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RESEARCH ARTICLE

Inhibitory potentials of *Ageratum conyzoides* L. and *Tridax procumbens* L. ethanolic leaf extracts against multidrug-resistant bacteria (MDRB) from cancer patients

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ABSTRACT

Cancer and its associated treatments often compromise the immune system, predisposing patients to opportunistic infections, including those caused by multidrug-resistant bacteria (MDRB). This study investigated the resistance patterns of bacterial pathogens isolated from cancer patients and evaluated the antibacterial efficacy of ethanolic leaf extracts of *Ageratum conyzoides* and *Tridax procumbens* at a concentration of 200 mg/mL against these MDRB pathogens. A retrospective analysis was conducted on data from cancer patients attending a tertiary healthcare facility. Bacterial isolates were identified from blood samples and screened for antibiotic susceptibility patterns. The susceptibility of MDRB isolates to the ethanolic leaf extracts of *A. conyzoides* and *T. procumbens* was assessed as a potential alternative therapy. The study revealed that breast cancer was the most prevalent type (38%) among the patient population (n = 160). In addition, the most common bacterial pathogens isolated from cancer patients included *Escherichia coli* (12 isolates), *Klebsiella pneumoniae* (15), *Streptococcus pneumoniae* (9), *Shigella dysenteriae* (10), *Staphylococcus aureus* (12), *Klebsiella aerogenes* (6), and *Salmonella typhi* (7). These pathogens exhibited significant multidrug resistance to conventional antibiotics. For instance, *Staphylococcus aureus* showed high resistance to cotrimoxazole (83%), ceftazidime (67%), erythromycin (75%), and cefuroxime (83%), whilst retaining susceptibility to gentamycin. Conversely, the ethanolic extracts of *A. conyzoides* and *T. procumbens* demonstrated inhibitory zones ranging from 8.26 ± 0.15 mm to 25.22 ± 0.83 mm and 8.30 ± 0.20 mm to 23.22 ± 0.83 mm, respectively against MDR bacterial pathogens evaluated. Findings revealed that *Streptococcus pneumoniae* was most susceptible to *A. conyzoides* (25.22 ± 0.83 mm), whilst *T. procumbens* exhibited notable activity against MDRB pathogens. Additionally, the combination of *T. procumbens* extracts and ofloxacin exhibited synergistic effects against *Salmonella typhi*. This study underscores the vulnerability of cancer patients to opportunistic bacterial infections and highlights the potential of *A. conyzoides* and *T. procumbens* as alternative sources of antibacterial agents. Hence, further purification and characterization of these extracts are recommended for developing effective therapeutic options against MDRB pathogens evaluated.

Keywords: inhibitory potentials, multidrug-resistant bacteria, antibiotic susceptibility testing, antibacterial activity testing, drug discovery, medicinal plants, *A. Conyzoides*, *T. procumbens*

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INTRODUCTION

Cancer occurs when a single progenitor cell accumulates mutations and other changes in the DNA, histones, and other biochemical compounds that make up the cell's genome [1]. Certain combinations of mutations in the given progenitor cell ultimately result in the cancer stem cell to display a number of abnormal, malignant cellular properties that, when taken together, are considered characteristic of cancer, including: the ability to continue to divide perpetually, producing an exponentially (or near-exponentially) increasing number of new malignant cancerous "daughter cells" (uncontrolled mitosis); the ability to penetrate normal body surfaces and barriers, and to bore into or through nearby body structures and tissues (local invasiveness); the ability to spread to other sites within the body [2, 3]. Cancer is one of the most dreadful diseases all over the world. Recently, it was forecasted that there could be 26.4 million new patients diagnosed with cancer by 2030, and an average of 1.7 million annual cancer deaths within five years of diagnosis [4, 5].

Over the years, scientists have conducted vital research in the treatment of cancer. The impact of treatment regimen, dietary intake and immunocompromised state of health predisposes cancer patients to opportunistic infections, including those from bacterial origin. Interestingly, the use of conventional antimicrobial agents have been effective in mitigating mortality rates as a result of cancer. However, the indiscriminate use of conventional antibiotics has resulted in multidrug-resistant patterns exhibited by pathogenic bacteria [6]. Therefore, the knowledge of bacterial infections in immunocompromised patients and their susceptibility patterns towards conventional antibacterial agents is critical to its management and overall treatment [7]. The study aims at investigating the resistance patterns of aetiological bacterial pathogens responsible for initiating opportunistic infections in cancer patients via their susceptibility patterns to conventional antibiotics (antibiotic susceptibility testing), and evaluation of *A. conyzoides* and *Tridax procumbens* ethanolic leaf extracts at 200mg/mL against multi-drug resistant bacteria (MDRB).

MATERIALS AND METHODS

Study Population

A total of 160 cancer patients (99 females and 61 males) diagnosed with various forms of bacterial infections who were attending Federal Medical Center, Owo (FMC) for symptom control, emotional/psychological support and treatments were recruited for participation in the research with the support of their families, using structured-based questionnaires and clinical bacterial isolates relating to patients who consented to the use of their clinical information for the research.

Questionnaire

The patients and their corresponding families were provided with a structural, closed-ended questionnaire required for subsequent analysis based on information provided.

Demographics of Cancer Patients and Types of Cancer Evaluated in the Study

In accordance with the method described in [8], data related to the gender, age, occupation, residence, and lifestyle distributions of the cancer patients studied were collected, using a structured, closed-ended questionnaire. Additionally, the report of the cancer diagnostic result was evaluated to ascertain the type of cancer implicated in each participant of the study and, the total number of all cancer types reported by the participants (patients and/or their families) were noted and documented for further statistical analysis.

Collection of Frequently Occurring Bacterial Pathogens Isolated From Cancer Patients Attending FMC

The following frequently occurring bacteria isolated from cancer patients' (participants) blood samples, who consented to the use of their clinical information were collected from the hematological/medical laboratory department at FMC. The clinical isolates include *Escherichia coli* (12), *Klebsiella pneumoniae* (15), *Streptococcus pneumoniae* (9), *Shigella dysenteriae* (10), *Staphylococcus aureus* (12), *Klebsiella aerogenes* (6) and *Salmonella typhi* (7). Moreover, the microorganisms collected were identified, using standard microbiological techniques, as described in [9-11].

Identification and Maintenance of Bacterial Pure Cultures Isolated From Cancer Patient's Blood Samples

The clinical isolates of frequently occurring bacterial organisms collected were sub-cultured repeatedly by streaking aseptically on nutrient agar, McConkey's agar, Manitol salt agar and blood agar for resuscitation. In addition, the different bacterial pure cultures grown were inoculated into nutrient agar slants and incubated for 24 h in order to ensure proper growth and then kept as stock cultures in the refrigerator at 4 °C for further investigative procedure with respect to identification of the microbes.

Characterization of Bacterial Isolates From Cancer Patients

The pure culture of each isolate was examined. Microscopic examination, staining techniques and biochemical tests were carried out on the bacterial isolates according to the methods described in [9].

Standardization of Inoculums

The inocula collected were prepared from the stock cultures. The pure culture of each bacterial isolates recovered from cancer patients were maintained on nutrient agar slant at 4 °C. These were subsequently sub-cultured onto nutrient broth aseptically, using a sterile inoculating loop and incubated at 37 °C for 18-24 hours before use. The nutrient broth setup for each clinical bacterial isolate was suspended in saline solution (0.85% NaCl) and adjusted with the aid of a spectrophotometer (Unico 1100RS) to match a turbidity of 0.5 McFarlands standard at wavelength of 540 nm in accordance with the method described in [12] before usage.

Antibiotic Susceptibility Testing of Frequently Occurring Bacterial Isolates Collected From Cancer Patients Attending FMC

The antibiotic resistance patterns of 71 clinical bacteria isolated from cancer patients was carried out in order to compare the susceptibility patterns of the isolates to different commercially available antibiotics and evaluate the multi-drug resistant patterns of the clinical bacterial test organisms to conventional antibiotics. The commercial antibiotic discs (Abtek Biologicals) which included **COT–cotrimoxazole** (25 μg) (negative disc), **CHL–chloramphenicol** (10 μg), **GEN–gentamicin** 10 μg), **OFL–ofloxacin** (30 μg), **AUG–augmentin** (30 μg), **CFX-cefixime** (30 μg), **CFT–ceftazidime** (30 μg), **NIT–nitrofurantoin** (300 μg), **CFU–cefuroxime** (30 μg), **ERY–erythromycin** (5 μg)**, CFR–ceftriaxone** (30 μg) (positive disc), and **CLX–cloxacillin** (5 μg), were used for the test organisms. The assay was carried out using the disc diffusion method, as described in [13]. Sterile Petri dishes were pour-plated aseptically with 1 mL each of the standardized broth cultures of the test organisms and 15 mL of sterilized Mueller-Hinton agar. The plates were swirled carefully for even distribution and allowed to gel under room temperature. Furthermore, the antibiotic discs were placed firmly on the set plates, using sterile forceps and incubated for 24 hours at 37 ºC. Following incubation, clear zones around the discs were measured with the aid of a ruler which represents the zones of inhibition and the areas without clear zones were also observed via physical eye examination [14]. Additionally, unseeded agar plates with antibiotics served as the control experiment and the zones of inhibition were measured with a calibrated ruler and recorded in millimeters (mm).

Ethanolic Extraction of *Ageratum Conyzoides* and *Tridax Procumbens*

The plant extracts including *Ageratum conyzoides* and *Tridax procumbens* were subjected to ethanolic extraction using the method described in [15].

Antibacterial Activities of *Ageratum Conyzoides* and *Tridax Procumbens* at 200 mg/mL Against Bacteria Isolated From Cancer Patients

The antibacterial activities of *A. conyzoides* and *T. procumbens* ethanolic leaf extracts against frequently occurring bacterial isolates from cancer patients were evaluated using Agar disc diffusion method, as described in [16].

Synergistic Activities of *Tridax Procumbens* Ethanolic Leaf Extract Combined With Conventional Antibiotics Against Bacteria Isolated From Cancer Patients

The synergistic activities of *Tridax procumbens* ethanolic leaf extract combined with conventional antibiotics against bacteria isolated from cancer patients, attending FMC was carried out using microbroth dilution methods, as described in [17].

Data Analysis

All data obtained were subjected to one way analysis of variance using SPSS 21.0v. and difference between means was determined by Duncan's new multiple range test at $p \leq 0.05$ in conjunction with the use of 3D GraphPad prism, and Microsoft Excel statistical tools.

RESULTS AND DISCUSSION

Demographical Results of Cancer Patients Attending FMC

The gender, age, occupation, and lifestyle distributions of the cancer patients studied were ascertained using a questionnaire. The result of the gender distribution is depicted in **Figure 1**, whereby the female patients had the highest occurrence of 62% (99 participants) in comparison with the male patients, presenting 38% (61 participants) of the total study population.

Furthermore, the result of the age distribution of the participants in the study is presented in **Figure 2**. As depicted in the result, the age distribution of the participant ranges from 21 to ≥ 61 years of age. In addition, the highest cancer occurrence was observed in patients who were 61 years and above (sexagenarians), and especially in septuagenarians with a total of 48 (30%) different cancer cases reported within this group, including 29 patients diagnosed with breast cancer (18.1%) and 12 (7.5%) patients diagnosed with prostate cancer. Conversely, the lowest cancer cases of 7 (4.4%) was reported amongst patients between 21-30 years of age, including glioblastoma which accounts for 1% (2 patients) of the patients within the study population. It was observed that the age group of 41 to 50 years had 35 (21.9%) cancer cases and 2/3 (12 patients; 14.6%) of these accounts for breast cancer, making it a common cancer amongst the patients evaluated in this study. Moreover, lung cancer accounts for 9.3% (15) of patients between 31-40 years within the study population. Additionally, the following forms of cancers were observed across the age groups of participants, and most especially, the sexagenarian group (60-69 years), these include oligodendroglioma, myeloma, leukemia, colorectal and skin cancer.

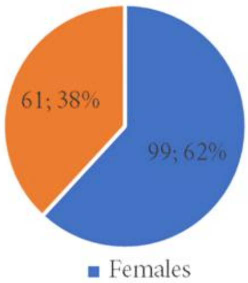

Figure 1. Gender distribution of cancer patients attending FMC (Source: FMC, Owo)

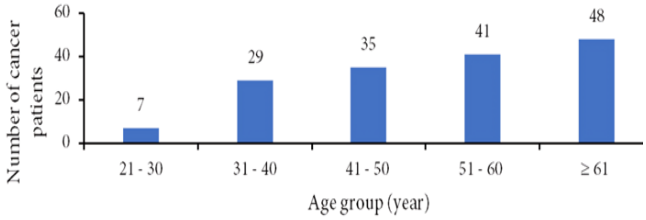

Figure 2. Age distribution of cancer patients attending FMC (Source: FMC, Owo)

Residential Distribution of Cancer Patients Attending FMC

The residential distribution of cancer patients attending FMC who participated in the study is documented in **Table 1**. The cancer patients from urban settlements had the highest incidence of cancer cases, with a resident of 112 cancer patients, amounting to 70% of the study population. Meanwhile, rural dwellers were 34 (21.25%), and the lowest cancer cases were residents from peri-urban settlers, with a total of 14 (8.75%) dwellers.

Table 1. Residential distribution of cancer patients attending FMC

Type of residence	Frequency	Percentage (%)
Rural	34	21.25
Peri-urban	14	8.75
Urban	112	70.00
Total	160	100

Figure 3. Occupational distribution of cancer patients attending FMC (Source: FMC, Owo)

Table 3. Cancer-related family history on cancer patients attending FMC

Patients with family history (cancer)	Total number of patients	Percentage occurrence (%)
Patients without family history	115	71.88
Patients with family history	26	16.25
Patients uncertain of family history	19	11.87
Total	160	100

Table 2. Diagnostic timeframe amongst cancer patients attending FMC

Cancer types	Duration of diagnosis (years)	Total number of patients	Percentage occurrence amongst participants (%)
Breast	1-4	61	38
Prostate	1-5	43	27
Lung	8-10	24	15
Leukemia	1-2	16	10
Myeloma	6-10	5	3
Skin	1-3	5	3
Glioblastoma	6-10	2	2
Oligodendroglioma	1-2	2	1
Colorectal	5-10	2	1

Occupational Distribution of Cancer Patients Attending FMC

The result of the occupational distribution of cancer patients who participated in the study is presented in **Figure 3**. The highest number of cancer patients, amounting to 83 (25%) was observed amongst the retirees, closely followed by the civil servants 58 (36%), and volunteers had 16 (10%) different cancer cases. The lowest number of cancer cases was reported amongst business owners, constituting 2% (3) of the entire study population (160 cancer patients).

Diagnostic Timeframe Amongst Cancer Patients Attending FMC

The duration of cancer development and diagnosis varies amongst the participants. The diagnostic timeframe ranges from 1-10 years, with those diagnosed within 1-4 years (breast cancer), rating high amongst the participants, consisting of 61 patients (38%) in this category. Comparatively, the lowest diagnostic timeframe amongst the participants was observed in patients diagnosed with oligodendroglioma within 1-2 years. Furthermore, patients diagnosed with prostate cancer amongst the participants were diagnosed within 1-5 years of its occurrence, rating 25% of the entire study population.

Additionally, patients diagnosed with glioblastoma (2%), myeloma (3%), colorectal (1%), skin (3%), leukemia (10%), and lung (15%) cancers were diagnosed within 6-10 years (glioblastoma and myeloma), 5-10 years, 1-3 years, 1-2 years, and 8-10 years, respectively (**Table 2**).

Cancer-Related Family History Patients Attending FMC

Following the analysis of records obtained in the participant's questionnaire, a large proportion (115) of the participants reported they do not have a family history of cancer, rating the highest percentage of 71.88%. Conversely, 26 (16.25%) patients amongst the participants reported they have family history related to cancer. However, 11.87% (19) of the participants in the study population (160 patients) expressed uncertainty regarding having a family history of cancer. The analysis of their family history submission is presented in **Table 3**.

Alcohol and Tobacco Use Amongst Cancer Patients Attending FMC

The details of the alcohol intake and the use of tobacco, including cigarette smoking by the participants is presented in **Table 4**. It was observed that 18 (11.2%) of the study population (participants) engaged in tobacco/cigarette smoking, whilst 44 (27.5%) of the participants engaged in the use of alcohol. Additionally, a total of 12 (7.5%) patients reported to have engaged in the use of alcohol and smoking; the sum is inclusive of other data collected regarding alcohol intake and smoking (tobacco/cigarette) as noted in **Table 4**. Conversely, a high record 96 (60%) of the participants neither drink (alcohol) nor smoke. Noteworthy, 2/3 of the participants who were diagnosed with lung cancer engaged in the use of alcohol, and 1/3 of these patients engaged in smoking (tobacco/cigarette). Overall, the data collected suggested some of the cancer patients engaged in smoking and the use of alcohol.

Table 4. Alcohol and tobacco use amongst cancer patients attending FMC

Cancer types/participants	Tobacco/cigarette smoking	Alcohol intake	Patients smoking & taking alcohol	No smoking & alcohol	Total
Breast (61)	3*	11*	3*	50	61
Prostate (43)	*5	*7	4*	36	43
Lung (24)	7*	19*	4*	5	24
Leukemia (16)	0	3	0	13	16
Myeloma (5)	0	1	0	4	5
Skin (5)	2	1	0	2	5
Glioblastoma (2)	0	1	0	1	2
Oligodendroglioma (2)	1	0	0	1	2
Colorectal (2)	0	1	1	0	2
Total: n (%)	18 (11.2)	44 (27.5)	12 (7.5)	96 (60.0)	160

Note. *Total number of participants in the group consisting of patient's smoking & taking alcohol is inclusive in other corresponding data in asterisks

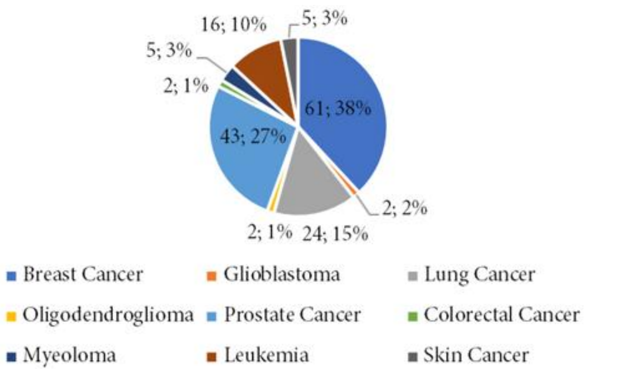

Figure 4. Types of cancer observed in patients attending FMC (Source: FMC, Owo)

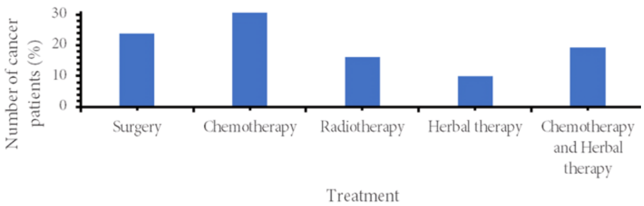

Figure 5. Treatment options received by cancer patients attending FMC (Source: FMC, Owo)

Types of Cancer Amongst Patients Attending FMC

The submissions of the participants with respect to the cancer types evaluated in this study was reported via the questionnaires provided to the patients and their corresponding families. Additionally, the total number of cancer types observed amongst the study population (FMC cancer patients) is presented in **Figure 4**. Findings from the result revealed that patients diagnosed with breast cancer had the highest percentage occurrence of 38% (61 patients), and the lowest percentage occurrence of 1% was observed in patients diagnosed with colorectal cancer (2 patients). Furthermore, other cancer types observed includes prostate cancer (43 patients; 27%), lung cancer (24 patients; 15%), leukemia (16 patients; 10%), myeloma (5 patients; 3%), skin cancer (5 patients; 3%), glioblastoma (2 patients; 2%), and oligodendroglioma observed in two cancer patients, accounting for 1% of the total study population.

Treatment Options Received by Cancer Patients Attending FMC

The treatment options received amongst the cancer patients within the study population (n = 160) include the following: chemotherapy 49 (30.63%), surgery 38 (23.75%), chemotherapy and herbal therapy 31 (19.38%), radiotherapy 26 (16.25%), and herbal therapy 16 (10.00%) (**Figure 5**).

Identification of Bacterial Isolates Collected From Cancer Patients Attending FMC

A total of 71 frequently occurring bacteria isolated from the blood samples of cancer patients attending FMC were collected from the hematological medical laboratory of the hospital. The clinical isolates include *Escherichia coli* (12), *Klebsiella pneumoniae* (15), *Streptococcus pneumoniae* (9), *Shigella dysenteriae* (10), *Staphylococcus aureus* (12), *Klebsiella aerogenes* (6), and *Salmonella typhi* (7). Confirmatory tests were carried out on all the bacterial isolates collected using standard microbiological techniques, including molecular biology techniques.

Antibiotic Susceptibility testing of Frequently Occurring Bacteria Isolated From Cancer Patients Attending: FMC, Owo

A total of 71 bacterial isolates were screened for their resistance patterns against several antibiotic disks via *in-vitro* assay and the result is presented in **Table 5**. Additionally, the frequency of occurrence of bacteria isolated from cancer patients who participated in the study is presented in **Figure 6**. Overall, the antibiotic sensitivity test result revealed plethora of the clinical test organisms exhibited multi-drug resistance (MDR) patterns against many or all of the antibiotic disks employed for the assay. For example, the percentage resistance of all the test bacterial organisms against cotrimoxazole was 66%, whereby 47 bacterial isolates were resistant to its inhibitory actions. Additionally, the following resistance patterns of the test clinical bacterial

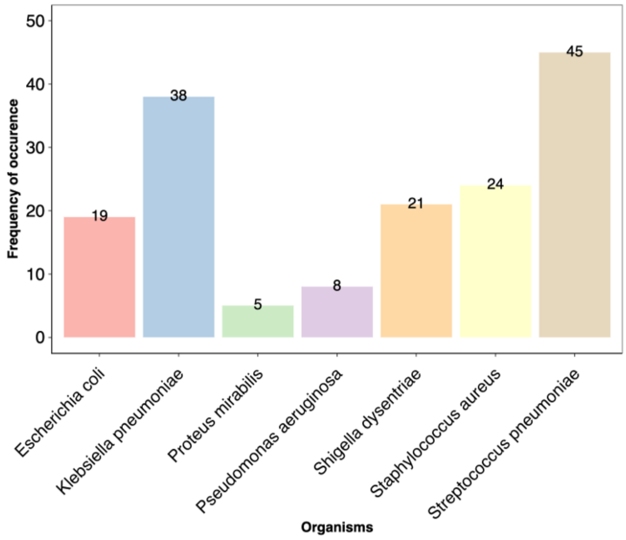

Figure 6. Frequency of occurrence of bacteria isolated from cancer patients (Source: FMC, Owo)

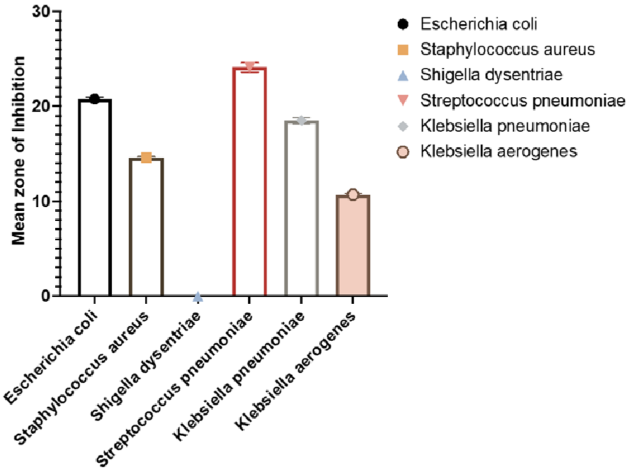

Figure 7. Antibacterial activities of *A. conyzoides* ethanolic leaf extract at 200 mg/mL against multi-drug resistant bacteria (MDRB) recovered from cancer patients attending FMC (Source: FMC, Owo)

isolates to the various antibiotic disks used were observed, whereby: 37% (26) of the bacterial isolates were resistant to chloramphenicol, 41% (29) were resistant to gentamycin, 13% (9) were resistant to ofloxacin, demonstrating the highest efficacy against the test bacterial isolates. Furthermore, 45% (32) of the total bacterial test isolates were resistant to augmentin, 55% (39) were resistant to ceftriaxone, 61% (43) were resistant to cefuroxime, 62% (44) were resistant to erythromycin, and 18% (25) were resistant against nitrofurantoin. Notably, the twelve different clinical isolates of *Escherichia coli* tested for its susceptibility patterns to different forms of antibiotics were resistant against chloramphenicol, nitrofurantoin, and erythromycin. Moreover, the clinical isolates (12) of *Staphylococcus aureus* were resistant to cotrimoxazole (83%), ceftazidime (67%), erythromycin (75%), and cefuroxime (83%) (**Table 5**). Meanwhile, a good number of *E. coli* was susceptible to erythromycin, nitrofurantoin and *S. aureus* was susceptible to the inhibitory action elicited by gentamycin.

Antibacterial Activities of *Ageratum Conyzoides* Ethanolic Leaf Extract at 200 mg/mL on Bacteria Isolated From Cancer Patients Attending FMC

The antibacterial activities of *A. conyzoides* ethanolic leaf extract at 200 mg/mL is reported in **Figure 7**. The zone of inhibition ranged from 8.26 ± 0.15 mm to 25.22 ± 0.83 mm. Additionally, the most susceptible test bacteria to the inhibitory action posed by ethanolic extract of *A. conyzoides* was the clinical isolate of *Streptococcus pneumoniae* with an inhibitory zone of 25.22 ± 0.83 mm and a mean inhibitory zone of 24.11 ± 0.50 mm for the seven bacterial tested in this group. Conversely, *Klebsiella aerogenes* demonstrated the lowest susceptibility to the ethanolic leaf extract of *A. conyzoides*, presenting an inhibitory zone of 8.26 ± 0.15 mm, with a mean inhibitory zone of 10.68 ± 0.12 mm for a total of

Table 5. Antibiotic resistance patterns of frequently occurring bacterial isolates collected from cancer patients attending FMC

Bacteria	Cot	Chl	Gen	Ofx	Aug	Cfx	Cft	Nit	Cfu	Ery	Cfr	Clx
E. coli (n = 12)	4 (33)	0 (0)	3 (25)	6 (50)	11 (92)	4 (33)	2 (17)	0 (0)	3 (25)	0 (0)	2 (17)	5 (42)
K. pneumoniae (n = 15)	12 (80)	5 (33)	15 (100)	1 (7)	5 (33)	4 (27)	7 (47)	3 (20)	8 (53)	15 (100)	6 (40)	5 (33)
S. pneumoniae (n = 9)	6 (67)	4 (44)	3 (33)	2 (22)	3 (33)	7 (77)	6 (67)	3 (33)	6 (67)	7 (77)	7 (77)	3 (33)
S. dysenteriae (n = 10)	7 (70)	2 (20)	2 (20)	1 (10)	3 (30)	8 (80)	7 (70)	3 (30)	6 (60)	6 (60)	8 (80)	4 (40)
S. aureus (n = 12)	10 (83)	4 (33)	0(0)	2 (17)	5 (42)	2 (17)	8 (67)	6 (50)	10 (83)	9 (75)	7 (58)	3 (25)
K. aerogenes (n = 6)	5 (83)	3 (50)	2 (33)	2 (33)	3 (50)	2 (33)	3 (50)	1 (17)	4 (67)	2 (33)	3 (50)	2 (33)
S. typhi (n = 7)	3 (42)	2 (29)	1 (14)	1 (14)	2 (29)	4 (57)	5 (71)	2 (29)	6 (86)	5 (71)	6 (86)	3 (42)
Total: 71 (%)	47 (66)	26 (37)	26 (37)	9 (13)	32 (45)	31 (44)	38 (54)	18 (25)	43 (61)	44 (62)	39 (55)	25 (35)

Note. Cot: Cotrimoxazole; Chl: Chloramphenicol; Gen: Gentamycin; Ofx: Ofloxacin; Aug: Augmentin; Cfx: Cefixime; Cft: Ceftazidime; Nit: Nitrofurantoin; Cfu: Cefuroxime; Ery: Erythromycin; Cfr: Ceftriaxone; Clx: Cloxacillin; & n: Number of clinical test isolates examined (the values in parenthesis represent percentage resistance of each bacterium to the antibiotic disk & values prior to the parenthesis represent number of resistant isolates)

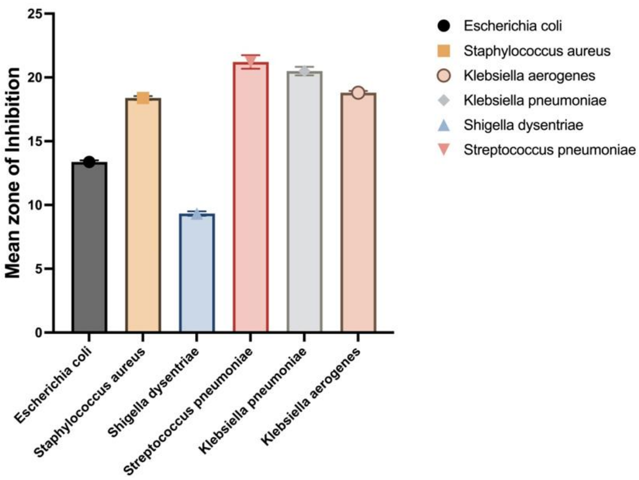

Figure 8. Antibacterial activities of *T. procumbens* ethanolic leaf extract at 200 mg/mL against multi-drug resistant bacteria (MDRB) recovered from cancer patients attending FMC (Source: FMC, Owo)

seven bacterial clinical isolates tested in this group. Moreover, it was observed that the clinical isolates of *Shigella dysenteriae* and *Salmonella typhi* tested were resistant to the ethanolic leaf extract of *A. conyzoides* (**Figure 7**).

Antibacterial Activities of *Tridax Procumbens* Ethanolic Extract at 200 mg/mL on Bacteria Isolated From Cancer Patients Attending FMC

The antibacterial activities of *T. procumbens* ethanolic leaf extract at 200 mg/mL against clinical bacterial isolates from cancer patients is presented in **Figure 8**. The zone of inhibition ranged from 8.30 ± 0.20 mm to 23.22 ± 0.83 mm. In addition, *Shigella dysenteriae* was the least susceptible test bacteria to the inhibitory action of *T. procumbens* ethanolic extract with an inhibitory zone of 8.30 ± 0.20 mm and a mean inhibitory zone of 9.33 ± 0.17 mm for the four bacterial tested in this group. Conversely, *Streptococcus pneumoniae* demonstrated the highest susceptibility to the ethanolic leaf extract of *T. procumbens*, presenting an inhibitory zone of 23.22 ± 0.83 mm, with a mean inhibitory zone of 21.21 ± 0.53 mm for a total of seven bacterial clinical isolates tested in this group. Furthermore, it was observed that the clinical isolates of *Salmonella typhi* tested was resistant to the ethanolic leaf extract of *T. procumbens* (**Figure 8**).

Synergistic Potentials of *Tridax Procumbens* Ethanolic Leaf Extract and Conventional Antibiotics Against Bacteria Isolated From Cancer Patients

The result of the synergistic potentials of *T. procumbens* ethanolic leaf extract combined with various forms of conventional antibiotics on multidrug-resistant bacteria (MDRB) isolated from cancer patients is presented in **Table 6**. Overall, a good number of the MDRB were susceptible to the inhibitory actions posed by the combination of *T. procumbens* ethanolic extract and the conventional antibiotics, resulting in synergistic efficacy. The combination extract of *T. procumbens* and ofloxacin were found to be the most effective against *Escherichia coli* (12), *Staphylococcus aureus* (12), and *Salmonella typhi* (7) with inhibitory zones range of 0.38-1.50 mm, 1.0-1.75 mm, and 0.50-1.75 mm, respectively. Moreover, it was observed that the clinical isolates of *Shigella dysenteriae* (10) were resistant to the combination consisting of *T. procumbens* and cotrimoxazole. Interestingly, the clinical isolates of *Salmonella typhi* which exhibited multidrug-resistant patterns against several antibiotics and plant extracts, including gentamycin, chloramphenicol, *Ageratum conyzoides* and *Tridax procumbens* ethanolic extracts, were found to be susceptible to the inhibitory actions of *T. procumbens* and ofloxacin, revealing its synergistic potentials (**Table 6**).

DISCUSSION

The types of cancer investigated in this research include breast, prostate, lung, leukemia, myeloma, skin, glioblastoma, oligodendroglioma and colorectal. Findings from this study revealed that breast cancer had the highest occurrence of 38% amongst the cancer types reported within the study population, accounting for 61 patients. As a result,

Table 6. Synergistic efficacy of *Tridax procumbens* ethanolic leaf extract combined with antibiotics against bacteria isolated from cancer patients (inhibitory zones range: mm)

Bacteria	TP+ Cot	TP+ Chl	TP + Gen	TP + Cpx	TP + Ofx	TP + Cfx	TP + Nit	TP + Ery
E. coli (n = 12)	0.32-0.60	0.26-0.50	0.50-1.50	0.38-0.50	0.38-1.50*	0.32-1.50	0.38-0.50	0.32-0.60
K. pneumoniae (n = 15)	0.32-1.50	0.38-1.50	0.26-0.50	0.25-1.50	0.50-2.00	0.75-1.50	0.50-1.0	0.25-1.50
S. pneumoniae (n = 9)	0.26-1.00	0.50-1.25	0.38-0.50	0.38-1.50	1.00-1.50	0.50-1.50	0.75-1.50	0.32-1.25
S. dysenteriae (n = 10)	0.00-0.00#	0.00-1.25	0.50-1.00	0.38-1.50	0.32-1.50	0.10-1.50	0.32-1.50	0.00-0.10
S. aureus (n = 12)	0.32-1.50	0.32-1.25	0.38-1.50	0.5-1.50	1.0-1.75*	0.5-1.00	0.55-1.75	0.50-1.50
K. aerogenes (n = 6)	0.38-0.10	0.26-0.10	0.50-1.50	0.25-1.50	1.50-2.00	0.50-1.00	0.50-0.75	0.00-1.00
S. typhi (n = 7)	0.25-2.50	0.38-1.50	0.31-0.75	0.25-1.75	0.50-1.75*	0.5-1.50	0.25-1.50	0.31-1.50

Note. TP: *T. procumbens*; Chl: Chloramphenicol; Gen: Gentamycin; Cpx: Ciprofloxacin; Cfx: Cefixime; Nit: Nitrofurantoin; & Ery: Erythromycin (*Synergistic effect & #Resistance) the high percentage occurrence of breast cancer could be as a result of various factors, including sedentary lifestyle, tobacco smoking and alcohol usage, hereditary factors, exposure to estrogen and dietary intake (high consumption of processed food) [18].

Prostate cancer accounted for 27% of cancer cases within the study population, majorly affecting 43 sexagenarians and septuagenarian male patients. This finding agrees with [19] which reported that prostate cancer is one of the leading diagnosed cancers in older men. The survival rate is dependent on its aggressiveness in relation to being metastatic or localized with nearly 100% five years survival rate amongst men with localized type and about 30% survival rate for metastatic prostate cancer.

Moreover, 15% of the study population were diagnosed with lung cancer, affecting 24 patients. It was posited that lung cancer is the leading cause of death amongst cancer patients, affecting over 1.7 million people yearly [1]. Additionally, it was reported that lung cancer is one of the deadliest cancers, resulting in a short prognosis amongst cancer patients [20]. The use of tobacco and/or cigarette smoking has been reported to be one of the predisposing factors leading to lung cancer, causing long term damage of the cells, which could result in generating mutant cells during host cell repair mechanism [20]. In addition, it was submitted that about fifty carcinogens have been identified in tobacco smoke which could likely initiate lung cancer over a long-term cell damage [21]. However, lung cancer patients evaluated in this study could also develop the disease via 24 other predisposing factors, including, lifestyle, environmental factors, radiation, exposure to occupational and environmental carcinogens [22].

Sixteen sexagenarians' patients were diagnosed with leukemia in this study, constituting 10% of cancer cases in the entire study population. This finding corroborates the submission of previous investigator [23] which reported that leukemia was majorly diagnosed in adult patients. Furthermore, leukemia's survival rate is closely linked with age, subtype and aggressiveness of the disease. The predisposing factor of leukemia could be linked with occupational exposure, for example, rubber workers exposure to benzene during manufacturing of rubber and could be acquired via hereditary factors [24].

The result of the gender distribution revealed that the female patients had the highest occurrence of 62% (99 participants) in comparison with the male patients, presenting 38% (61 participants) of the total study population. In addition, 38% female patients were diagnosed with breast cancer which had the highest percentage occurrence amongst the cancer types reported within the participants. Furthermore, it was noted in the research that the highest cancer occurrence was observed in patients who were 61 years and above (sexagenarians), and especially in septuagenarians (70-79 years) with a total of 48 (30%) different cancer cases reported within this group, including 29 patients diagnosed with breast cancer (18.1%) and 12 (7.5%) patients were diagnosed with prostate cancer. These findings suggest that cancer is an age-dependent disease exacerbated with comorbidities because of opportunistic bacterial infections development due to the immunocompromised state of cancer patients, and damage caused by treatment such as chemotherapy impact when acting against cancerous cells. This finding corroborates the submission in [25] which posited that cellular repair mechanisms in humans are likely less effective as patients increase in age.

The residential distribution data collected from cancer patients attending FMC revealed that a high percentage of 70% patients resides in urban cities and majority had migrated back home at adulthood, following their awareness of being diagnosed with cancer. It was reported that residential factor regarding people dwelling in urban regions could contribute to the development of cancer due to the following factors: lifestyle, dietary intake (exposure to consumption of high processed foods, which could likely make the cells to grow quicker and die quicker, leading to a production of a mutant cells during host-cellular repair mechanism), exposure to industrial and environmental carcinogenic agents such as vinyl chloride, benzene and formaldehyde [26].

Moreover, the highest number of cancer patients was observed amongst the retirees, accounting for 52% (83) of the patients who participated in the study which was closely followed by the civil servants 58 (36%), and volunteers had 16 (10%) different cancer cases, including breast, leukemia, lung, oligodendroglioma, myeloma, colorectal and skin cancers. In accordance with [27], various forms of cancers could be developed as a result of high exposure to work-related carcinogens. Findings from the studies conducted in [28] reported that Great Britain recorded 8,000 cancer deaths in 2005 and there were 13,600 cancer registrations in 2004, which were linked with occupational exposure to carcinogenic agents. Additionally, some localized occupation cancer (benign) forms which are not aggressive takes time to develop over the years and could rapidly result in patient deterioration once manifested after retirement period, characterized with sedentary lifestyle [28, 29].

The duration of cancer development and diagnosis of cancer varies amongst the participants. The diagnostic timeframe ranges from 1-10 years, with those diagnosed within 1-4 years (breast cancer), rating high amongst the participants, consisting of 61 patients (38%) in this category. Comparatively, the lowest diagnostic timeframe amongst the participants was observed in patients diagnosed with oligodendroglioma within 1-2 years. Furthermore, patients diagnosed with prostate cancer amongst the participants were diagnosed within 1-5 years of its occurrence, rating 25% of the entire study population. In accordance with the submission in [30], the early diagnoses of cancers in patients which are treated promptly at benign stage and when it has not metastasized, are likely to be successful. Additionally, the report posits that virtually all women diagnosed with breast cancer are able to survive their disease for five years or more if diagnosed at an early stage. Conversely, with a sharp contrast, the survival rate falls to 3 in 10 women, if diagnosed with breast cancer at an advanced stage [30]. However, the management of cancer in older patients could be complex due to increase chances of comorbidities, infections, frailty, deterioration of somatic cell functions, and limited life expectancy, resulting in low survival rate amongst older people despite treatments [31].

A number of 115 patients reported they do not have a family history relating to cancer, rating the highest percentage of 71.88%. However, 26 (16.25%) patients amongst the participants reported they have family history related to cancer. Following their studies, it was reported that 10% of various cancer cases are likely caused by hereditary factors [32]. Additionally, it was reported that family history is one of the most important methods in evaluating risk factors relating to genetics and behavioral patterns [33]. Notably, other predisposing factors causing cancer could be attributed to alcohol intake and the use of tobacco or cigarette smoking. Findings from this research revealed that 11.2% (18) of the study population (participants) engaged in tobacco/cigarette smoking, whilst 44 patients (27.5%) engaged in the use of alcohol. Additionally, a total of 12 (7.5%) patients reported to have engaged in the use of alcohol and smoking. Noteworthy, 2/3 of the participants who were diagnosed with lung cancer engaged in the use of alcohol, and 1/3 of these patients engaged in smoking (tobacco/cigarette). As a result, the use of alcohol and tobacco smoking could be responsible for the development of lung cancer on a long-term damage and this result agrees with [34] which reported that in 2020, about 4% cancer cases, which accounts for more than 740,000 cases were initiated based on the use of alcohol and smoking worldwide.

Furthermore, the treatment options received amongst the cancer patients within the study population include the following: chemotherapy 49 (30.63%), surgery 38 (23.75%), chemotherapy and herbal therapy 31 (19.38%), radiotherapy 26 (16.25%), and herbal therapy 16 (10%). It is evident that chemotherapy ranks the highest method of treatment in this study. However, choosing a specific method of treatment following positive diagnoses of cancer in patients is dependent on a number of factors, including the types of cancer, stage (benign or malignant), duration of cancer and appearance of the malignance [35]. The frequent use of chemotherapy in this study could be closely linked with its effectiveness in the types of cancers evaluated. Additionally, cancer is a disease that has been found to weaken the immune system due to its proliferation, especially when it is metastatic [2, 22]. Plus, the use of chemotherapy as a method of treatment predisposes cancer patients to opportunistic infections due to the side effect of chemotherapeutic agent administered on the somatic cells [36]. Moreover, findings revealed that infection is commonly observed amongst cancer patients, leading to short- or long-term hospitalization, interfering with treatment options, and increased cost of health care delivery on cancer patients with a reduction in survival rate. Furthermore, bacterial infection remains a primary and leading cause of death amongst cancer patients [37].

The management of bacterial infection in cancer patients is usually based on the appropriate use of antibacterial agents with a comprehensive understanding of the frequently occurring bacterial pathogens and their antibiotic susceptibility patterns [13]. Notably, previous investigators revealed that bloodstream infections in conjunction with pneumonia were major factors contributing to high mortality rates in cancer patients. As a result, it was reported that sepsis resulted in a 36% mortality rate in cancer patients [13, 38]. Additionally, other frequently occurring infections in cancer patients, resulting in patient's death include pneumonia, influenza, sepsis, and parasitic infections [39].

The frequently occurring clinical bacterial isolates from cancer patients attending FMC, were collected from the hospital having gained their consent, these include *Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae, Shigella dysenteriae, Staphylococcus aureus, Klebsiella aerogenes* and *Salmonella typhi*. Clearly, the majority of these pathogens are Gram-negative organisms, including *E. coli*, *K. pneumoniae*, *K. aerogenes* and *S. typhi*. Findings from this research corroborates the submission in [40] which reported various Gram-negative bacteria isolated from blood samples of cancer patients which were numerous in comparison with gram positive organisms isolated from adult patients. Additionally, it was reported that a higher percentage of 69.9% of Gram-negative bacteria isolated from cancer patients in their research, constituting a larger proportion in comparison with Gram-positive isolates [13]. Moreover, previous investigators reported that *Klebsiella* spp., *Staphylococcus aureus*, and *Escherichia coli* were the most frequently occurring opportunistic bacterial isolates recovered from cancer patients which are noted for initiating various bacterial infections in cancer patients [33]. Notably, it was posited that infections initiated by Gram-negative organisms are implicated in high mortality rates in immunocompromised patients [41]. For example, Gram-negative organisms have been noted for initiating various infections, including *Pneumoniae*, *septicemia*, urinary tract infections, and surgical wound infections [42, 43]. The cancer patients attending FMC for symptom control, emotional/psychological support and treatments could be suffering from various bacterial infections due to the presence of opportunistic bacterial pathogens present in their blood samples, as a result of their weak immune system. This result corroborates the findings in [13] which reported various bacterial infections initiated by Gram-negative bacteria isolated from the blood samples of cancer patients investigated in their study.

Furthermore, the clinical bacterial isolates from cancer patients, attending FMC were evaluated for their susceptibility patterns against various conventional antibiotics, including cotrimoxazole, chloramphenicol, gentamycin, ofloxacin, augmentin, and erythromycin. Overall, the result of the antibiotic susceptibility testing of the clinical bacteria from cancer patients evaluated in this study revealed that plethora of the test organisms exhibited multidrug-resistant (MDR) patterns. For example, the percentage resistance of all the test bacterial organisms against cotrimoxazole was 66%, whereby 47 bacterial isolates were resistant to its inhibitory actions. Furthermore, 45% (32) of the total bacterial test isolates were resistant to augmentin, 55% (39) of the clinical isolates were resistant to ceftriaxone, 61% (43) were resistant to cefuroxime, 62% (44) were resistant to erythromycin, and 18% (25) were resistant against nitrofurantoin. Notably, the twelve clinical isolates of *Escherichia coli* tested for their susceptibility patterns to different forms of the antibiotics employed for the study were resistant against chloramphenicol, nitrofurantoin, and erythromycin. Additionally, the clinical isolates (12) of *Staphylococcus aureus* demonstrated high percentage resistance to cotrimoxazole (83%), ceftazidime (67%), erythromycin (75%), and cefuroxime (83%). The high rate of resistance exhibited by the MDRO in this study could be linked to unregulated dosage intake of various antibiotics by the participants (cancer patients) for infection control and/or during self-medication without adequate prescription by a medical practitioner, following medical consultation, thereby resulting in the resistance of the pathogens against the antibiotics. It was reported that the widespread use of antibiotics, both inside and outside of medicine plays a significant role in the emergence of resistant bacteria [44]. As a result, the inappropriate use of conventional antibacterial agents without proper prescription from a medical professional might have invariably resulted in the development of antibiotic resistance which is constituted as a major public health threat globally [45]. In addition, as noted by previous investigators, it was posited that resistance patterns exhibited by microorganisms could be associated with the presence of large plasmids and their ability for conjugation process [46]. Moreover, trans-conjugated plasmids are known to possess high molecular weight, which could be responsible for plasmids, harboring antibiotic resistance genes, leading to resistance [46]. Furthermore, findings from this study agree with previous investigator who reported genetic acquisition of resistance traits, prolonged exposure to therapeutics, and broad-spectrum use of antibiotics in cancer patients could significantly contribute to antibiotic resistance [29].

The result of the antibacterial activities of *A. conyzoides* and *T. procumbens* ethanolic leaf extracts at 200 mg/mL against MDRO, isolated from cancer patients were effective in its *in-vitro* inhibitory potentials. Findings from this research revealed the antibacterial potentials of *A. conyzoides* ethanolic extract at 200 mg/mL to be effective in inhibiting the clinical bacterial isolates from cancer patients, including the clinical isolate of *Streptococcus pneumoniae* with an inhibitory zone of 25.22 ± 0.83 mm. This result agrees with the submission in [47] which found *A. conyzoides* to be a potential source of antibacterial agent in controlling bacterial infections. Additionally, the ethanolic extract of *T. procumbens* was found to be effective against a good number of the clinical bacterial isolates from cancer patients, including inhibiting *S. pneumoniae* with a clear zone of inhibition of 8.30 ± 0.20 mm, showcasing its potential as a good source of antibacterial agent. This finding corroborates the submission of previous investigator, reporting *T. procumbens* to possess high rate of phytochemicals, including flavonoids, alkaloids, and saponins which could be responsible for their antibacterial activities against pathogenic microorganisms responsible for initiating bacterial infections [46].

Moreover, the synergistic effect of *Tridax procumbens* ethanolic leaf extracts and conventional antibiotics was very significant as it exhibited a broad-spectrum activity on the MDR bacterial isolates recovered from cancer patients. Overall, a good number of the MDR organisms were susceptible to the inhibitory actions posed by the combination of *Tridax procumbens* ethanolic leaf extract and the conventional antibiotics, resulted in synergistic efficacy. Interestingly, the combination extract of *Tridax procumbens* and ofloxacin were found to be the most effective against *Salmonella typhi* which exhibited multidrug resistant patterns against several antibiotics, including gentamycin, chloramphenicol and were also resistant against *Ageratum conyzoides* and *Tridax procumbens* ethanolic leaf extracts at 200 mg/mL. This finding suggests there could be an active ingredient embedded in *Tridax procumbens* ethanolic leaf extract and/or ofloxacin which could amplify their efficacy in conferring antibacterial activity against the resistant bacterial isolate - *S. typhi*. As a result, this finding revealed the significance of synergism and the result agrees with the submission in [48] which reported a significant synergistic interaction between plant extracts and some antibiotics against antibiotic-resistant bacterial isolates in their study.

Furthermore, whilst many of the bacterial isolates recovered from cancer patients exhibited MDR patterns against the conventional antibiotics used in this study, some bacterial isolates, including *Escherichia coli* was susceptible to erythromycin and nitrofurantoin. In addition, *Staphylococcus aureus* was susceptible to the inhibitory action elicited by gentamycin. Comparatively, the antibiotics were noted for their efficacy in inhibiting the bacterial isolates when compared with the antibacterial activities of *A. conyzoides* and *T. procumbens* which may be due to the purity level of conventional antibiotics. This result is in line with the submissions of previous investigators who reported that higher potency of antibiotics is closely linked to their high level of purity and inhibitory potentials in comparison with the crude state of plant extracts [17, 49]. Additionally, antibiotics are a product of large-scale industrial fermentation and the product of such process is usually pure, due to good manufacturing practice, great quality control, resulting in standardized products. Furthermore, the molecular size of antibiotics which aid their solubility in diluents may be another factor for their better performance, enhancing their penetration via cell wall into the cytoplasm of the organism where they act [7].

CONCLUSION

The findings of this research confirmed that cancer patients, due to their immunocompromised state, are highly susceptible to opportunistic bacterial infections despite the availability of various treatment options to manage their health. Notably, frequently isolated bacterial pathogens recovered from cancer patients investigated, including *Staphylococus aureus* and *Escherichia coli* exhibited multidrug-resistant (MDR) patterns against the conventional antibiotics tested in this study. However, the ethanolic leaf extracts of *Ageratum conyzoides* and *Tridax procumbens* demonstrated significant antibacterial activity against MDR bacterial pathogens recovered from cancer patients, including *Streptococcus pneumoniae*, highlighting their potential as promising sources of antibacterial agents. Furthermore, the synergistic efficacy observed between *T. procumbens* ethanolic extract and conventional antibiotics exhibited effective inhibitory action against MDR pathogens, especially against *Salmonella typhi*.

In conclusion, the findings of this research highlight the potential of Ageratum conyzoides [italicize and delete] and Tridax procumbens [italicize and delete] ethanolic leaf extracts as promising sources of antibacterial agents for managing opportunistic bacterial infections in immunocompromised cancer patients. Further purification and evaluation of the bioactive compounds from these medicinal plants are recommended for drug discovery and clinical trials. This approach could serve as an alternative therapy to combat antibiotic resistance observed in multidrug-resistant bacterial (MDRB) pathogens.

Author contributions: OOO & MKO: study design; **OOO:** data collection, statistical analysis, and manuscript first draft preparation, interpretation of results. All authors have agreed with the results and conclusions.

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Ethics declaration: The authors stated that the study does not require any ethical approval. In addition, the clinical bacterial isolates tested in this study were collected from the tertiary hospital, and subjected to confirmatory test in the laboratory, using modern microbiological techniques including molecular biology for identification purposes.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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