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Bacterial Endophytes from *Moringa oleifera* Leaves as a Promising Source for Bioactive Compounds

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Abstract: Bacterial endophytes reside within the tissues of living plant species without causing any harm or disease to their hosts. Bacterial endophytes have produced a variety of bioactive compounds that can be used for different biomedical applications. In the current study, two bacterial endophytes were isolated from healthy *Moringa oleifera* leaves, and identified genetically as *Stenotrophomonas maltophilia* and *Alcaligenes faecalis*. Phytochemical results illustrated that *A. faecalis* produced phenolics at 547.2 mg/g, tannins at 156.7 µg/g, flavonoids at 32.8 µg/g, and alkaloids at 111.2 µg/g compared to *S. maltophilia*, which produced phenolics at 299.5 mg/g, tannins at 78.2 µg/g, flavonoids at 12.4 µg/g, and alkaloids at 29.4 µg/g. GC-MS analysis indicated that *A. faecalis* extract has 24 bioactive compounds, including 9 major compounds, namely octadecanoic acid, hexadecanoic acid, linoleic acid ethyl ester, octadecenoic acid, methyl ester, methyl stearate, nonacosane, indolizine, palmitoleic acid, and heptacosane. On the other hand, *S. maltophilia* extract has 11 bioactive compounds, including 8 major compounds, namely oleic acid, octadecanoic acid, hexadecanoic acid, cis-2-phenyl-1, 3-dioxolane-4-methyl, ergotamine, diisooctyl phthalate, diethyl phthalate, and pentadecanoic acid. To check the safety of these extracts, the cytotoxicity of Ethyl acetate (EA) extracts of *S. maltophilia* and *A. faecalis* were evaluated against the Vero normal cell line, and the results confirmed that these extracts are safe to use. Moreover, results revealed that EA extracts of *S. maltophilia* and *A. faecalis* exhibited anticancer activity against the cancerous MCF7 cell line, where IC_{50} was 202.4 and 119.7 µg/mL, respectively. Furthermore, EA extracts of *S. maltophilia* had antibacterial and antifungal activity against Gram-positive and Gram-negative bacteria, and unicellular fungi. Likewise, the EA extract of *A. faecalis* exhibited antibacterial and antifungal activity against Gram-positive bacteria, as well as unicellular fungi, but did not show any activity against Gram-negative bacteria. Also, EA extracts of *S. maltophilia* and *A. faecalis* exhibited moderate antioxidant activity where IC_{50} were 146.2 and 147.6 µg/mL, respectively. In conclusion, the two isolated endophytic bacteria *S. maltophilia* and *A. faecalis* have promising bioactive compounds that have antibacterial, antioxidant, and anticancer activities.

Keywords: endophytes; *Moringa oleifera*; GC-MS; antimicrobial activity; antioxidant activity; anticancer activity

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1. Introduction

Over the past few decades, the prevalence of microbial diseases has increased rapidly [1]. Additionally, the abuse and misuse of antimicrobial medications led to the appearance of multi-drug resistant microbes, which have emerged as a major worldwide health issue [2]. An increasing number of bacteria and fungi are able to withstand the effects of antimicrobials by employing resistance mechanisms, such as enzyme activation, changed target locations, decreased cell permeability, and enhanced efflux due to over-expression [3]. All of these factors, when combined with the lack of new, effective antimicrobial agents,

are contributing to this trend [4]. This has caused the production of new antimicrobial medications to steadily decline, necessitating the search for and development of novel antimicrobial drugs derived from natural sources [5,6].

Plants are a very reliable source of microorganisms such as fungi, bacteria, and actinomycetes [7]. All plant species have endophytic microorganisms, such as bacteria, actinomycetes, and fungi, that are constantly present within their tissues, without causing any injury or disease [8]. These microorganisms are used in many different industries, such as agriculture, industry, and medicine, since they are thought of as a reservoir that hold many biologically active compounds [9–12]. Endophytes develop symbiotic relationships with several plant species and have the ability to control a wide range of host functions, including immune system stimulation, growth and development, and resistance to abiotic and biotic challenges [13,14]. *Moringa oleifera*, one of the most significant medicinal plants, has a variety of bioactive substances in its seeds, leaves, flowers, and pods [15,16]. *M. oleifera* is considered an effective agent against hypocholesterolaemia and hypolipidemia [17]. Endophytic microorganisms isolated from *M. oleifera* plants could be a promising source of broad-spectrum novel bioactive components as antimicrobial compound [18], against human pathogens as *B. cereus, S. aureus, E. coli*, and *S. marcescen* [19]. Endophytic microorganisms help to ensure environmental balance, and participate in the enhancement of crop yields and productivity as biofertilizers and biofungicides [20–22]. Along with the production of bioactive chemical compounds, many endophytic bacteria have shown an expected capacity for medical applications as antifungal and bactericidal activities [23]. Through ortho- and meta-cleavage, phenanthrene diols were converted to o-hydroxynaphthoates or naphthalene-1,2-dicarboxylic acid by *S. maltophilia* [24]. *S. maltophilia* was able to cause the synthesis of the amino acid tyrosine, which it then used in protein synthesis [25]. By producing an extracellular protease, *S. maltophilia* was able to shield sugar beetroot from Pythium-mediated damping-off [26]. *S. maltophilia* can produce lipase enzyme [27], hydroxylated and cyclopropane fatty acids [28], production of lytic enzymes, siderophores [29], metallo-β-lactamases [30], bio surfactants, enzymes including chitinase, lipase, and protease [31], The plant growth-promoting substances included hydrolytic enzymes, hydrogencyanide, phenolics, antioxidant substances, phytohormones, IAA, gibberellic acid, transzeatin ribosides, abscisic acid, ammonia, and phosphatise [32]. *A. faecalis* can produce maleic acid *cis-trans* isomerase, nicotinic acid, picolinic acid [33], abundant antifungal volatiles against *F. graminearum, F. equiseti, Alternaria alternata, Botrytis cinerea, Aspergillus niger*, and *Colletotrichum graminicola* [34], 1,2-benzenedicarboxylic acid bis (2α-methylheptyl) ester, cyclo (L-Pro-L-Val), cyclo (Gly-L-Pro), 3-pyridinecarboxylic acid, cyclo(L-Pro-L-Tyr), adenosine and L-Val [35], succinoglucan and exocellular acidic polysaccharide [36], and nitrilase [37]. Herein, this study aims to (1) isolate and identify bacterial endophytes from *Moringa oleifera* leaves, (2) determine phytochemicals and bioactive compounds using GC-MS, and (3) assess their antimicrobial, antioxidant, and anticancer activities.

2. Materials and Methods

2.1. Isolation of Molecular Identification of Endophytic Bacteria

Sterilization of *Moringa oleifera* leaves was carried out according to method used by Khalil et al. [38] for removing the epiphytic microorganisms. One gram of sterilized *M. oleifera* leaves was crushed in 9 mL of sterile water saline solution using a disinfected mortar, under sterile conditions. The leaf extract was diluted in sterile aqueous solution (10^{-1}, 10^{-2} and 10^{-3}). The samples were put on sterilized nutrient agar (NA) plates and spread by a sterilized glass transmitter. Plates were incubated at 30 °C for 5 days. The colonies were counted as colony forming units (CFU) per gram. They were then sub-cultured twice on NA and stored at 4 °C. The purified colonies were subcultured for further studies [39]. Then, molecular identification of isolated bacterial endophytes was carried out; DNA extraction of *S. maltophilia* and *A. faecalis* was carried out using Zymo Research kit (Zymo Research, Tustin, CA, USA). PCR and sequencing was carried out according to method used by [6]. For phylogenetic analysis, BLAST was used to retrieve similar sequences from NCBI [40].

2.2. Extraction of Bioactive Compounds from Bacterial Endophytes

The secondary metabolites from bacterial endophytes strains were obtained by culturing 200 µL of bacterial suspension into 500 mL nutrient broth in a 1 L flask, then culture was incubated at 28 °C for 5 days at 130 rpm. The culture was centrifuged at 5000 rpm for 30 min, then the supernatant was mixed with ethyl acetate (1:1 volume) and left overnight at 4 °C. Then, secondary metabolites were disjointed using separating funnel. The extract was evaporated using a rotary evaporator at 40 °C to prepare the EA crude extract metabolites. The residue was re-dissolved in EA. The concentrated crude extract was then stored at 4 °C for further experiments [41].

2.3. Screening of Bacterial Phytochemicals

A total phenolic was estimated by adding of 0.5 mL of bacterial filtrate was mixed well with 0.5 mL of Folin's reagent and agitated for 3 minutes. Next, 3 mL of distilled water and 1 mL of saturated sodium carbonate solution were added, and these two components were thoroughly mixed. The result was measured at 725 nm [42]. After being dissolved in 2 mL of methanol, 500 µL of the bacterial extract were combined with 3 mL of distilled water, 100 µL of potassium acetate (1 M), and 100 µL of aluminium chloride to obtain the total flavonoids. The samples were then kept in the dark for 30 min. At 415 nm, the mixture's absorbance was determined [43].

The total tannins were determined by adding a few drops of 10% ferric chloride solution (light yellow) to 2 mL of the bacterial extract's aqueous solution. Gallic tannins were present when a blackish–blue hue appeared, and catechol tannins were present when the green–black hue appeared. Using Wagner's reagent, bacterial crude extracts were examined for the synthesis of alkaloids. Wagner's reagent, which contains 1.27 g of iodine and 2 g of potassium iodide in 100 mL of water, was applied to a portion of the extract and left to stand for three to five drops, while a reddish–brown precipitate was looked for [44].

2.4. Gas Chromatography-Mass Spectroscopy (GC–MS) Analysis

The bacterial bioactive compounds were observed, counted, and recognized using GC-MS. When compared to the spectrum of known chemicals kept in the WILEY 09 (Wiley, New York, NY, USA) and NIST 11 libraries, the name, retention time peak area, molecular weight, and structure of the identified molecules were also assayed [45].

2.5. Antimicrobial Activity

Antimicrobial activity of EA extracts from *S. maltophilia* and *A. faecalis* were evaluated toward *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 *Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6051, *Candida albicans* ATCC 90028 and *Cryptococcus neoformans* ATCC 14116, using the agar well diffusion method. Using a sterile cork-borer, wells (8 mm) were cut, and 100 µL of EA extracts, AMC and FLU (1000 µg/mL) were put to each well individually on a streaked Mueller-Hinton and PDA for bacteria and fungi, respectively. All plates were incubated for 48 h at 28 °C for unicellular fungi, and 24 h at 37 °C for bacteria. The inhibition zones were measured and noted following incubation [46–48]. The microdilution method was used to identify the minimal inhibitory concentration (MIC_{90}) for EA extracts of bacterial endophytes against all tested bacterial and fungal species [49,50].

2.6. Antioxidant Activity

EA extracts of bacterial endophytes were evaluated for antioxidant activity using the DPPH (2, 2-diphenyl-1-picrylhydrazyl) method [38], with a few modifications. The EA extracts and positive control (ascorbic acid) were tested to scavenge DPPH radicals at various concentrations (1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.81, and 3.9 µg/mL).

Antioxidant activity of positive control and extracts was determined as DPPH scavenging activity (%) (Equation (1)):

$$\text{DPPH scavenging activity}(\%) = \frac{\text{OD of control} - \text{OD of sample}}{\text{OD of control}} \times 100 \quad (1)$$

2.7. In Vitro Cytotoxicity

The cytotoxicity of EA extracts of bacterial endophytes and positive control (Taxol) at different concentrations from 1000 to 31.25 μg/mL was determined using the MTT protocol [51], with minor modifications against normal Vero and cancerous MCF7 cell lines which were collected from the ATCC. As illustrated in Equations (2) and (3), the viability and inhibition percentages were determined as follows:

$$\text{Viability } \% = \frac{\text{Test OD}}{\text{Control OD}} \times 100 \quad (2)$$

$$\text{Inhibition } \% = 100 - \text{Viability } \% \quad (3)$$

2.8. Statistical Analysis

The data were expressed as the mean ± St DEV value, which was calculated by using Minitab 18 software extended with a statistical package and Microsoft Excel 365.

3. Results and Discussion

3.1. Identification of Bacterial Strains

As a consequence, 16S rRNA gene sequence-based bacterial identification has been recognized as an accurate approach to bacterial identification. The 16S rRNA gene nucleotide sequences provide a bacterium-specific signature. The results in Figure 1 showed that the two bacterial isolates were identified genetically as *Alcaligenes faecalis* and *Stenotrophomonas maltophilia*, and recorded in the gene bank with accession numbers OQ860078 and OQ860079. This result agreed with previous studies they revealed *A. faecalis* and *S. maltophilia* as endophytic bacteria isolated from different healthy plants [52–55]. Ray, Swapnil, Singh, Singh, Sarma and Singh [52] reported that *Alcaligenes faecalis* has ability to induce host defence against *Sclerotium rolfsii* through induction of phenolics and antioxidant enzymes. Furthermore, endophytic *A. faecalis* (CFRB1) can be used as a novel bio-stimulant for enhancing in planta forskolin content during the cultivation of *C. forskohlii* [53]. Also, BHU 12, BHU 16, and BHU M7, three endophytic *Alcaligenes* sp. strains, were isolated from the leaves of *Abelmoschus esculentus* and *Andrographis paniculata* [56]. Moreover, *Alcaligenes* sp. was also isolated from *Helianthus annuus L.* under drought stress [56]. Furthermore, *Alcaligenes* sp. isolated from *Cannabis sativa* plants watered with oil tissues [57]. In the North West province of South Africa, *S. maltophilia* JVB5 was isolated from the endosphere of sunflower roots [58]. *S. maltophilia* is widespread in the environment, and they are frequently found around plants [59]. Additionally, *S. maltophilia* SEN_1 was recorded as a seed endophyte [54]. Moreover, *Stenotrophomonas* was isolated from the stems of sugar cane variety SP80 [60]. Numerous investigations have identified *Moringa oleifera* as a plant reservoir for endophytic microorganisms, which are thought to be a source of bioactive components [8,61].

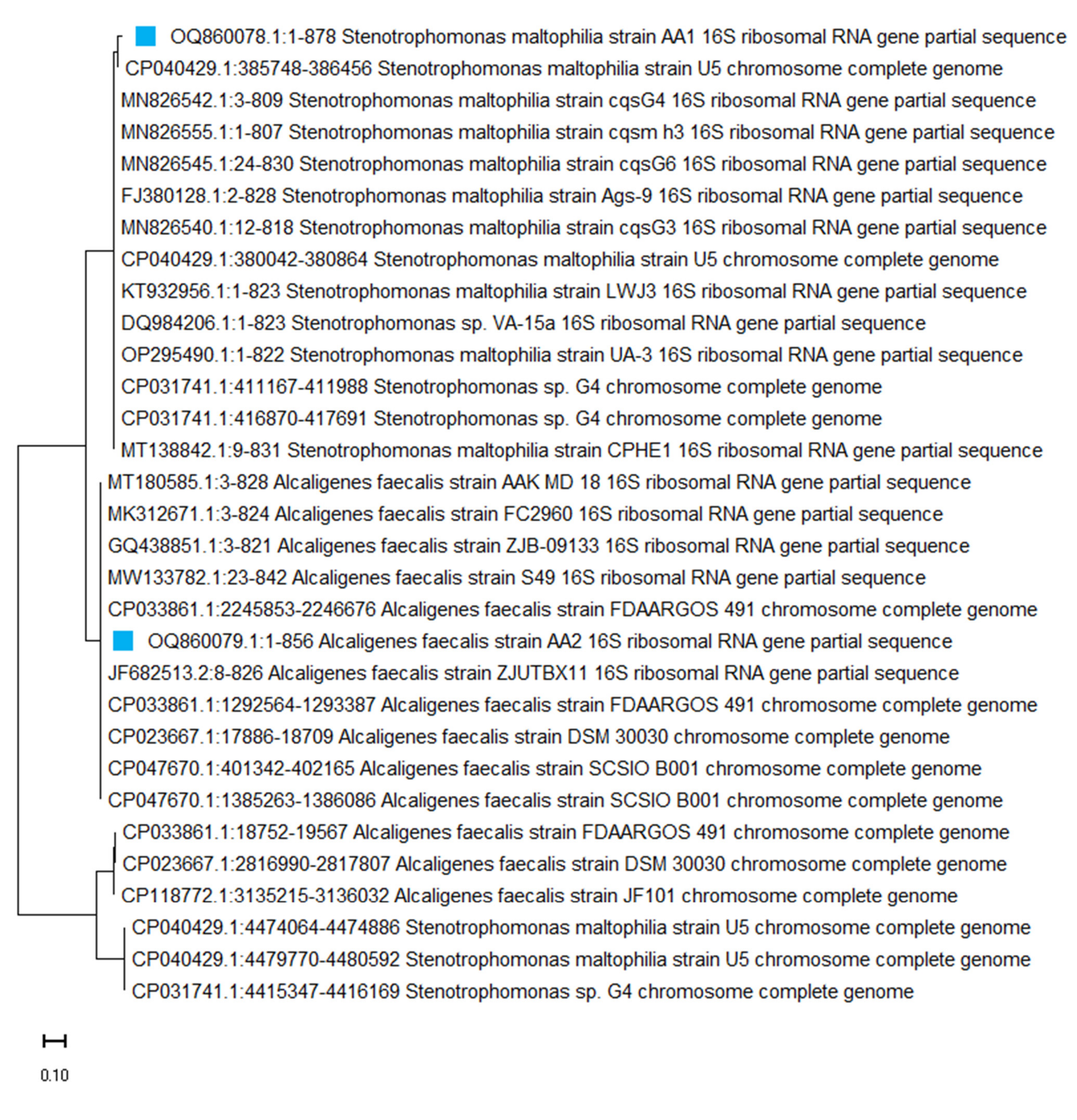

Figure 1. Phylogenetic tree of *S. maltophilia* and *A. faecalis* with accession numbers OQ860078 and OQ860079.

3.2. Screening of Bacterial Phytochemicals

Endophytic microorganisms, including fungi, actinomycetes, and bacteria, can produce a wide range of bioactive secondary metabolites [62]. Results in Figure 2 indicated the ability of tested bacterial strains to produce high amounts of phenolics, tannins, flavonoids, and alkaloids. Further, *A. faecalis* produced 547.2 mg/g of phenolics, which are significantly ($p < 0.05$) higher than those produced by *S. maltophilia* 299.5 mg/g. Salicylic, caffeic, and ellagic acids, among others phenolic, could enhance the bactericidal activities against human pathogenic bacteria; thus, the presence of these phenolics is considered an indicator of the bacterial extract as antimicrobial agents through the antioxidant mechanism [63].

A. faecalis produced more flavonoids (32.8 µg/g) compared to *S. maltophilia* (12.4 µg/g). Humans can benefit from a wide range of pharmacological properties of flavonoids, including their capacity to neutralize free radicals, ability to prevent coronary heart disease, and anti-atherosclerotic, hepatic-protective, anti-inflammatory, and anticancer properties [63]. Flavonoids are regarded as dietary supplements that promote health and fight disease. Today, it is regarded a crucial ingredient in a range of nutraceuticals, pharmacological, medical, cosmetic, and other applications [64,65]. Furthermore, *A. faecalis* produced more alkaloids (111.2 µg/g) than *S. maltophilia* (29.4 µg/g). In a previous study, it was proven that *S. maltophilia* metabolites contain a novel alkaloid called new pyrazinoquinazoline [66]. Alkaloids rank among the most significant categories of natural products, due to their abundance, structural variety, and complexity. Alkaloids are divided into isoquinolines, quinolines, indoles, piperidine alkaloids, etc., depending on their fundamental chemical structures. Alkaloids' antibacterial properties have been identified through in-depth investigations [67]. *A. faecalis* created more total tannins (156.7 µg/g) than *S. maltophilia* (78.2 µg/g). Additionally, tannins have been demonstrated to be effective antimicrobials and powerful inhibitors of viral infections in a variety of ecological settings and in vitro assessments [68].

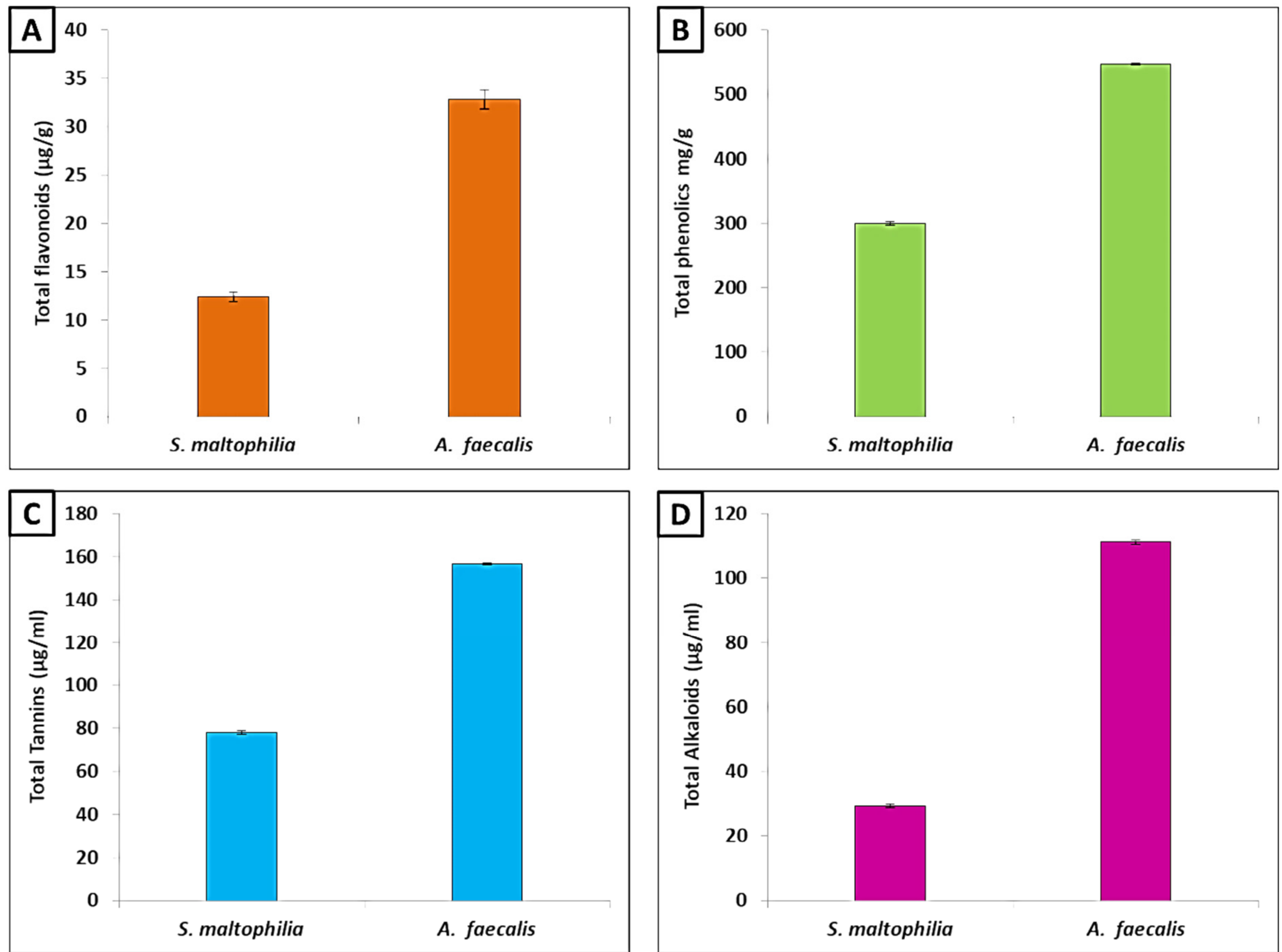

Figure 2. Phytochemical analysis of *S. maltophilia* and *A. faecalis*. (**A**) Total flavonoids; (**B**) total phenolics; (**C**) total tannins; (**D**) total alkaloids.

3.3. Gas Chromatography–Mass Spectroscopy (GC–MS) Analysis

Results in Figure 3A and Table 1 indicated that the *A. faecalis* extract has 24 bioactive compounds, including nine major compounds, namely octadecanoic acid, hexadecanoic

acid, linoleic acid ethyl ester, octadecenoic acid, methyl ester, methyl stearate, nonacosane, indolizine, palmitoleic acid, and heptacosane. The amount of evidence indicating that endophytic bacteria have a great potential for creating a variety of as-yet-undisclosed compounds is accumulating [69]. Our results are similar to Zote et al. [70], who reported that *Alcaligenes* sp. metabolites contain many bioactive compounds. Fatty acids perform vital roles as metabolites and nutritive substances in living organisms [71]. These fatty acids are recorded as antifungal and antibacterial agents. Due to the presence of biologically active compounds, endophytic *Alcaligenes* sp. metabolites have pharmacological and therapeutic properties [72]. Additionally, ester compounds (octadecenoic acid, methyl ester and linoleic acid ethyl ester) have antibacterial properties [73,74]. Results in Figure 3B and Table 1 indicated that the *S. maltophilia* extract has 11 bioactive compounds, including eight major compounds, namely oleic acid, octadecanoic acid, hexadecanoic acid, cis-2-phenyl-1, 3-dioxolane-4-methyl, ergotamine, and pentadecanoic acid. These results are similar to previous studies that proved the present of novel compounds in *S. maltophilia* metabolites [32]. Thus, it can applied in biological control of pathogens, including multi-drug-resistant anticancer and antioxidant activities [75]. Fatty acids, including octadecanoic acid, hexadecanoic acid, linoleic acid ethyl ester, octadecenoic acid, methyl ester, and palmitoleic acid, have strong fungicidal and bactericidal activity [76].

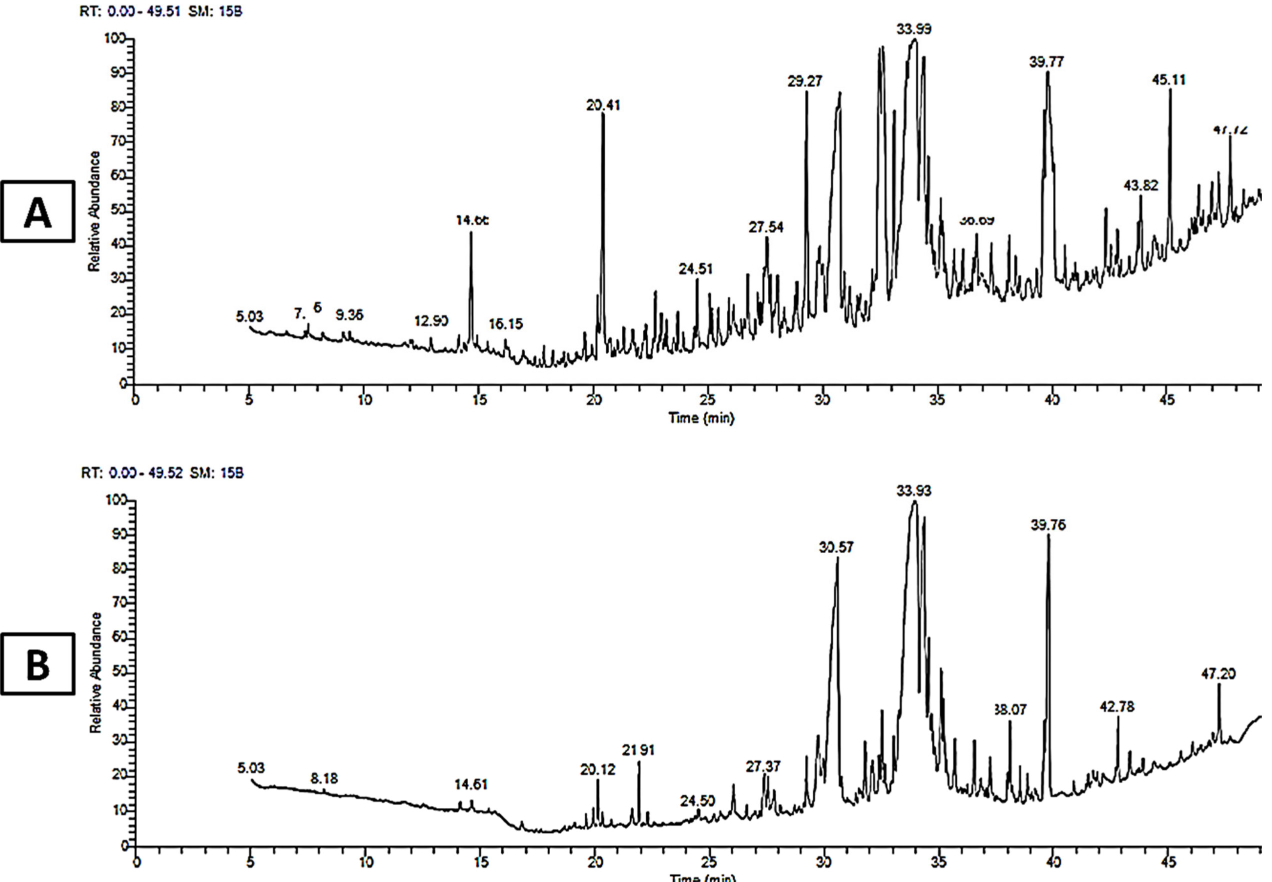

Figure 3. Gas chromatography–mass spectroscopy (GC–MS) analyses of endophytic bacterial extracts (**A**) *A. faecalis* and (**B**) *S. maltophilia*.

Table 1. Gas chromatography–mass spectroscopy (GC–MS) analyses of *A. faecalis* and *S. maltophilia*.

No.	Compound Name	RT (min)	Peak Area %		Activity	Ref
			Bacterial Strain			
			A. faecalis	*S. maltophilia*		
1	Indolizine	14.67	1.64	-	Antimicrobial and antimutagenic	[77]
2	Caryophyllene	17.82	0.24	-	Anticancer, antioxidant, antimicrobial properties	[78]
3	Docosane	19.61	0.38	-	Antimicrobial activity	[79]
4	Dotriacontane	20.72	0.17	-	Cytotoxic effects against hepatocarcinoma, antioxidant activity, antibacterial and antiviral	[80]
5	Dodecanoic acid	21.70	0.32	-	Antimicrobial	[81]
6	Carotol	22.27	0.40	-	Antifungal	[82]
7	Apiol	23.89	0.24	-	Cancer, chemotherapy antimicrobial	[83]
8	Tetradecanoic acid	26.03	-	0.73	Antibacterial activity	[84]
9	Pentadecanoic acid	27.37	-	1.10	Antibacterial	[85]
10	Heptatriacotanol	27.93	0.44	-	Antimicrobial	[86]
11	Hexadecanoic acid	29.28	8.06	5.35	Antioxidant, antibacterial, anti-inflammatory, antimicrobial.	[9]
12	Palmitoleic acid	29.84	1.22	-	Antibacterial properties	[87]
13	Oleic Acid	29.98	0.89	29.44	Antibacterial activity and antifungal activity.	[76,88]
14	cis-11-Eicosenoic acid	31.13	0.49	0.98	Antioxidant, antimicrobial and anticancer	[89]
15	Hepatadecanoic acid	31.48	0.31	-	Antimicrobial and antifungal	[90]
16	Octadecenoic acid, methyl ester	32.66	3.24	-	Antimicrobial, antioxidant and anticancer	[91]
17	Methyl stearate	33.08	2.33	-	Antibacterial, antioxidant and antifungal	[92]
18	Linoleic acid ethyl ester	33.62	3.38	0.95	Antifungal	[92]
19	Octadecenoic acid	34.01	17.49	9.57	Antimicrobial, antioxidant and anticancer	[91]
20	Cis-2-phenyl-1, 3-dioxolane-4-methyl	34.52	-	1.87	Antimalarial	[93]
21	Ergotamine	36.70	0.78	1.34	Pharmacological activity as vasoconstriction, adrenergic blockade.	[94]
22	Stearic anhydride	38.51	-	0.73	Antibacterial	[95]
23	Ethyl Iso-allocholate	41.70	-	0.35	Antimicrobial	[96]
24	Nonacosane	45.12	2.24	-	Nematicides	[97]
25	Isochiapin-B	46.05	0.35	-	Antimicrobial and antioxidant	[98]
26	Digitoxin	46.35	0.65	-	Cardiac drugs, antileishmanial, anticytomegalovirus	[99–101]
27	Methyl commate	46.91	0.58	-	Antioxidant and antimutagenic	[102]
28	Cholest-22-ene-21-ol, 3,5-dehydro-6-methoxy-, pivalate	47.23	0.77	-	Anti-inflammatory	[103]
29	Heptacosane	47.73	1.13	-	Antimicrobial, anti-multidrug resistance	[104–106]

3.4. Cytotoxicity

The first stage in determining the safety of bioproducts is considering their cytotoxicity on normal cell lines in vitro [105]. Vero cells are derived from the kidney of an African green monkey, and are one of the more commonly used mammalian continuous cell lines in microbiology and molecular and cell biology research. In the current study, the cytotoxicity of EA extracts of *S. maltophilia* and *A. faecalis* was evaluated against the Vero normal cell line, as illustrated in Figure 4A,B. Results showed that IC_{50} of EA extract of *S. maltophilia* and *A. faecalis* was 451.2 and 272.8 µg/mL, respectively. Cell viability percentages of Vero cells at different concentrations of *S. maltophilia* of 31.25, 62.5, 125, 125, and 500 µg/mL were 99.7, 99.5, 89.9, 69.4, and 43.7%, respectively. Also, percentages at different concentrations of *A. faecalis* if 31.25, 62.5, 125, 250, and 500 µg/mL were 99.8, 99.3, 80.6, 55.5, and 26.6%, respectively. In general, if the IC_{50} is $\geq$90 µg/mL, the material is classified as non-cytotoxic [106].

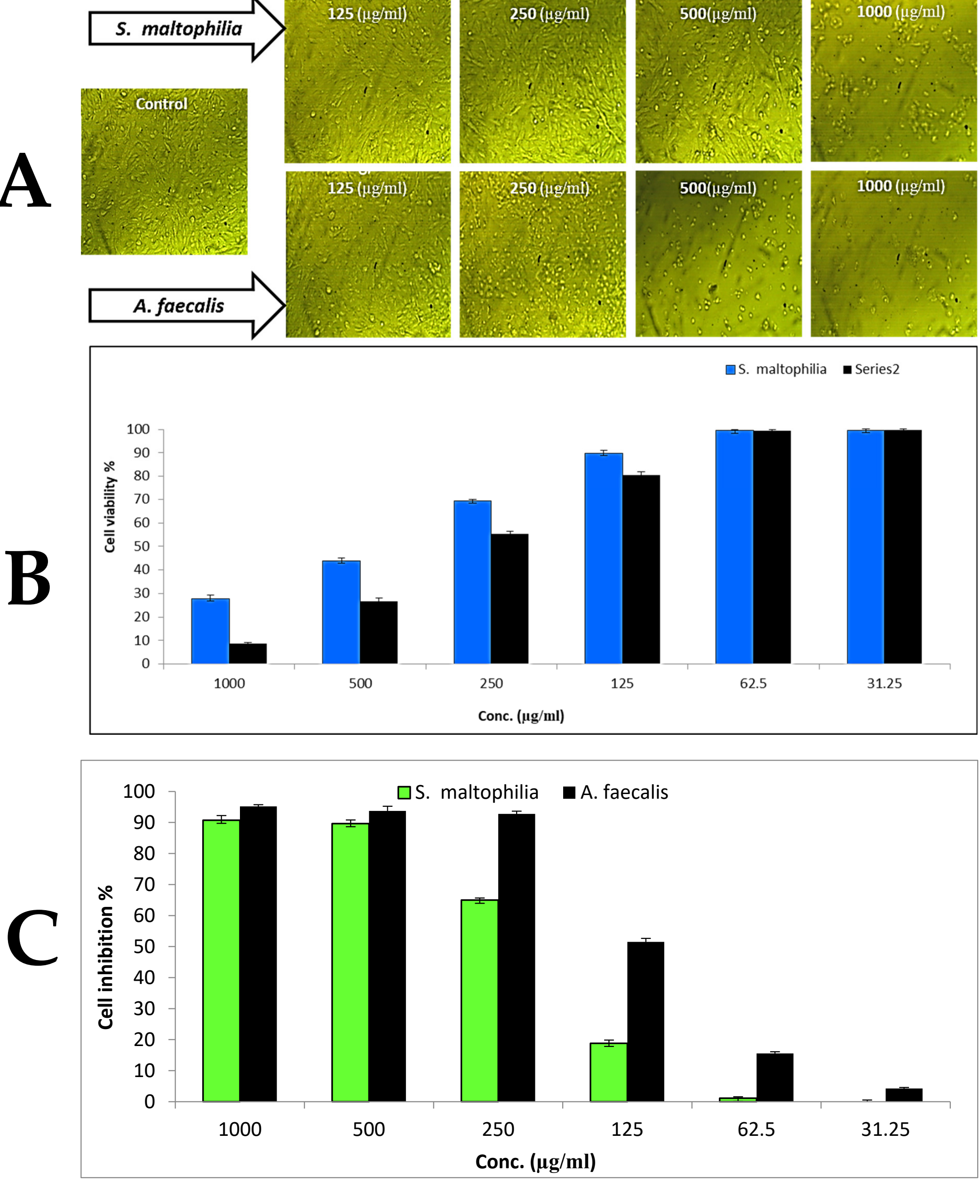

Figure 4. Cytotoxicity of Taxol and EA extracts of *S. maltophilia* and *A. faecalis* toward Vero normal line (**A**,**B**) and cancerous MCF7 cell line (**C**).

Cancer is caused by both extrinsic (tobacco, alcohol, smoking, unhealthy diet, lifestyle, and external conditions such as ultra-violet or ionizing and non-ionizing radiation exposure) and intrinsic (ageing, DNA mutation, hormonal disturbance, and a compromised immune system) factors that cause the activation or inactivation of specific genes, resulting in abnormal cell growth [107]. The number of reported instances of cancer each year is rising, making it one of the leading causes of mortality in the world. The discovery and development of novel and improved chemotherapeutics derived from natural sources are recent developments in the treatment of cancer [108]. According to recent research, endophytes are used as an alternate source for the development of new anticancer medications, due to their naturally occurring bioactive chemicals. In this study, the anticancer activities of EA extracts of *S. maltophilia* and *A. faecalis* were assessed toward the cancerous MCF7 cell line (Figure 4C). Results revealed that Taxol as positive control of anticancer agents exhibited promising anticancer activity towards the MCF7 cell line where IC50 was 6.7 μg/mL. Also, both EA extracts of *S. maltophilia* and *A. faecalis* exhibited anticancer activities against MCF7, but significantly lower ($p < 0.05$) than that of Taxol. Additionally, both EA extracts of *S. maltophilia* and *A. faecalis* exhibited anticancer activity against MCF7, where the activity of *A. faecalis* was higher than that of *S. maltophilia.* Moreover, the IC_{50} of *S. maltophilia* and *A. faecalis* was 202.4 and 119.7 μg/mL, respectively. Furthermore, cell inhibition percentages of *A. faecalis* were 95.2, 93.7, 92.7, and 51.5% at concentrations 1000, 500, 250, and 125 μg/mL, respectively. Also, cell inhibition percentages of *S. maltophilia* were 90.7, 89.6, 64.9, and 18.8%, respectively.

3.5. Antimicrobial Activity

The development of pathogenic fungi and bacteria that resist available antibiotics, and the ineffectiveness of current antifungal and antibacterial agents to treat a variety of bacterial and fungal infections, has led to worldwide health issues; therefore, novel and potent antimicrobial agents are required [109]. Recently, natural substances derived from bacteria, fungi, and plants have been used alone or in combination with antibiotics to treat multidrug-resistant-causing infectious diseases [110]. In the current study, the antimicrobial activity of the EA extract of *S. maltophilia* and *A. faecalis* against Gram-negative bacteria, Gram-positive bacteria, and unicellular fungi was assessed, as illustrated in Table 2. Results illustrated that the EA extract of *S. maltophilia* exhibited antibacterial activity against both Gram-negative and Gram-positive bacteria, as well as against unicellular fungi. The inhibition zones of the EA extract of *S. maltophilia* at a concentration of 2000 μg/mL against *E. coli, P. aeruginosa, E. faecalis, S. aureus* and *B. subtilis* were 11.8 ± 0.35, 14.9 ± 0.90, 15.0 ± 1.00, 10.3 ± 0.58 and 18.2 ± 0.76 mm, respectively, as shown in Figure 5, where the efficacy was the highest toward *B. subtilis,* while lowest against *S. aureus*. Moreover, the EA extract of *S. maltophilia* showed antifungal activity against *C. albicans* and *C. neoformans*, where the inhibition zones were 14.1 ± 1.21 and 11.9 ± 0.90 mm, respectively. Likewise, the MIC_{90} of the EA extract of *S. maltophilia* toward *C. albicans* and *C. neoformans* were 125 and 250 μg/mL, respectively.

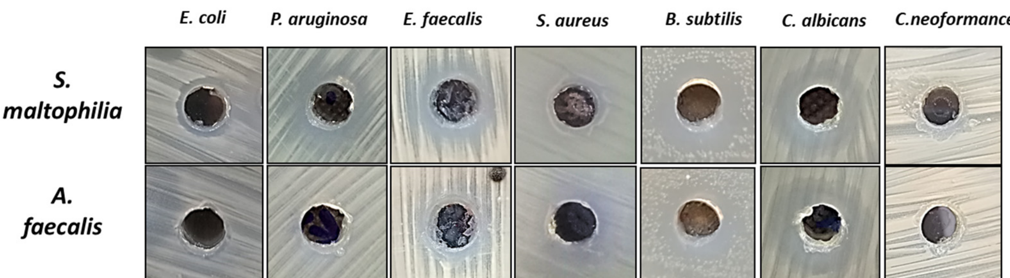

Figure 5. Inhibition zones of EAs extract of *S. maltophilia* and *A. faecalis* toward all tested bacterial antifungal strains.

Table 2. Antimicrobial activity of EA extracts of *S. maltophilia* and *A. faecalis*.

Test Microorganism	EA	EA Extract of *S. maltophilia*		EA Extract of *A. faecalis*		AMC/FLU	
		IZ */mm	MIC_{90}	IZ/mm	MIC_{90}	IZ/mm	MIC_{90}
E. coli	0.0	11.8 ± 0.35^{cd}	500	0.0 ± 0.00^{e}	N D	9.65 ± 0.65^{c}	1000
P. aeruginosa	0.0	14.9 ± 0.90^{b}	250	0.0 ± 0.00^{e}	N D	10.5 ± 0.3^{bc}	1000
E. faecalis	0.0	15.0 ± 1.00^{b}	250	12.9 ± 1.10^{bc}	500	9.2 ± 0.5^{c}	1000
S. aureus	0.0	10.3 ± 0.58^{d}	1000	11.1 ± 1.10^{cd}	500	10.45 ± 0.55^{bc}	1000
B. subtilis	0.0	18.2 ± 0.76^{a}	125	15.0 ± 1.00^{ab}	250	12.7 ± 0.7^{a}	500
C. albicans	0.0	14.1 ± 1.21^{bc}	250	17.3 ± 1.32^{a}	125	11.75 ± 0.75^{b}	500
C. neoformans	0.0	11.9 ± 0.90^{cd}	500	10.3 ± 0.58^{d}	1000	9.7 ± 0.3^{c}	1000

* IZ means inhibition zone at concentration 1000 µg/mL, means minimum inhibitory concentration 90. Values are the means and standard deviation of three independent replicates followed by different letters, which are significantly different ($p \leq 0.05$) according to the Tukey test.

On the other hand, the EA extract of *A. faecalis* exhibited weak antibacterial activity toward Gram-positive bacteria only ($p < 0.05$), and did not give any inhibition on Gram-negative bacteria. Results in Table 2 illustrated that the inhibition zones of the EA extract of *A. faecalis* at a concentration of 1000 µg/mL were 12.9 ± 1.10, 11.1 ± 1.10 and 15.0 ± 1.00 mm toward *E. faecalis*, *S. aureus* and *B. subtilis*, respectively, where the MIC_{90} was 250–500 µg/mL. Furthermore, the EA extract of *A. faecalis* had antifungal activity toward *C. albicans* and *C. neoformans* where the inhibition zones were 17.3 ± 1.32 and 10.3 ± 0.58, respectively. Compared to AMC/FLU as the standard antibacterial/antifungal agent, results showed that the antimicrobial activity of the EA extract of *S.* maltophilia was significantly higher than AMC/FLU ($p < 0.05$). Also, results revealed the MIC_{90} of AMC/FLU toward bacterial and fungal strains was in the range of 500–1000 µg/mL. Rojas-Solís et al. [111] isolated endophytic *S. maltophilia* from *Physalis ixocarpa*, and found that it exhibited promising antifungal activity against *Botrytis cinerea*, due to *S. maltophilia* having the ability to produce sulphur-containing compounds, such as the antimicrobial volatile dimethyl disulphide (DMDS). Legrifi et al. [112] reported that endophytic *Alcaligenes faecalis ACBC1* and *Bacillus amyloliquefaciens* SF14 showed promising results, as they were highly effective in controlling the disease severity of the olive root rot disease caused by *P. schmitthenneri*.

The antibacterial and antifungal activities of the EA extracts of *S. maltophilia* and *A. faecalis* may be attributed to the presence of more compounds that have antibacterial/antifungal activity, such as hexadecanoic acid, oleic acid, octadecanoic acid, linoleic acid, diisooctyl phthalate, cis-13-octadecenoic acid and palmitoleic acid (Table 1). There are many mechanisms illustrating the antimicrobial activity of the endophytic bacterial extract, such as the suppression of fatty acid production, which is the mechanism via which unsaturated fatty acids of bacterial endophyte exert their antibacterial effects [113]. The fatty acid methyl ester is a promising antibacterial drug due to its safety and effectiveness. Its primary site of action is the pathogenic microorganism cell membrane. Additionally, it affects how cells produce energy, inhibits the functioning of enzymes and, ultimately, directly lyses pathogenic microorganisms cells [114].

3.6. Antioxidant Activity

ROS causes cancer, cardiovascular disease, ischemia, Alzheimer's, diabetes, hypertension, and aging [115]. Antioxidant-active substances protect cells from ROS and oxygen-derived free radicals, which cause DNA damage, carcinogenesis, and cellular degeneration [116,117]. Therefore, one way to limit the harm that reactive species might cause the body is by comprehending and managing their intracellular amounts. Endophytic bacteria are thought to be a significant source for a variety of natural products with a variety of uses, and may be a source of novel antioxidant chemicals [118]. In this study, the antioxidant

activities of the EA extracts of *S. maltophilia* and *A. faecalis* were evaluated using DPPH method (Table 3). Results showed that both *S. maltophilia* and *A. faecalis* have moderate antioxidant activity. Compared to AA where IC50 of AA was 6.32 μg/mL, the antioxidant activity of *S. maltophilia* was significantly higher than *A. faecalis* ($p < 0.05$), where the IC_{50} was 146.2 and 147.6 μg/mL, respectively. Table 3 shows that the antioxidant activity of *S. maltophilia* at concentrations of 1000, 500, 250, 125, and 62.5 was 88.67 ± 1.53, 80.67 ± 1.15, 61.03 ± 1.05, 47.83 ± 1.26 and 30.67 ± 1.15%, respectively. Moreover, the antioxidant activity of *A. faecalis* at concentrations of 1000, 500, 250, 125, and 62.5 was 81.17 ± 1.26, 73.33 ± 1.15, 50.90 ± 0.85, 40.10 ± 1.15 and 20.07 ± 0.90%, respectively. On the other hand, concentrations of 7.81 and 3.9 in both *S. maltophilia* and *A. faecalis* did not show any activity.

Table 3. Antioxidant activity of EA extracts of *S. maltophilia* and *A. faecalis*.

Conc (μg/mL)	Antioxidant Activity %			IC_{50} (μg/mL)		
	AA	*S. maltophilia*	*A. faecalis*	AA	*S. maltophilia*	*A. faecalis*
1000	99.27 ± 0.46 ^{a}	88.67 ± 1.53 ^{a}	81.17 ± 1.26 ^{a}	6.32	146.2	247.6
500	98.67 ± 0.58 ^{a}	80.67 ± 1.15 ^{b}	73.33 ± 1.15 ^{b}			
250	95.00 ± 1.00 ^{b}	61.03 ± 1.05 ^{c}	50.90 ± 0.85 ^{c}			
125	89.93 ± 0.90 ^{c}	47.83 ± 1.26 ^{d}	40.10 ± 1.15 ^{d}			
62.5	80.33 ± 0.76 ^{d}	30.67 ± 1.15 ^{e}	20.07 ± 0.90 ^{e}			
31.25	73.47 ± 1.29 ^{e}	20.47 ± 1.75 ^{f}	11.67 ± 0.58 ^{f}			
15.62	64.27 ± 0.64 ^{f}	6.33 ± 0.58 ^{g}	4.33 ± 0.58 ^{g}			
7.81	52.33 ± 1.53 ^{g}	0.00 ^{h}	0.00 ^{h}			
3.9	41.27 ± 1.10 ^{h}	0.00 ^{h}	0.00 ^{h}			

AA means Ascorbic acid, (Data represent mean ± SD, n = 3) (Letters from a to h revealed to significance power).

4. Conclusions

In this study, two endophytic bacteria *S. maltophilia* and *A. faecalis* were isolated and identified according to molecular method. Phytochemical results illustrated that *A. faecalis* produces phenolics at 547.2 mg/g, tannins at 156.7 μg/g, flavonoids at 32.8 μg/g and alkaloids at 111.2 μg/g, compared to *S. maltophilia*, which produces phenolics at 299.5 mg/g, tannins at 78.2 μg/g, flavonoids at 12.4 μg/g, and alkaloids at 29.4 μg/g. GC-MS analysis indicated that the *A. faecalis* extract has 24 bioactive compounds, including nine major compounds, but the *S. maltophilia* extract has 13 bioactive compounds, including eight major compounds. The EA extracts of *S. maltophilia* and *A. faecalis* showed anticancer activity towards the cancerous MCF7 cell where I_{C50} was 202.4 and 119.7 μg/mL, where these concentrations are safe. Furthermore, the EA extract of *S. maltophilia* had antibacterial and antifungal activity against Gram-positive bacteria, Gram-negative bacteria, and unicellular fungi. Likewise, the EA extract of *A. faecalis* exhibited antibacterial and antifungal activity against Gram-positive bacteria only as well as unicellular fungi. Also, the EA extracts of *S. maltophilia* and *A. faecalis* exhibited moderate antioxidant activity where I_{C50} was 146.2 and 147.6 μg/mL, respectively.

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