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Expanding the Therapeutic Landscape: Exploring the Antimicrobial and Bioactive Potential of Mangrove-Derived Endophytic Fungi

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ABSTRACT

The escalating rise of antibiotic resistance poses a significant challenge to discovering new, effective antibiotics. This crisis represents one of the most critical threats to global health, potentially leading to a future where even minor infections could become fatal. Endophytic fungi have recently emerged as a promising source of novel bioactive compounds. This review highlights the potential of endophytic fungi isolated from mangrove vegetation to produce new antimicrobial agents. Mangrove-derived endophytic fungi are found in healthy leaves, hypocotyls, roots, stems, and flowers. The symbiotic relationship between mangrove vegetation and these fungi promotes the synthesis of diverse bioactive compounds, including newly discovered molecules such as cytospyrone, cytospomarin, penicibrocazines, thiocladospolides, coumarin, isocoumarins, and dihydroradicinin. Beyond their antimicrobial potential, these fungi also produce compounds with antifungal, antioxidant, anticancer, anti-inflammatory, anti-filarial, antibiofilm, influenza antiviral, antimycobacterial, and biological control properties. The traditional approach to antibiotic development is complex, challenging, costly, time-consuming, and labor-intensive. To overcome these obstacles, research must integrate machine learning for big data analysis and molecular-based exploration, including genomics, proteomics, and transcriptomics.

1. INTRODUCTION

The groundbreaking discovery of penicillin over 90 years ago revolutionized the management of infectious diseases, establishing antibiotics as a cornerstone of modern medicine. However, the efficacy of these life-saving drugs is increasingly threatened by the alarming rise of antibiotic resistance (ABR). This global health crisis, recognized by the World Health Organization (WHO), significantly impedes our ability to treat common infections, leading to prolonged hospitalizations, increased healthcare costs, and elevated mortality rates (Agustini et al., 2018; Chinemerem-Nwobodo et al., 2022).

Despite the urgent need, the development of novel antibiotics faces significant hurdles. Research in this area is characterized by protracted timelines, exorbitant costs, and high failure rates (Anderson et al., 2023). Consequently, most antibiotics introduced in the past three decades are mere modifications of existing drug classes rather than truly novel compounds, and many exhibit diminished efficacy compared to their predecessors (Ventola, 2015; World Health Organization, 2019). This slow pace of discovery is particularly concerning given the escalating

threat from drug-resistant microbes. The WHO has responded to this challenge by publishing a prioritized list of pathogens, categorizing bacteria into three levels of antibiotic resistance: critical, high, and medium. This list serves as a crucial guide for directing research efforts toward developing new antibiotics against these highly resistant threats, particularly Gram-negative bacteria, which exhibit a higher propensity for resistance and for which there are a limited number of effective treatments (Breijyeh et al., 2020; Mancuso et al., 2021; World Health Organization, 2019).

The global surge in ABR is driven by a complex interplay of factors, including the widespread overuse and misuse of antibiotics in human medicine, animal husbandry, poultry farming, and agriculture, as well as inadequate infection prevention and control strategies (Chinemerem-Nwobodo et al., 2022; Chokshi et al., 2019; Klein et al., 2018; Manyi-Loh et al., 2018; Silbergeld et al., 2008). While bacterial adaptation to antimicrobial compounds is a naturally occurring process, these human activities dramatically accelerate the development and dissemination of resistance. Therefore, novel strategies are desperately needed to replenish the diminishing arsenal of effective antibiotics.

To combat this escalating threat, various approaches are being pursued for the discovery of new antibiotics. These include leveraging cutting-edge technologies, modifying existing compounds, and intensifying the exploration of natural microbial resources. Among these, the investigation of bioactive compounds produced by endophytic fungi has emerged as a promising avenue. Endophytic fungi, particularly those residing in underexplored environments like mangrove ecosystems, are prolific producers of a wide array of diverse secondary metabolites, including terpenoids, furanones, quinones, alkaloids, iso-coumarins, steroids, and phenols (Bai et al., 2014; Cai et al., 2017; Deng et al., 2020; Guo et al., 2020; Li et al., 2017; May-Zin et al., 2017; Rao et al., 2020; Zhang et al., 2021). These compounds have demonstrated significant inhibitory and biocidal activity against various pathogenic microorganisms.

Despite the recognized potential of endophytic fungi, there remains a significant gap in our understanding of the full scope of their antimicrobial capabilities, especially concerning their efficacy against the WHO's prioritized multidrug-resistant pathogens, particularly Gram-negative bacteria. Furthermore, while numerous studies highlight the diverse secondary metabolites produced by endophytic fungi, a comprehensive assessment of the specific classes of compounds responsible for potent antibacterial activity against critical priority pathogens is often lacking. Addressing these gaps is crucial for translating promising discoveries into viable therapeutic agents.

2. MATERIALS AND METHODS

This review elucidates the potential of endophytic fungi isolated from mangrove vegetation as a source of novel antimicrobial compounds. A systematic literature search was conducted using the keywords "mangrove AND endophytic fungi AND antimicrobial" within the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). The inclusion criteria encompassed original research articles published between 2011 and 2021, written in either Indonesian or English, and with available full-text access. An initial extraction yielded 99 manuscripts detailing the exploration of mangrove-derived endophytic fungi and their antimicrobial activity. However, this review focused on studies employing the dilution method (minimal inhibitory concentration, MIC) for antimicrobial testing. Consequently, a refined selection of 33 manuscripts was included for comprehensive analysis.

3. RESULTS AND DISCUSSION

3.1. Mangrove Ecosystem

Mangroves constitute the intertidal, salt-tolerant ecosystems at the interface between terrestrial and marine environments. Globally, mangrove forests encompass an estimated 137,760 km² (Giri et al., 2011). Notably, Indonesia possesses approximately 3.4 million hectares of mangrove forests, representing roughly 20% of the world's total mangrove coverage (Ministry of International Affairs, 2022). Within Indonesia, these vital ecosystems are particularly abundant along the coastlines of Sumatra, Kalimantan, Papua, the Aru Islands, Sulawesi, and Java. The structural composition of Indonesian mangrove forests is generally characterized by a relatively simple architecture, predominantly dominated by species belonging to the genera *Rhizophora*, *Ceriops*, *Avicennia*, *Xylocarpus*, *Sonneratia*, and *Lumnitzera* (Ministry of International Affairs, 2022).

Diverse organisms inhabit mangrove ecosystems, including shrubs, ferns, palms, and trees. Their ability to thrive in freshwater and saline environments contributes to the inherent complexity of mangrove habitats (Deshmukh et al., 2020). These ecosystems deliver a multitude of ecological, social, and economic benefits. They provide critical support for many species, encompassing fish, crustaceans, mollusks, birds, and mammals (Husain et al., 2020). The intricate root systems and canopy structures of mangroves create a mosaic of microhabitats, fostering the development of highly diverse organismal communities (Vorsatz et al., 2021).

Mangrove habitats are pivotal in protecting coastal regions from erosion and tsunamis. The extensive root systems of mangroves effectively stabilize shorelines, while their dense canopy structures serve as a formidable barrier, mitigating the force of incoming waves. Furthermore, mangroves act as natural filters, removing pollutants and trapping sediment, enhancing water quality and preventing the siltation of downstream ecosystems (Spalding et al., 2014). Consequently, the sediment within these habitats often presents a limited source of nutrients. This nutrient scarcity, coupled with intense interspecies competition among microbial populations, frequently triggers the production of secondary metabolites. Under these stressed conditions, microbes synthesize bioactive metabolite compounds, including antimicrobials, as a survival mechanism in the face of interspecies competition (Sengupta et al., 2015; Wang et al., 2014).

This review focused on mangrove vegetation harboring endophytic fungi, specifically including *Kandelia candel*, *Ceriops tagal*, *Bruguiera gymnorrhiza*, *Acanthus ilicifolius*, *Myoporum bontioides*, *Rhizophora apiculata*, *Rhizophora mucronata*, *Avicennia marina*, *Rhizophora stylosa*, *Xylocarpus moluccensis*, *Bruguiera sexangular*, and *Pongamia pinnata*. Mangrove ecosystems are recognized as reservoirs of medicinal plants with significant potential for developing novel pharmaceuticals. Indeed, several of these plants have traditionally been employed to treat various ailments, including inflammation, infection, and muscle pain (Mardiyanto Rahayu & Sunarto, 2020; Vinoth et al., 2019). Notably, there has been a demonstrable increase in publications on mangrove vegetation and plants (**Figure 1)**.

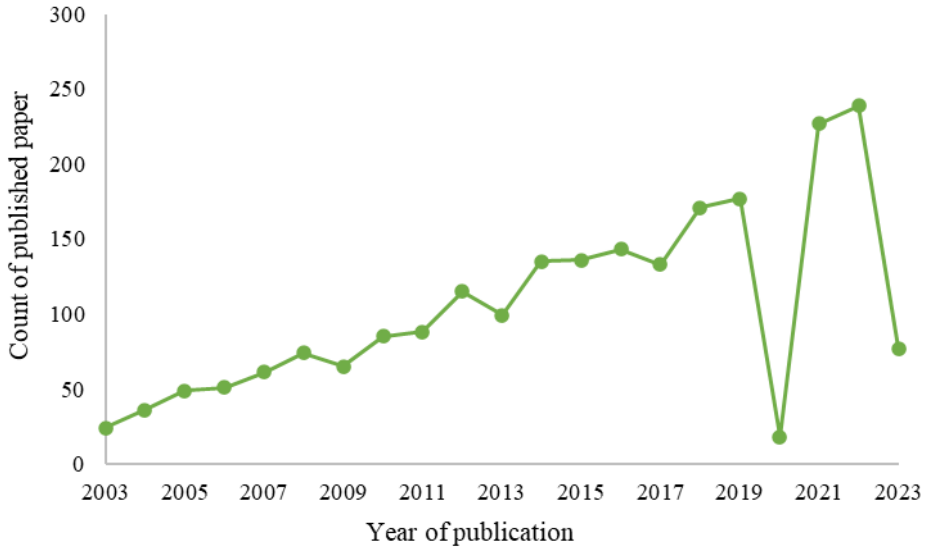

Figure 1. The chronological distribution of publications concerning "mangrove plants" indexed within the PubMed database, spanning 2003 to 2023.

3.2. Endophytic Fungi

Mangrove ecosystems are experiencing significant depletion due to urban expansion and ecological degradation. Various endophytes have been successfully isolated from their host plants and cultivated in controlled media to mitigate this loss of biological resources. The term "endophyte" was first defined by De Bary in 1866. Subsequently, Darnelin conducted pioneering field experiments on the weed *Agrostemma githago* in 1904, elucidating the biology of these organisms (Gouda et al., 2016). Building upon these foundational studies, contemporary research has unveiled various microbial endophytes associated with plant species' roots, stems, seeds, leaves, and fruits.

Endophytic fungi establish symbiotic relationships within plant tissues, residing asymptomatically within their hosts (Deshmukh et al., 2020; Gouda et al., 2016). Scientific investigations have demonstrated that these fungi possess a significant capacity to synthesize a wide array of bioactive compounds, a capability attributed to their intricate interactions with host plant metabolism (Deng et al., 2020; Guo et al., 2020; Li et al., 2017; May-Zin et al., 2017). Notably, mangrove-derived endophytic fungi have been shown to produce diverse biologically active metabolites, including antimicrobial, antitumor, antioxidant, antiviral, immunomodulatory, and anti-inflammatory compounds (Deshmukh et al., 2020; Gunatilaka, 2006; Heinig et al., 2013; Imhoff, 2016; Kharwar et al., 2011).

Endophytic fungi derived from mangrove ecosystems are routinely isolated from healthy roots, stems, leaves, hypocotyls, and flowers. Notably, stem tissues exhibit the most remarkable diversity of endophytic fungal populations compared to other investigated plant tissues (Zhang et al., 2021; Zheng et al., 2016). These endophytes' isolation and comprehensive characterization are crucial for elucidating their diversity, ecological functions, and potential applications in developing novel pharmaceuticals and biocontrol agents. Endophytic fungal isolation has been extensively documented across all tracheophyte groups, encompassing herbaceous and woody plants (Zheng et al., 2016). This widespread association underscores the integral role of endophytic fungi as natural components of plant life. The increasing global interest in endophytic fungal research is reflected in the growing number of publications (**Figure 2**).

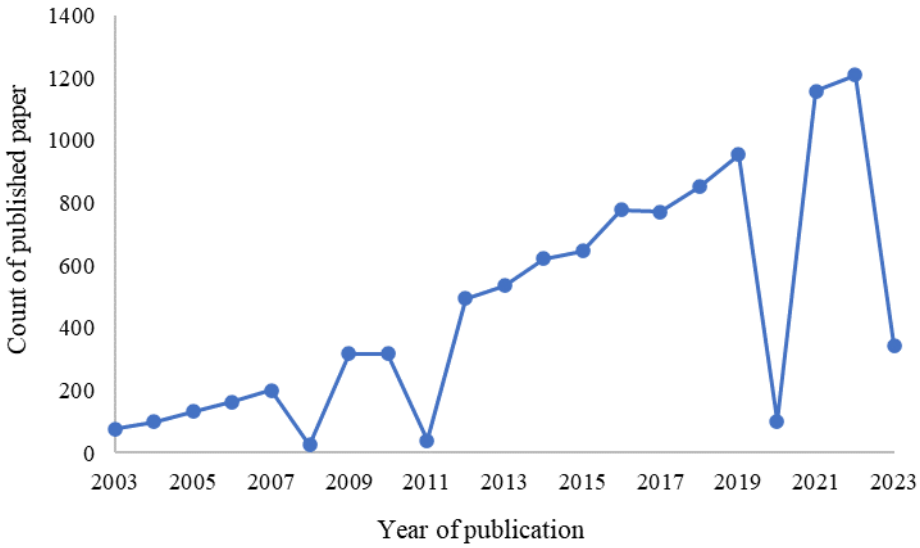

Figure 2. The escalating trend in published research on "endophytic fungi" within the PubMed database from 2003 to 2023.

3.3. Isolation and Characterization of Endophytic Fungi

Various methodologies have been successfully employed to isolate and characterize endophytic fungi. Generally, the isolation and characterization process combines techniques, including surface sterilization, tissue culture, and molecular analyses (Zhang et al., 2021; Zheng et al., 2016). Endophytic fungi are commonly isolated from surface-sterilized plant tissue. This technique entails the rigorous decontamination of plant surfaces using disinfectant solutions to eliminate epiphytic contaminants. Subsequently, targeted plant tissues, such as the epidermis, cambium, xylem, and phloem, are aseptically transferred to culture media conducive to endophytic fungal growth. To enhance fungal diversity, sterilized plant tissue is often segmented into smaller pieces, macerated or crushed, and then incubated on nutrient agar plates (Sun & Guo, 2012). Endophytic fungi can be cultivated on a range of general-purpose solid media, including potato dextrose agar (PDA), malt extract agar (MEA), and Sabouraud dextrose agar (SDA). In certain instances, incorporating plant extracts into the media may further promote the growth of specific endophytic fungal species (Dos-Reis et al., 2022).

Identifying endophytic fungi is primarily accomplished through two fundamental methodologies: direct observation and cultivation-dependent approaches. Direct observation involves the microscopic examination of endophytic fungal structures within living plant tissues, utilizing light and electron microscopy. This technique can detect the entire endophytic mycobiont within a given plant tissue (Lucero et al., 2011). However, a significant limitation arises from the fact that many endophytic fungi within plant tissues exhibit a predominantly hyphal morphology, lacking discernible spore-producing structures or distinct sexual or asexual spores (Deckert et al., 2001; Sun & Guo, 2012). Consequently, taxonomic classification based solely on morphological characteristics becomes challenging. Furthermore, the direct observation approach precludes the collection of viable endophytic isolates for future microbial resource utilization. Therefore, this method is infrequently employed in contemporary endophyte diversity research.

A significant proportion of endophytic fungal isolates, often exceeding half, fail to sporulate under standard culture conditions (Dos-Reis et al., 2022; Wang & Guo, 2007). This phenomenon renders traditional fungal classification, which relies on reproductive structures, impractical. Consequently, polymerase chain reaction (PCR)- based molecular methodologies have been developed to identify endophytic fungi through DNA sequence analysis. These techniques enable the identification of endophytic fungi directly from plant tissue samples, circumventing the need for cultivation. The molecular analysis approach typically comprises the following steps: (1) extraction of total genomic DNA (encompassing both fungal and plant DNA) from surface-sterilized plant tissues; (2) amplification of specific DNA fragments (e.g., ITS, 28S, and 18S genes) from the extracted DNA using fungal-specific primers; and (3) subsequent DNA sequencing.

3.4. Diversity of Endophytic Fungi

The global flora encompasses over 300,000 documented plant species, with ongoing taxonomic research suggesting continued expansion. Given that each plant species harbors at least one endophytic species, the resulting diversity of endophytic fungi is exceptionally vast (Zheng et al., 2016). Endophytic fungi can be characterized by analyzing morphological traits, including growth rate, colony morphology, spore structure, and pigmentation. These characteristics serve as valuable indicators for the taxonomic identification of fungal species.

Over the past several years, researchers have extensively investigated the potential of endophytic fungi derived from diverse mangrove vegetation (**Table 1**), identifying a range of species including *Aspergillus candidus*, *Aspergillus flavipes*, *Aspergillus terreus*, *Aspergillus* sp., *Cladosporium cladosporioides*, *Cladosporium oxysporum*, *Cladosporium* sp., *Cytospora* sp., *Daldinia eschscholtzii*, *Epicoccum nigrum*, *Eurotium chevalieri*, *Flavodon flavus*, *Fusarium napiforme*, *Fusarium solani*, *Lasiodiplodia theobromae*, *Nigrospora sphaerica*, *Nigrospora* sp., *Penicillium brocae*, *Penicillium citrinum*, *Penicillium* sp., *Pestalotiopsis* sp., *Phoma* sp., *Phomopsis longicolla*, and *Phomopsis* sp. **Figure 4** demonstrates a marked increase in publications on mangrove-associated fungi over the past two decades.

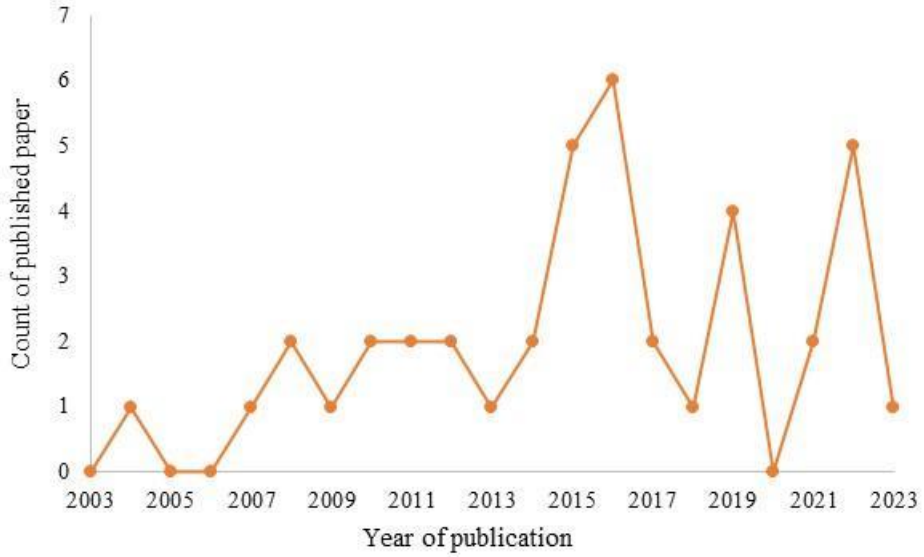

Figure 4. The chronological distribution of publications concerning "mangrove-associated fungi" as indexed within the PubMed database spans 2003 to 2023.

3.5. Metabolite Production and Screening

The biological screening of endophytic fungi for producing antimicrobial metabolites typically commences with an initial, streamlined screening process designed to identify promising candidate strains for subsequent, in-depth analysis. Endophytic fungi are cultivated in solid or liquid media, from which crude organic or aqueous extracts are obtained (Caruso et al., 2022). Secondary metabolite synthesis predominantly occurs during the later developmental phases of these organisms (Calvo et al., 2002). The temporal characteristics of secondary metabolism are genetically determined, although environmental manipulations can significantly influence their expression.

The metabolic profiles of endophytic fungi are highly susceptible to variations in culture parameters, including medium composition, temperature, pH, and light (Prajapati et al., 2025; Widjajanti et al., 2022). Notably, nutrient deficiencies can serve as potent triggers for secondary metabolite production. Furthermore, introducing specific inducers, reductions in growth rate, or the perception of environmental signals emanating from competing organisms can also modulate secondary metabolism (Bogas et al., 2022). Consequently, the OSMAC (one strain, many compounds) approach has emerged as a powerful strategy, significantly enhancing the probability of discovering diverse novel metabolites from a single fungal strain (Aly et al., 2011).

The extracts produced can be subjected to rapid screening methods, such as disk diffusion, broth microdilution, and agar dilution assays, to assess their activity against selected test organisms. Disk diffusion involves an antimicrobial agent from a disk into a solid culture medium previously inoculated with the target microorganism. This technique measures an inhibition zone, inversely proportional to the bacterial sensitivity to the antimicrobial agent impregnated in the disk (Hudzicki, 2009). Conversely, broth and agar dilution methods determine the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of the assayed antimicrobial that inhibits the visible growth of the tested bacteria. The MIC is typically expressed in µg/ml or mg/l. Under rigorously controlled in vitro conditions, the MIC represents the concentration at which complete inhibition of visible growth is achieved for the test strain of an organism (Kowalska-Krochmal & Dudek-Wicher, 2021).

The isolation and purification of bioactive compounds from endophytes are critical processes. The prevailing methodology involves liquid-liquid extraction, utilizing organic solvents derived from the liquid media of fungal cultures. Depending on the solubility characteristics of the target metabolite, single or combined solvents are employed for extraction. Ethyl acetate, methanol, dichloromethane, hexane, and ethanol are among the most frequently utilized solvents for the extraction of metabolites from broth cultures, which are subsequently concentrated via rotary evaporation (Madhusudhan et al., 2015).

Fungi typically synthesize secondary metabolites in limited quantities, often accompanied by a complex mixture of other compounds that can impede downstream applications (Caruso et al., 2022). Consequently, purification is essential to isolate the bioactive compounds and eliminate impurities. Thin-layer chromatography (TLC) is a rapid, cost-effective, and straightforward technique that provides researchers with a preliminary assessment of the number of components present within a mixture. Furthermore, TLC is employed to confirm the identity of specific compounds within a complex matrix (Shahverdi et al., 2007). The bioautography technique, which involves directly applying microbial test organisms to a TLC plate, allows for detecting

antimicrobial components within chromatographed extracts. This methodology is regarded as one of the most efficient assays for identifying antimicrobial compounds.

This review highlighted the potential of novel bioactive compounds to inhibit the growth of a broad spectrum of pathogenic microorganisms, including Gram-negative bacteria such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus faecalis*, *Vibrio anguillarum*, *Vibrio parahaemolyticus*, *Edwardsiella tarda*, *Edwardsiella ictarda*, and *Proteus* sp., as well as Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Bacillus cereus*, and *Micrococcus luteus*. Furthermore, these compounds demonstrated efficacy against clinically relevant fungi, including *Candida albicans*, *Fusarium graminearum*, *Microsporum gypseum*, and *Gaeumannomyces graminis*.

Table 1. A comprehensive overview of potential endophytic fungi isolated from diverse mangrove vegetation and their potential for the production of novel bioactive compounds.

No	References	Mangrove plants	Endophytic fungi	Tested Bacteria	MIC (µM)	Discovery compounds
1	(Chen et al., 2019)	*Kandelia candel*	*Phoma* sp. SYSU-SK-7	*Pseudomonas aeruginosa* and MRSA	1.67-6.28	colletotric B, 3-hydroxy-5-methoxy-2,4,6-trimethylbenzoic acid, colletotric C, chaetochromone D, and 8-hydroxy-pregaliellalactone B
2	(Wei et al., 2020)	*Ceriops tagal*	*Cytospora* sp.	*Escherichia coli* GIM1.201	350	cytospyrone, cytospomarin
3	(Cai et al., 2019)	*Kandelia candel*	*Aspergillus* sp. ZJ-68	*Staphylococcus aureus, Escherichia coli, Bacillus subtilis,* and *Pseudomonas aeruginosa*	4.15-12.5	Three new asperfuranoids and two new phenylpropanoid derivatives
4	(Ukwatta et al., 2019)	*Bruguiera gymnorrhyza*	*Aspergillus terreus*	*Bacillus subtilis* TISTR 088, and *Bacillus cereus* TISTR 688	1-2	cowabenzophenone A
5	(Chen et al., 2016)	*Acanthus ilicifolius*	*Lasiodiplodia theobromae* ZJ-HQ1	*Staphylococcus aureus*	1.6-13	chloropreussomerins A and B
6	(Zhou et al., 2019)	*Rhizophora apiculata* Blume	*Fusarium solani*	*Vibrio parahaemolyticus*	6.25	fusaricates H-K

No	References	Mangrove plants	Endophytic fungi	Tested Bacteria	MIC (µM)	Discovery compounds
7	(Yan et al., 2019)	*Acanthus ilicifolius*	*Epicoccum nigrum* SCNU-F0002	*Bacillus subtilis* (ATCC 6538), *Escherichia coli* (ATCC 8739), and *Staphylococcus aureus* (ATCC 6538)	25-50	coumarin, isocoumarins, dihydroradicinin, and dihydroradicinin, benzofuranone derivatives
8	(Zhang et al., 2019)	*Bruguiera gymnorrhiza*	*Cladosporium cladosporioides* MA-299	*E. coli*, *S. aureus*, *E. tarda*, *E. ictarda*, and *P. aureginosa*	1.0-64	5R-hydroxyrecifeiolide, 5S-hydroxyrecifeiolide, ent-cladospolide F, cladospolide G, and cladospolide H
9	(Deng et al., 2020)	*Ceriops tagal*	*Cytospora* sp.	*Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Basillus subtilis*	58.3 to 561.6	new biscyclic sesquiterpene seiricardine D
10	(May Zin et al., 2017)	*Rhizophora mucronata*	*Eurotium chevalieri* KUFA 0006	*Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC, and MRSA 27853	64	acetylquestinol, prenylated indole 3-carbaldehyde derivatives, an anthranilic acid derivative, and an isochromone derivative
11	(Supratman et al., 2021)	*Rhizophora mucronata*	*Fusarium napiforme*	*Staphylococcus aureus* and *Pseudomonas aeruginosa*	3.17-6.3	6-hydroxy-astropaquinone B and astropaquinone D

No	References	Mangrove plants	Endophytic fungi	Tested Bacteria	MIC (µM)	Discovery compounds
12	(Ukwatta et al., 2019)	*Bruguiera gymnorrhyza*	*Nigrospora sphaerica*	*Bacillus subtilis* TISTR 088 and *Bacillus cereus* TISTR 688	2-4	nigronapthaphenyl
13	(M. Bai et al., 2019)	*Ceriops tagal*	*Cladosporium* sp. JS1-2	*Staphylococcus aureus*	1.25-25.0	1,1'-dioxine-2,2'-dipropionic acid and 2-methyl acetate-3,5,6-trimethyl pyrazine
14	(W. Wang et al., 2020)	*Avicennia marina (Forssk.) Vierh*	*Cladosporium oxysporum*	*Edwardsiella tarda*	4	thiocladospolides F-J
15	(Cai et al., 2017)	*Acanthus ilicifolius*	*Phomopsis* sp. HNY29-2B	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *B. subtilis*	25 and 50	phomopyrone A
16	(Zhou et al., 2021)	*Rhizophora apiculata Blume*	*Aspergillus candidus* LDJ-5	*Proteus* sp.	19	asperterphenyllins A-F
17	(Xu et al., 2020)	*Rhizophora stylosa*	*Pestalotiopsis* sp. HHL101	*Escherichia coli* and *Pseudomonas aeruginosa*	12.5-50	pestalotiopisorin B
18	(Jiang et al., 2018)	*Bruguiera gymnorrhiza*	*Penicillium* sp. GD6	Methicillin-resistant *Staphylococcus aureus*	80	2-deoxy-sohirnone C, 5S-hydroxynorvaline-S-Ile

No	References	Mangrove plants	Endophytic fungi	Tested Bacteria	MIC (µM)	Discovery compounds
19	(Kongyen et al., 2015)	*Bruguiera gymnorrhiza*	*Daldinia eschscholtzii* PSU-STD57	*Staphylococcus aureus, methicillin-resistant S. aureus*, and *Microsporum gypseum*	200	new hydronaphthalenone derivative
20	(P. Wang et al., 2018)	*Xylocarpus moluccensis*	*Aspergillus* sp. XY02	*Staphylococcus aureus* ATCC 25923	31.5 to 41.9	(7R,10S)-7,10-epoxysydonic acid, (7S,10S)-7,10-epoxysydonic acid, (7R,11S)-7,12-epoxysydonic acid, (7S,11S)-7,12-epoxysydonic acid, 7-deoxy-7,14-didehydro-12-hydroxysydonic acid, (Z)-7-deoxy-7,8-didehydro-12-hydroxysydonic acid, and (E)-7-deoxy-7,8-didehydro-12-hydroxysydonic acid
21	(Zheng et al., 2019)	*Bruguiera sexangula var. rhynchopetala*	*Penicillium citrinum* HL-5126	*Staphylococcus aureus*	20	penibenzophenones A-B
22	(He et al., 2017)	*Bruguiera sexangula var. rhynchopetala*	*Penicillium citrinum* HL-5126	*Vibrio parahaemolyticusparahaemolyticus*	10	4-chloro-1-hydroxy-3-methoxy-6-methyl-8-methoxycarbonyl-xanthen-9-one and 2'-acetoxy-7-chlorocitreorosein
23	(Guo et al., 2018)	*unidentified*	*Aspergillus* sp. YHZ-1	*Staphylococcus aureus* CMCC (B) 26003, *Streptococcus pyogenes* ATCC 19615, *Bacillus subtilis* CICC 10283, and *Micrococcus luteus*	32	asperphenone A-C

No	References	Mangrove plants	Endophytic fungi	Tested Bacteria	MIC (µM)	Discovery compounds
24	(Shang et al., 2012)	*Pongamia pinnata*	*Nigrospora* sp. MA75	MRSA, *E. coli, S. epidermidis, V. mali*, and *S. solani*	0.5-8.0	2,3-didehydro-19α-hydroxy-14-epicochlioquinone B
25	(Bai et al., 2014)	*Acanthus ilicifolius*	*Aspergillus flavipes*	*Staphylococcus aureus* and *Bacillus subtilis*	0.25-8.0	flavipesins A and B
26	(Li et al., 2017)	*Bruguiera sexangula var. rhynchopetala*	*Phomopsis longicolla* HL-2232	*Vibrio parahaemolyticus* and *Vibrio anguillarum*	2.5-40	5,5'-dimethoxybiphenyl-2,2'-diol
27	(Meng et al., 2015)	*Avicennia marina*	*Penicillium brocae* MA-231	*Staphylococcus aureus, Micrococcus luteus*, and *Gaeumannomyces graminis*	0.25-64	penicibrocazines A-E
28	(Hemberger et al., 2013)	*Rhizophora mucronata*	*Pestalotiopsis* sp.	*Escherichia coli, Enterococcus faecalis, Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*	125-250	pestalotiopens A and B
29	(Klaiklay et al., 2013)	*Rhizophora apiculata*	*Flavodon flavus* PSU-MA201	*Staphylococcus aureus* ATCC 25923	0.25	flavodonfuran

3.6. Prospects of Endophytic Fungi Application

The pharmaceutical industry's continued reliance on raw materials derived directly from source plants poses a significant threat to the sustainability of specific biological resources. The escalating demand for these materials necessitates a critical balance between production and conservation. Endophytic fungi offer a promising solution, as their capacity to synthesize compounds identical to those found in their host plants can substantially reduce dependence on traditional plant-based sourcing. Furthermore, utilizing microorganisms as a source of potent secondary metabolites offers a more efficient and cost-effective production paradigm. Fungal cultivation allows for the rapid and large-scale production of active compounds, addressing the growing need for medicinal resources (Pimentel et al., 2011).

This review underscores the continued significance of mangrove-associated fungi as a prolific source of novel bioactive natural compounds for pharmaceutical applications (e.g., **Figure 5**). Beyond their demonstrated potential to produce diverse antimicrobial agents, endophytic fungi from mangrove ecosystems also yield compounds with potent antifungal (Chen et al., 2019; Liu et al., 2011; Wang et al., 2013; Wang et al., 2015; Zhu et al., 2019), antioxidant (Chen et al., 2019; Wang et al., 2015; Wu et al., 2018; Zhu et al., 2019), and anticancer properties (Cai et al., 2019; Chen et al., 2016; Chen et al., 2019; Liu et al., 2011; Liu et al., 2019; Ukwatta et al., 2019; Wei et al., 2020; Yang et al., 2017; Zheng et al., 2019; Zhu et al., 2016; Zhu et al., 2019). Furthermore, these fungi produce compounds exhibiting anti-inflammatory, anti-filarial (Ukwatta et al., 2019), antibiofilm (May et al., 2017), influenza antiviral (Wang et al., 2014), and anti-mycobacterial activities (Wang et al., 2013). Notably, they have also been identified as a source of biological control agents against insect larvae, specifically *Helicoverpa armigera* (Bai et al., 2019).

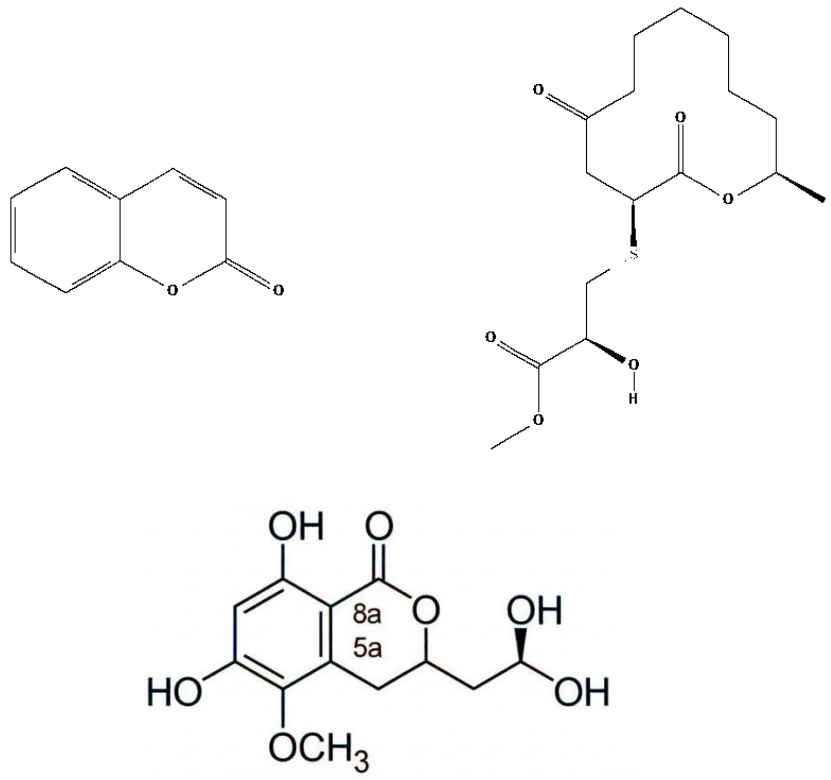

Figure 5. Examples of novel bioactive natural compounds produced by mangrove-associated fungi showcase the chemical diversity of these fungal metabolites: coumarin (a), thiocladospolides A (b), and cytospomarin (c).

An evaluation of fungal isolation techniques from diverse marine organisms reveals that the yield of fungal isolates is contingent upon the specific isolation method and the composition of the isolation medium (Kossuga et al., 2012; Jayasekara et al., 2022). Furthermore, the structural diversity and quantity of secondary metabolites produced by a single fungal strain are significantly influenced by a range of cultivation parameters, including media composition, pH, temperature, the incorporation of enzyme inhibitors, and oxygen availability (Bogas et al., 2022; Kossuga et al., 2012; Jayasekara et al., 2022). Consequently, optimizing the culture medium is imperative to promote endophytic fungi's growth and subsequent metabolite production.

The conventional drug development paradigm is characterized by its inherent complexity, significant challenges, substantial costs, protracted timelines, and labor-intensive procedures. To overcome these obstacles, cutting-edge technologies, including artificial intelligence and machine learning, are increasingly employed to analyze vast datasets generated from diverse sources such as genomics, metagenomics, and transcriptomics, facilitating the exploration of previously uncharacterized microbial entities (Dakal et al., 2025; Nam et al., 2023). Genomic approaches empower researchers to delve deeper into untapped reservoirs, identify novel microbial sources, and unlock their latent chemical potential. These methodologies have proven instrumental in accelerating the drug development pipeline. Traditional experimental procedures would be prohibitively expensive for the in-silico exploration of extensive chemical spaces using machine learning models. These models can be leveraged to design novel therapeutic strategies based on learned patterns of chemical structures that confer antibacterial activity.

Endophytic fungi, particularly those sourced from unique environments like mangroves, represent an abundant resource for discovering novel antimicrobial compounds. While traditional isolation and screening methods have yielded numerous findings, this approach often fails to identify the majority of secondary metabolites that fungi are capable of producing. This limitation stems from the prevalence of silent or unexpressed biosynthetic gene clusters (BGCs) under standard laboratory conditions. This is precisely where the role of genomics becomes crucial in the search for new antimicrobial candidates. Endophytes often fail to activate cryptic BGCs and tend to stop producing secondary metabolites when grown in a lab over time. However, there are several ways to turn on these silent BGCs, such as co-cultivation, epigenetic modification, one strain of many compounds, cluster-specific transcription factor, and heterologous expression methods (Zakariyah et al., 2024).

Various bioinformatic tools are available to detect potential BGCs, which are typically dedicated to the biosynthesis of natural products (Hammami & Fliss, 2010; Niu & Li, 2019). By sequencing the entire genomes of endophytic fungi, researchers can perform genome mining to identify these BGCs *in silico* using bioinformatics tools like antiSMASH or fungiSMASH (accessible at https://fungismash.secondarymetabolites.org/). The identification of these BGCs not only reveals hidden biosynthetic potential but also enables the prediction of metabolite types that might be produced, even if these compounds have never been isolated or phenotypically expressed. This genomic insight paves the way for activating these silent clusters through genetic or environmental manipulation.

Recent studies powerfully illustrate this integrated approach. For example, Wei et al. (2025) presented a comprehensive global analysis of fungal BGCs, aiming to understand the diversification of diketopiperazine biosynthesis. Their study constructed the largest fungal BGC atlas to date, comprising an astonishing 303,983 BGCs predicted from 13,125 fungal genomes, revealing that 99.6% of the 43,984 identified gene cluster families (GCFs) remain uncharacterized,

underscoring the vast, unexplored biosynthetic potential within fungi. Similarly, Petijova et al. (2024) conducted *in silico* prediction of polyketide BGCs within the genomes of *Hypericum*-borne endophytic fungi, seeking new bioactive natural compounds with anticancer activity. They successfully predicted a candidate bis-anthraquinone BGC in the *C. subthermophilus* genome (isolated from *Hypericum*), comprising genes encoding enzymes crucial for anthraquinone skeleton formation, dimerization, and tailoring. These examples emphatically confirms that integrating isolation, genomics, and BGC analysis is indispensable for unlocking the full potential of endophytic fungal secondary metabolites in the future development of antimicrobial agents. The selection of specific gene clusters facilitates the production of pharmacologically and medicinally significant compounds and the elucidation of their biosynthetic mechanisms.

Molecular docking has emerged as a potent drug development tool, enabling the efficient screening of candidate compounds from extensive drug libraries. By computationally predicting the binding affinity and mode of interaction between these vast numbers of potential lead compounds (ligands) and specific microbial protein targets (receptors), such as enzymes vital for bacterial survival, fungal cell wall components, or ribosomal proteins, molecular docking drastically accelerates the initial screening phase. This approach allows researchers to rapidly filter promising candidates, saving considerable time, resources, and effort compared to traditional high-throughput screening methods, ultimately guiding experimental validation towards the most promising new antimicrobial agents.

4. CONCLUSIONS

The symbiotic relationship between mangrove vegetation and endophytic fungi promotes the biosynthesis of diverse bioactive compounds. This includes the production of novel molecules such as cytospyrone, cytospomarin, penicibrocazines, thiocladospolides, coumarin, isocoumarins, and dihydroradicinin. Furthermore, endophytic fungi yield compounds with significant potential as antifungals, antioxidants, anticancer agents, anti-inflammatory agents, anti-filarial agents, antibiofilm agents, influenza antivirals, antimycobacterial agents, and biological control agents. The conventional approach to antibiotic development is characterized by its complexity, challenges, high costs, lengthy timelines, and labor-intensive procedures. To overcome these limitations, research must integrate machine learning to analyze large datasets and molecular-based exploration utilizing genomics, proteomics, and transcriptomics.

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