of each plant extract is those showed in Table 4.

Table 11. Minimal inhibitory concentrations of antibiotics combined with epicarp of *Musa sapientum*

Antibiotics	MICs of plant extract	Bacterial strains and concentrations of antibiotics										PBS (%)
		E. coli		*E. aerogenes*		*K. pneumoniae*		*P. stuartii*		*P. aeruginosa*		
		ATCC8739	AG102	ATCC13048	CM64	ATCC11296	KP55	ATCC29916	NAE16	PA01	PA124	
Oxacillin	0	32	32	64	64	64	8	64	64	64	32	
	MIC/2	0.25(128)	0.25(128)	32(2)	32(2)	16(4)	4(2)	64(1)	64(1)	8(8)	8(4)	**80**
	MIC/4	0.25(128)	0.5(64)	32(2)	32(2)	32(2)	4(2)	64(1)	64(1)	8(8)	8(4)	**70**
Thiamphenicol	0	2	2	4	4	32	16	16	8	2	32	
	MIC/2	0.5(4)	0.25(8)	4(1)	4(1)	32(1)	8(2)	32(0.5)	16(0.5)	0.5(4)	16(2)	50
	MIC/4	0.5(4)	0.25(8)	4(1)	4(1)	32(1)	16(1)	32(0.5)	16(0.5)	1(2)	16(2)	40
Erythromycin	0	1	2	16	16	16	8	16	16	16	2	
	MIC/2	2(0.5)	1(2)	32(0.5)	32(0.5)	0.5(32)	8(1)	32(0.5)	16(1)	16(1)	2(1)	20
	MIC/4	2(0.5)	1(2)	32(0.5)	32(0.5)	2(8)	8(1)	32(0.5)	16(1)	16(1)	2(1)	20
Gentamicin	0	2	1	16	8	16	8	16	8	16	4	
	MIC/2	0.25(8)	1(1)	4(2)	8(1)	0.5(32)	0.125(64)	16(1)	16(0.5)	16(1)	4(1)	40
	MIC/4	0.25(8)	1(1)	4(2)	8(1)	2(8)	0.25(32)	16(1)	16(0.5)	16(1)	4(1)	40
Ciprofloxacin	0	1	2	1	4	8	8	16	16	8	32	
	MIC/2	0.125(8)	0.25(8)	1(1)	8(0.5)	16(0.5)	0.125(64)	16(1)	16(1)	8(1)	64(0.5)	30
	MIC/4	0.125(8)	0.25(8)	1(1)	8(0.5)	16(0.5)	0.5(16)	16(1)	16(1)	8(1)	64(0.5)	30
Doxycycline	0	2	8	2	2	4	8	2	16	4	16	
	MIC/2	0.5(4)	0.25(32)	0.25(8)	1(2)	4(4)	0.25(32)	2(1)	16(1)	4(1)	2(8)	**70**
	MIC/4	0.5(4)	2(4)	0.25(8)	1(2)	8(2)	1(8)	2(1)	16(1)	4(1)	2(8)	**70**
Azithromycin	0	4	16	16	16	4	4	4	16	4	64	
	MIC/2	4(1)	8(2)	2(8)	32(0.5)	4(1)	1(4)	4(1)	16(1)	1(4)	64(1)	40
	MIC/4	4(1)	16(1)	2(8)	32(0.5)	4(1)	2(2)	4(1)	16(1)	2(2)	64(1)	30
Ofloxacin	0	2	2	2	16	4	2	2	16	4	1	
	MIC/2	0.5(4)	1(2)	0.5(4)	16(1)	0.5(16)	2(1)	0.25(8)	16(1)	4(1)	0.5(2)	60
	MIC/4	0.5(4)	1(2)	0.5(4)	16(1)	4(2)	2(1)	0.5(4)	16(1)	4(1)	1(1)	50
Flucloxacillin	0	16	2	32	4	32	8	2	32	4	32	
	MIC/2	16(1)	1(2)	16(2)	2(2)	8(4)	8(1)	0.5(4)	32(1)	8(0.5)	4(8)	60
	MIC/4	16(1)	2(1)	16(2)	4(1)	8(4)	8 (1)	0.5(4)	32(1)	8(0.5)	16(2)	40

The numbers in parenthesis represent the improvement activity factors (IAF) [there is synergism when IAF≥2, indifference when IAF=1 and antagonism when IAF≤0.5] IAF values were obtained by calculating the MIC of antibiotic alone over MIC of the combination 0: MICs values of antibiotics tested alone PBS : percentage of bacterial susceptibility *E. coli: Escherichia coli* *E. aerogenes: Enterobacter aerogenes* *K. pneumoniae: Klebsiella pneumoniae* *P. aeruginosa: Pseudomonas aeruginosa* *P. stuartii: Providencia stuartii* The MIC values of each plant extract is those showed in Table 4.

Conclusion

This work aimed at evaluating the antibacterial potential of some edible plant extracts against a panel of MDR Gram-negative phenotypes. Each extract contained at least three phytochemicals and extracts from different parts of *Cocos nucifera* (leaves, bark and epicarp) were most active. They showed significant activities and bactericidal effects against several strains, while extract from *Glycine max* seeds moderately inhibited the growth of few bacteria. However, extracts from all parts of *Musa sapientum* (epicarp and mesocarp) did not exhibit any activity against all studied bacterial strains. Therefore, all tested plant extracts potentiated the activity of all used antibiotics against several studied bacteria indicating the synergistic effects between bioactive compounds of plants and these antibiotics. Taken together, these results including the pharmacological properties of tested plants indicate that *Cocos nucifera* is a very promising plant and may has a potential benefit as an alternative antibiotic agent through its antibacterial activity to overcome infections caused by resistant bacteria. In other words, drugs and supplements can be formulated with coconut products for prophylactic and therapeutic purposes.

Abbreviations

Abbreviations

ATCC :	American Type Culture Collection
MIC :	Minimal inhibitory concentration
MBC :	Minimal bactericidal concentration
DMSO :	Dimethylsulfoxide
INT :	p-Iodonitrotetrazolium chloride
SFR/CAM :	Society of forest reserve of Cameroon
NHC :	National herbarium of Cameroon
MHA :	Mueller Hinton agar
MHB :	Mueller Hinton broth
OD :	Optical density
RND :	Resistance-nodulation-cell division
EPI :	Efflux pumps inhibitor
IAF :	Improvement activity factor
EY :	Extractive yield
OXA :	Oxacillin
THI :	Thiamphenicol
ERY :	Erythromycin
GEN :	Gentamicin
CIP :	Ciprofloxacin
DOX :	Doxocyclin
AZI :	Azithromycin
OFL :	Ofloxacin
FLU :	Flucloxacillin
PSBS :	percentage of susceptible bacteria to substances
PBS :	percentage of bacterial susceptibility

Authors' Contribution

CMNN realized antibacterial activities of samples alone and in combination with antibiotics. Phytochemical screening was done by MGGF. Mechanisms of action of the most active sample were carried out by BENW and PN. The manuscript was written by SBT and the work was supervised by VK and ATM.

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Conflict of interest

The authors declare no conflict of interest

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