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ARTICLE

BIOACTIVITY OF ENDOPHYTIC FUNGI EXTRACT ISOLATED FROM THE LEAVES OF MISTLETOE (*Dendrophthoe pentandra* (L.) Miq.) ON THE LIME PLANT (C*itrus aurantifolia*)

[*Bioaktivitas Ekstrak Jamur Endofit yang Diisolasi dari Daun Benalu (Dendrophthoe pentandra* (L.) Miq.*) pada Tanaman Jeruk (Citrus aurantifolia)*]

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ABSTRACT

Mistletoe (*Dendrophthoe pentandra* (L.) Miq.) is a parasitic plant used in traditional medicine. This study evaluates the bioactivity of endophytic fungi in mistletoe found in the lime plant. Endophytic fungal species were determined through morphological identification. Potato Dextrose Broth (PDB) media was used for the cultivation, and ethyl acetate was used as solvent to extract secondary metabolites. The antioxidant test was carried out using the DPPH method, while the paper disc diffusion method performed the antibacterial test. A total of 4 isolates of endophytic fungi were obtained from mistletoe leaves, namely isolates DB1 – DB4. The results of morphological analysis showed that DB1 was *Paecilomyces* sp., DB2 was *Papulaspora* sp., DB3 was *Aspergillus* sp., and DB4 was *Mucor* sp. The endophytic fungus DB3 (*Aspergillus* sp.) showed the most potential antioxidant and antibacterial activity. This endophytic fungal extract can potentially be a source of new drugs through further research by isolating the active compound.

Keywords: bioactivity, *Dendrophthoe pentandra* (L.) Miq., endophytic fungi, mistletoe

ABSTRAK

Benalu (Dendrophthoe pentandra (L) Miq.) merupakan tanaman parasit yang telah dimanfaatkan sebagai obat tradisional. Penelitian ini mengevaluasi bioaktivitas jamur endofit dari daun benalu pada tanaman jeruk. Identifikasi awal jamur endofit ditentukan berdasarkan morfologinya. Media Potato Dextrose Broth (PDB) digunakan untuk kultivasi dan ekstraksi metabolit sekundernya menggunakan etil asetat. Uji antioksidan dilakukan dengan metode DPPH sedangkan uji antibakteri menggunakan metode difusi cakram kertas. Sebanyak 4 isolat jamur endofit diperoleh dari daun benalu, yaitu isolat DB1 – DB4. Hasil analisis morfologi menunjukkan bahwa DB1 adalah Paecilomyces sp., DB2 adalah Papulaspora sp., DB3 adalah Aspergillus sp., dan DB4 adalah Mucor sp.. Jamur endofit DB3 (Aspergillus sp.) menunjukkan aktivitas antioksidan dan antibakteri yang paling potensial. Ekstrak jamur endofit ini berpotensi menjadi sumber obat baru melalui penelitian lanjut dengan mengisolasi senyawa aktifnya.

***Kata kunci** : bioaktivitas, Dendrophthoe pentandra (L.) Miq , jamur endofit, benalu*

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INTRODUCTION

Medicinal plants are in great demand as raw materials for herbal medicine (Courric *et al*., 2023; Qari *et al*., 2024; Silveira & Boylan, 2023; H. Wang *et al*., 2023). People believe that consuming plants with medicinal properties boost the immune system because they have preventive and promotive activities through their secondary metabolite (Hooda *et al*., 2024; Purwati *et al*., 2023; Sukhikh *et al*., 2023). Mistletoe has medicinal properties that often used on society.

Mistletoe is a parasitic on the host plant that can be found easily on large trees in tropical areas (Awang *et al*., 2023; de Almeida *et al*., 2023; Kong *et al*., 2023; Morales-Saldaña *et al*., 2024). Based on observations and interviews with the people of Ogan Ilir, South Sumatra, they stated that the mistletoe that lives on the lime has very good properties in curing diseases, especially diarrhea and irregular menstruation. Despite its detrimental properties against trees, mistletoe is used traditionally to treat fever, diarrhea, hemorrhoids, hypertension, and cancer, especially mistletoe, which grows on lime (Diyah *et al*., 2021; Pelzer *et al*., 2022; Z. Zhang *et al*., 2023). The medicinal properties of mistletoe are related to its secondary metabolite content, such as polyphenols, flavonoids, alkaloids, and tannins (Roy *et al*., 2022). Studies reveal that mistletoe leaf extract has antibacterial activity against *Staphylococcus aureus*, *Salmonella typhi*, *Pseudomonas*, and *Eschericia coli* (Hardiyanti *et al*., 2019; Kong *et al*., 2023) due to its flavonoids and quercetin.Mistletoe extract from the lime plant can also be used as a source of antioxidants because it contains flavonoids and phenols. People believe that mistletoe that grows on lime hosts is more efficacious than mistletoe that grows on hosts other than lime (Nicoletti, 2023; Skrypnik *et al*., 2022). Based on these studies, mistletoe can potentially be a source of new medicinal ingredients. However, the limited availability of mistletoe is an obstacle to its use as a medicinal source. Therefore, another alternative is to use endophytic fungi associated with mistletoe.

Endophytic fungi live symbiotically in host plant tissue without causing disturbances or harmful symptoms (Garc *et al*., 2023; Srinivasa *et al*., 2022). Endophytic fungi can specifically produce bioactive compounds that are similar or differ from their host plants because endophytic fungi can copy and modify compounds from their host plants (Gu *et al*., 2022; Santra & Banerjee, 2022; Xu *et al*., 2021). Many studies describe that endophytic fungal extracts isolated from plants, especially plants that have medicinal properties, have excellent bioactivity equivalent to or even better than their host plants (Al-Rajhi *et al*., 2022; Alam *et al*., 2021; Khan *et al*., 2023; Sumilat *et al*., 2022). Therefore, the extraction and isolation of compounds from endophytic fungi is effective and efficient due to the short cultivation time. Bioactive compounds produced by endophytic fungi from mistletoe might have antioxidant activity, so they can prevent free radicals that cause serious diseases, such as hypertension, cancer, and the other degenerative diseases. Because it requires very little plant biomass, this endophytic fungal technology does not threaten nature conservation and the bioactive compounds can be produced in a short time. This study aims to evaluate the bioactivity of endophytic fungi from mistletoe leaves on lime plants.

MATERIALS AND METHODS

Mistletoe collection

The mistletoe (*D. pentandra*) grown on the lime tree (C*itrus aurantifolia*) was collected and used to isolate its endophytic fungi. The mistletoe leaves were collected from Ogan Ilir Regency, South Sumatra. Generasi Biologi Indonesia has identified the plant with number 08.209/Genbinesia/XI/2023. Samples were taken fresh in January 2023. The sample used is the leaves of the mistletoe that lives on lime. The leaves are used based on information from the local community because they use the leaves as traditional medicine. Based on this assumption, the endophytic fungus is expected to have similar properties.

Table 1. Information about sample (*Informasi tentang sampel)*

Name of Sample (*Nama sampel*)	**Latitude** (*Lintang*)	**Longitude** (*Bujur*)	**Altitude** (*Ketinggian*) **(m)**	**Soil pH** (*pH Tanah*)	**Temperature** (*Suhu*) **(℃)**	**Humidity** (*Kelembaban*) **(%)**	**Sample Colector** (*Kolektor Sampel*)	**Date (Tanggal)**	**Time**
Dendrophtoe pentandra	- 3.207183	104.645507°	52	6.2	29	79	Ummi Hiras Habisukan	13 January 2023	09.00 WIB

Isolation of Endophytic Fungi

Isolation of endophytic fungi starts with sterilization, disinfection, or surface sterilization of *D. pentandra* leaves. The leaves were washed under running water until clean for ± 5 minutes. Then, it was dipped in 70% alcohol for ±3 minutes. Next, rinse with sterile distilled water for ± 1 minute, then dip in 3% (w/v) sodium hypochlorite (NaOCl) for 1 minute. The surface sterilized leaves are aseptically cut to ± 2 cm. Samples were inoculated in plates containing potato dextrose agar (PDA) media and incubated at room temperature for 3-14 days. Observations are carried out every day until the emerging hypae are visible. Fungal colonies that grow around the leaves on PDA media with different morphological characteristics (color, size, and texture) are then purified. Purification was carried out by transferring the colony to a plate containing new PDA media by isolating a single spore and then incubating at room temperature for 2 × 24 hours. The purified fungal colonies are then transferred to culture media (Hapida *et al*., 2022; Oktiansyah *et al*., 2023).

Identification of Endophytic Fungi based on morphological characters

Phenotypic characteristics, macroscopic and microscopic, were used to identify endophytic fungi. Observation of colony characteristics includes the color of the colony surface and reverse side; colony texture (cottony, granular, powdery, slimy); the presence of exudate droplets; the presence of radial lines; there are concentric circles. Microscopic characterization analysis uses the slide culture method by observing hyphae, spores, color, and other specific characteristics under a microscope up to 1000X magnification. Macroscopic and microscopic characterizations were compared with fungal identification literature (Choi *et al*., 2021; PITT, J. I.; HOCKING, 2013; Walsh *et al*., 2018; Watanabe, 2010; Q. Zhang *et al*., 2014) and other relevant identification journals.

Extraction and Cultivation

All endophytic fungal isolates were cultured by placing 6 pure culture agar blocks (diameter ± 6 mm) in 300 ml potato dextrose broth (PDB) media. Each isolate was cultured in 15 culture flasks. The culture was then incubated for 4 weeks at room temperature under static conditions. After 4 weeks, medium and biomass are separated using filter paper. Then, ethyl acetate solvent was added to the culture medium (1:1) and extracted by partition (repeated three times). The ethyl acetate extract was concentrated using a rotary evaporator. The extract was concentrated using an oven at 45°C. The concentrated extract is weighed on an analytical balance (Aini *et al*., 2022; Habisukan *et al*., 2021).

Antioxidant Activity Test

Antioxidant activity was determined using the DPPH method. The endophytic fungal extract was dissolved in methanol at 1000, 500, 250, 125, 62.5, 31.25, 15.625 µg/mL (three repetitions). 0.2 mL extract of each concentration was mixed with 3.8 mL of 0.5 mM DPPH solution. The mixture was homogenized and left in the dark for 30 minutes. Absorption was measured using a UV Vis spectrophotometer at λmax 517 nm (Fadhillah *et al*., 2019). Ascorbic acid was used as a standard. Antioxidant activity is measured by IC_{50} value (Abbas *et al*., 2021).

Antibacterial Activity Test

Antibacterial activity was performed using the Kirby-Bauer method with MHA (Muller Hinton Agar) media against 2 Gram-negative bacteria (*Escherichia coli* InaCCB5 and *Salmonella typhi* ATCC1048) and 2 Gram-positive bacteria (*Staphylococcus aureus* InaCCB4 and *Bacillus*

subtilis InaCCB1204). Sterile paper discs were dripped with endophytic fungal extract at 400 µg/disc. Fungal extract was diluted using Dimethylsulfoxide (DMSO). The positive control was tetracycline at a concentration of 30 µg/disc. The paper discs were placed on MHA (Muller Hinton Agar) media, which had been inoculated with bacteria. The plate was then incubated for 1x24 hours in an incubator at 37°C, and then the inhibition zone was measured using a caliper. The criteria for antibacterial activity are based on the inhibition zone's diameter (Elfita *et al*., 2019, 2023).

RESULTS

Isolation of endophytic fungi from *D. pentandra* leaves resulted in 4 isolates (DB1 to DB4). Four endophytic fungal isolates had diverse macroscopic characteristics (shape and color) and distinctive microscopic characters (Figure 1). Endophytic fungi colonies that appeared on the mistletoe leaf showed yellow, cream, and brown colour. The macroscopic and microscopic characteristics of endophytic fungal isolates are presented in Table 1 and Table 2.

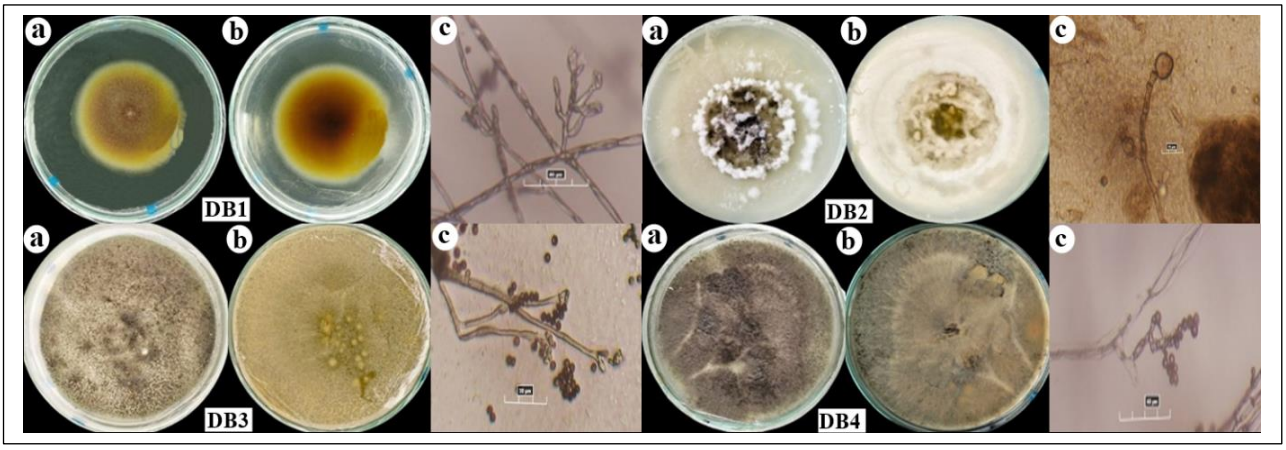

Figure 1. Morphological characteristics of endophytic fungi isolated from *D. pentandra* leaves. Notes: a: front view, b: reverse view, c: microscopic characteristic (100x/0.65) (*Karakteristik morfologi jamur endofit yang diisolasi dari daun D. pentandra. Catatan: tampak depan, b: tampak belakang, c: karakteristik mikroskopis (100x/0.65).*

Tables 1 and 2 describe the morphological characteristics of endophytic fungal colonies obtained from mistletoe (*D. pentandra*) leaves. There were 4 genera of endophytic fungi, namely *Paecilomyces* (DB1), *Papulaspora* (DB2), *Aspergillus* (DB3), and *Mucor* (DB4).

Table 1. Characteristics of Endophytic Fungal Colonies from Leaves of *D. pentandra* (*Karakteristik Koloni Jamur Endofit dari Daun D. pentandra*).

Code (*Kode*)	**Color of Surface Colony** (Warna *Permukaan Koloni*)	**Color of Reverse Colony** (Warna *Sebalik Koloni*)	**Structure** (*Struktur*)	**Elevation** (*Bentuk Puncak*)	**Pattern** (*Pola*)	**Exudate Drops** (*Tetes Eksudat*)	**Radial line** (*Garis Radial*)	**Concentric circle** (*Lingkar Kosentris*)
DB1	Yellow (*Kuning*)	Yellow to brown (*Kuning kecoklatan*)	Velvety (*Seperti beludru*)	Rugose (*Berkerut*)	Zonate (*Membentuk Zonasi*)	-	-	√
DB2	White to grey (*Putih keabu-abuan*)	White (*Putih*)	Cottony (*Berbulu*)	Rugose (*Berkerut*)	Zonate (*Membentuk Zonasi*)	-	-	-
DB3	Black (*Hitam*)	Grey (*Abu-abu*)	Cottony (*Berbulu*)	Umbonate (*Memuncak pada bagian tengah*)	Zonate (*Membentuk Zonasi*)	-	-	-
DB4	Black (*Hitam*)	White to grey (*Putih keabu-abuan*)	Cottony (*Berbulu*)	Umbonate (*Memuncak pada bagian tengah*)	Zonate (*Membentuk Zonasi*)	-	-	-

Table 2. Microscopic Characteristics of Endophytic from Leaves of *D. pentandra* (*Karakteristik Mikroskopis Endofit dari Daun D. pentandra*)

Isolate (*Isolat*)	**Spore** (*Spora*)	**Shape** (*Bentuk*)	**Hyphae** (*Hifa*)	**Characteristic** (*Karakteristik*)	**Species of Identification** (*Spesies Identifikasi*)
DB1	Conidia (*Konidia*)	Subglobose	Septate (*Bersekat*)	The conidia are unicellular; the hyaline conidiophores are erect and branched (*Konidia bersifat uniseluler, konidiofor hialin tegak dan bercabang*)	*Paecilomyces* sp.
DB2	Conidia (*Konidia*)	Globose	Non-Septate (*Tidak Bersekat*)	The hyphae are nonseptate with short conidiophores that do not differentiate from the hyphae (*Hifa tidak bersepta dengan konidiofor pendek yang tidak berdiferensiasi dari hifa*)	*Papulaspora* Sp.
DB3	Sporangia	Globose	Septate (*Bersekat*)	Hyphae are septate and branched, conidia are round and form chains, conidiophores are erect and long (*Hifa bersepta dan bercabang, konidia berbentuk bulat dan membentuk rantai, konidiofor tegak dan panjang*)	*Aspergillus* sp.
DB4	Conidia (*Konidia*)	Globose	Non-Septate (*Tidak Bersekat*)	Hyphae are nonseptated and unbranched sporangiophores are hyaline, erect, branched conidiophores (*Hifa tidak bersekat, sporangiofor tidak bercabang merupakan hialin, tegak, dan bercabang*).	*Mucor* sp.

Endophytic fungal extracts from mistletoe leaves have antibacterial and antioxidant activity (Table 3). The extract showed antimicrobial activity against *Salmonella typhii*, *Escherichia coli*,

Bacillus subtilis, and *Streptococcus aureus,* as well as potent and very potent antioxidant activity. There was one endophytic fungal extract with potent antibacterial activity against the four tested bacteria and very strong antioxidant activity (IC_{50} < 20 µg/mL), namely isolate DB3 (*Aspergillus* sp.).

Table 3. Percentage of antibacterial activity of endophytic fungal extract compared to that of tetracycline and antioxidant activity compared to that of ascorbic acid as a standard (*Persentase aktivitas antibakteri ekstrak jamur endofit dibandingkan dengan tetrasiklin dan aktivitas antioksidan dibandingkan dengan asam askorbat sebagai standar*)

Code Isolate (*Kode Isolat*)	**Genus/Identified Species** (*Genus/Spesies yang teridentifikasi*)	**Weight of extract (***Berat ekstrak***) (g)**	**Percentage of Antibacterial Activity** (Persentase *Aktivitas Antibakteri*) **(%)**				**IC_{50} (µg/mL)**
			E. coli	***S. aureus***	***S. typhi***	***B. subtilis***	
Mistletoe leaf methanol extract		2,5	73,46 ± 0,43 ***	72,45 ± 0,31 ***	79,54 ± 0,68 ***	78,6 ± 0,68 ***	15,06 ***
DB1	*Paecilomyces* sp.	1,2	68,15 ± 0,48 **	65,30 ± 0,94 **	71,9 ± 0,77 ***	72,5 ± 0,22 ***	55,82 ***
DB2	*Papulaspora* Sp.	0,9	61,8 ± 0,18 **	65,5 ± 1,62 **	75,2 ± 0,35 ***	74,4 ± 1,68 ***	106,34 **
DB3	*Aspergillus* sp.	1,6	75,3 ± 1,11 ***	76,3 ± 0,39 ***	79,2 ± 0,05 ***	80,7 ± 0,31 ***	17,57 ***
DB4	*Mucor* sp.	1,2	70,1 ± 0,72 ***	73,6 ± 0,84 ***	73,0 ± 0,75 ***	72,6 ± 0,11 ***	75,49 ***
	Positive Control (Kontrol Positif)		Tetracycline 100 ***	Tetracycline 100 ***	Tetracycline 100 ***	Tetracycline 100 ***	Ascorbic Acid 10,08 ****

Note: Antibacterial activity percentage: *** strong (≥ 70%), **moderate (50-70%), and *weak (< 50%). Antioxidant activity IC_{50} (µg/mL): ****very strong < 20 µg/mL ***strong < 100 µg/mL; **moderat 100-500 µg/mL; * weak > 500 µg/mL.(*Catatan: Persentase aktivitas antibakteri: *** kuat (≥ 70%), **sedang (50-70%), dan *lemah (< 50%). Aktivitas antioksidan IC_{50} (µg/mL): ****sangat kuat < 20 µg/mL ***kuat < 100 µg/mL; **sedang 100-500 µg/mL; *lemah > 500 µg/mL*).

DISCUSSION

The methanol extract of the host plant (mistletoe) showed more potent antibacterial and antioxidant activity than the endophytic fungal extract. It might be because the host plant contains more complex secondary metabolite content, and the secondary metabolite groups likely have different functions even though they are in the same group (Erb & Kliebenstein, 2020; Mipeshwaree Devi *et al*., 2023). Endophytic fungal extracts provide antibacterial effects in various categories ranging from moderate to potent antibacterial against the four tested bacteria. DB3 isolate had the most potential antibacterial and antioxidant activity. However, compared to standards, the antibacterial percentage and IC_{50} of endophytic fungal extracts are still lower. Nonetheless, the percentage of antibacterial activity and IC_{50} value of the endophytic fungal isolate DB3 are closest to the values of tetracycline and ascorbic acid as standards.

Based on morphological identification, the DB3 isolate was *Aspergillus* sp. Genus *Aspergillus* is an opportunistic pathogenic fungus and can be found in various environment conditions. The characteristics of spores that spread easily through the air (aerosol) have the potential to be inhaled by humans so they can enter the respiratory tract and cause the development of allergies (Mousavi *et al*., 2016; Yadav & Meena, 2021; Z. F. Zhang *et al*., 2021). However, even though it is pathogenic, research has revealed that the ability of the endophytic fungus of the genus *Aspergillus* to spread rapidly can be associated with plants, and there is no information regarding its host specificity (Ortega *et al*., 2021; R. Wang *et al*., 2022). The ability of fungi to invade causes pathogenic fungi to become endophytic fungi and produce secondary metabolite compounds (Adedayo & Babalola, 2023; Elfita *et al*., 2012; Sharma *et al*., 2018). As studies have revealed, fungi isolated from medicinal plants are known to have good bioactivity. It shows that the *Aspergillus*

genus found in mistletoe leaves from lime trees can also produce secondary metabolites in the host plant. Several studies have reported that the *Aspergillus* isolated from medicinal plants acts as an antimicrobial and antioxidant because the compounds it contains have similar structures to their host plants. Genus Aspergillus associated with lime trees (*Citrus aurantiifolia*) have broad bioactivity potential. This is due to their ability to produce a variety of beneficial secondary metabolites, such as alkaloids, terpenoids, flavonoids, and polyphenols. These metabolites are known to have significant antimicrobial, antioxidant, and anticancer activities, making them a potential source for the development of natural medicines. The antimicrobial compounds produced can inhibit plant pathogens and pathogenic microorganisms in humans, while antioxidant compounds, such as flavonoids, can protect cells from oxidative stress associated with various degenerative diseases. In addition, the anticancer activity of some of these endophytic secondary metabolites has been shown to induce apoptosis and inhibit the cell cycle in cancer cells, which has the potential to be a safer and more natural alternative cancer therapy (Esheli *et al*., 2022; Sharma *et al*., 2018; Umaru *et al*., 2020; Vasantharaj *et al*., 2013).

Research shows that the extract produced by *Aspergillus* sp. DB3 has powerful antioxidant and antibacterial activity against the four test bacteria (Table 3). Various studies show that endophytic fungi of the genus *Aspergillus* contain secondary metabolite compounds, including fatty acids, pyranone, alkaloids, and phenols as their dominant contents (El-Zahar *et al*., 2022; Nievierowski *et al*., 2021; Norizan *et al*., 2012). Phenolic compounds show structural diversity, such as the presence number, position of substitution of hydroxyl groups and the length of saturated side chains, which causes these compounds the ability to act as antioxidants and antibacterials (Akter *et al*., 2022; Benjamin *et al*., 2022; Chutulo, 2020; Losada-Barreiro *et al*., 2022; Silva *et al*., 2024). Fatty acids can reduce and resist free radical oxidative stress through physiological and biochemical reactions. Based on this biological mechanism, the endophytic fungus of the genus *Aspergillus* isolated from mistletoe leaves (*D. pentandra*) which live on the lime treescan be used as a promising source of natural products for medicinal purposes.

CONCLUSION

Four endophytic fungi were isolated from mistletoe (*D.* pentandra) grown on lime trees, i.e., *Paecilomyces* sp., *Papulaspora* sp., *Aspergillus* sp., and *Mucor* sp. The fungus *Aspergillus* sp. has a very strong antioxidant activity category and potent antibacterial activity against all tested bacteria. In future studies, the isolation of antioxidant and antibacterial compounds should be conducted for advanced research.

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AUTHOR CONTRIBUTIONS

U.H.H. designed the research and supervised all the processes. R.O. collected and analyzed the data. N and L.A. assisted with the laboratory work.

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