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A Review on Antibacterial Potential of Marine Bacteria Isolated from *Gracilaria* sp. to Combat Tropical Diseases

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ABSTRACT

Marine bacteria associated with *Gracilaria* sp. have emerged as a promising source of novel antibacterial compounds for combating tropical diseases. Tropical diseases, predominantly affecting low- and middle-income countries, pose significant health challenges due to the emergence of multidrug-resistant pathogens. This review explores the antibacterial potential of marine bacteria isolated from *Gracilaria* sp. and their possible applications in addressing the growing threat of tropical diseases. Recent studies have investigated the diversity of bacteria associated with *Gracilaria* sp., revealing a wide array of microorganisms with unique metabolic pathways and the ability to produce bioactive compounds with antimicrobial properties. These compounds include polyketides, terpenoids, nitrogenous compounds, peptides, alkaloids, bile acids, phenolic compounds, and derivatives of fatty acids, which exhibit antibacterial activity through various mechanisms such as disrupting bacterial cell walls, inhibiting protein synthesis, or interfering with DNA replication. Notably, marine bacteria isolated from *Gracilaria* sp., such as *Bacillus licheniformis*, have demonstrated significant antibacterial efficacy against pathogens relevant to tropical diseases, including *Mycobacterium tuberculosis*. The unique chemical compositions and innovative mechanisms of action of these marine-derived antibiotics offer advantages in combating antibiotic resistance, as they target bacterial pathways distinct from those affected by traditional antibiotics and exhibit lower toxicity to human cells. Furthermore, the synergistic effects of these compounds with existing antibiotics highlight their potential in enhancing the effectiveness of current treatments. The identification of bioactive substances and the extensive potential of marine bacteria associated with *Gracilaria* sp. underscore their promise as sources for developing novel antibacterial drugs to address the challenges posed by tropical diseases.

INTRODUCTION

Tropical diseases remain significant health challenges, predominantly affecting low- and middle-income countries. These diseases encompass a range of parasitic,

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bacterial, and viral infections, impacting over one billion individuals worldwide and resulting in considerable morbidity and mortality **(Tidman *et al.*, 2021; Ogieuhi *et al.*, 2025)**. A major concern is the treatment of bacterial infections associated with tropical diseases, which is further complicated by the emergence of multidrug-resistant organisms such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*. These pathogens have developed resistance to multiple antibiotics, complicating infection management with the current pharmacological arsenal **(Douglas *et al.*, 2023)**. This situation necessitates the exploration of novel sources for antimicrobial compounds.

Marine environments offer a vast and largely untapped reservoir of biodiversity with significant potential for therapeutic applications. This biodiversity represents a rich source of bioactive compounds that can be utilized across various industries, particularly pharmaceuticals **(Snelgrove, 2016)**. Among the diverse marine organisms, seaweeds have attracted considerable attention due to their association with a wide array of microorganisms including bacteria. These marine bacteria have evolved unique metabolic pathways that enable them to thrive in the challenging and competitive marine ecosystem, often producing bioactive compounds with antimicrobial properties relevant to various human health issues **(Perera *et al.*, 2023)**. *Gracilaria* sp., a genus of red seaweeds, is recognized not only for its economic importance in agar production but also as a host for potentially beneficial bacteria **(Beleneva & Zhukova, 2006)**.

This review focuses on the antibacterial potential of marine bacteria isolated from *Gracilaria* sp. and their possible applications in combating tropical diseases. We will examine recent studies that have investigated the diversity of bacteria associated with *Gracilaria* sp., their antimicrobial activities, and the bioactive compounds they produce. Additionally, we will discuss the challenges and opportunities in harnessing these marine bacterial resources for the development of new antibacterial agents to address the growing threat of tropical diseases.

REVIEW

Overview of tropical diseases and antibacterial resistance

Tropical diseases are diseases that primarily occur in tropical and subtropical areas. These diseases are frequently related to poverty, inadequate sanitation, and limited access to healthcare, rendering them a considerable public health issue in low- and middle-income nations **(Simon, 2016; Costa & De Oliveira, 2020; Vuitika *et al.*, 2022; Tebano *et al.*, 2024)**. The spread of tropical diseases is affected by a multifaceted interaction of environmental, behavioral, and socioeconomic elements, alongside the effects of climate change and global warming **(Wu *et al.*, 2014)**. Climate change is anticipated to influence disease transmission patterns directly **(Michael, 2010)**; nevertheless, human activities and poverty also significantly affect the prevalence of tropical diseases **(Adhikari *et al*., 1970; Shen, 2019; Magalhães *et al.*, 2023)**. Given the

significant burden and persistence of tropical diseases, the identification of effective antibacterial agents has emerged as a critical strategy for mitigating their impact.

The most common tropical diseases include tuberculosis, malaria, dengue, cutaneous leishmaniasis, lymphatic filariasis, and neglected tropical diseases like Chagas disease and schistosomiasis **(Cresswell, 2009; Reed & McKerrow, 2018; Scott *et al.*, 2022; Montresor, 2023)**. These diseases are conveyed by diverse microbes, parasites, and arthropods **(Cresswell, 2009)**. Current therapeutic modalities comprise preventive chemotherapy, illness management, and vector control **(Montresor, 2023)**; nonetheless, issues in the management of tropical diseases involve re-emergence in impoverished areas and disparities in climate and healthcare infrastructures **(Hollingsworth *et al.*, 2015; Ganasegeran & Abdulrahman, 2021)**. However, despite the existence of numerous therapeutic modalities, antibiotic resistance continues to pose a considerable obstacle. Antibiotic resistance in tropical locations is affected by complex factors, including unregulated antibiotic usage, insufficient healthcare infrastructure **(Bartoloni & Gotuzzo, 2010; Ouedraogo *et al.*, 2017)**, and sociocultural behaviors. Resolving this issue requires establishing a unified health policy **(Bartoloni & Gotuzzo, 2010; Ouedraogo *et al.*, 2017)**, improving surveillance systems **(Omulo *et al.*, 2015; Canellas *et al.*, 2021)**, and formulating a comprehensive strategy to identify natural products to combat antibiotic resistance **(Cao *et al.*, 2020)**.

Gracilaria sp. and its ecological importance

Gracilaria sp. is a red marine macroalgae recognized for its substantial ecological and commercial importance. They are chiefly esteemed for their superior agar production, which is widely utilized in the culinary, medicinal, and cosmetic sectors **(Umashree & Arunkumar, 2022; Mouedden *et al.*, 2024)**. *Gracilaria* sp. is essential to marine ecosystems, has potential for bioremediation and wastewater treatment, and contains significant nutritional and medicinal properties. *Gracilaria* sp. provides crucial habitat for a broad assemblage of related mollusks, enhancing their abundance, richness, and diversity **(Duarte *et al.*, 2020)**. Furthermore, *Gracilaria* sp. is a prolific source of bioactive chemicals with potential applications across multiple industries, including food, medicines, and biomedicine. It comprises valuable components such as mycosporine-like amino acids, agarans, lipids, steroids, and phenolic acids, with documented bioactivities such as antioxidant, anti-inflammatory, and antibacterial effects **(Torres *et al.*, 2019; Kumar *et al.*, 2023)**. *Gracilaria corticata* is abundant in protein, carbs, and lipids, and it demonstrates antioxidant capabilities, positioning it as a possible source of nutrition and antioxidants **(Mora-Ravelo, 2017)**.

Marine bacteria as a source of novel antibacterial agents

Marine bacteria are emerging as potential sources of novel antibacterial compounds due to their tolerance to extreme marine environments that cultivate significant biological and genetic diversity. These bacteria exhibit potential in synthesizing bioactive

substances with notable antibacterial features, rendering them valuable for medicinal applications **(Debnath *et al.*, 2007; Mazalan *et al.*, 2012; Khan *et al.*, 2015)**. Marine bacteria have been discovered to synthesize many different types of antibiotic compounds, including polyketides, terpenoids, nitrogen compounds, and others.

Previous study indicated that marine *Bacillus* species, such as *Bacillus flexus, Bacillus tequilensis, Bacillus subtilis,* and *Bacillus aerophilus*, demonstrate considerable antibacterial efficacy against harmful bacteria. The antibacterial action is linked to the presence of several bioactive chemicals. These bacteria notably synthesize nitrogenous chemicals, including Pyrrolo[1,2-a]pyrazine-1,4-dione, as well as phthalate derivatives such as phthalic acid butyl isohexyl ester and bis-(2-ethylhexyl) phthalate. Furthermore, tris(2,4-di-tert-butylphenyl) phosphate, phenolic derivatives, and fatty acid derivatives, such as n-hexadecanoic acid, cis-vaccenic acid, and farnesol isomer A, enhance their antibacterial capabilities **(Murniasih *et al.*, 2022)**.

It was discovered that *Streptomyces rochei* synthesizes borrelidin, a powerful antibacterial agent effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). Moreover, several bacterial species, like *Bacillus toyonensis* and *Bacillus cereus*, are recognized for producing antibacterial fatty acids that demonstrate effectiveness against pathogenic organisms such as *Candida albican*s and drug-resistant strains of *Escherichia coli*. The bioactive chemicals these marine bacteria produce encompass several chemical families, such as quinones, lactones, and macrolides, all exhibiting considerable antibacterial efficacy. Actinomycins and napyradiomycins are recognized for their efficacy against MRSA, but *Salinispora arenicola* synthesizes salinaphthoquinones, which demonstrate activity against drug-resistant bacterial strains **(Nweze *et al.*, 2020a)**.

Marine bacteria in drug discovery

Drug discovery from natural sources in marine ecosystems has become an emerging trend, and the exploration of the marine ecosystem focuses on identifying various complicated and unique chemical entities **(Ashawat *et al.*, 2012)**. In the last 50 years, approximately 20,000 natural compounds have been identified from marine sources, resulting in the approval of 17 medications and numerous candidates in clinical studies **(Gerwick & Fenner, 2013)**. Some promising compounds have been discovered in marine environments, including antibacterial, antiviral, anticancer, anti-inflammatory, antioxidant, and enzyme inhibitors **(Kim, 2013; Barreca *et al.*, 2020; Tischler, 2020)**. Marine organisms synthesize a diverse range of novel chemical compounds, such as halogenated compounds, polyketides, alkaloids, and cyclopeptides, which strengthen the pharmacological activity and pharmacokinetic characteristics of these substances and are rarely observed in terrestrial animals **(Wang *et al.*, 2022)**. Marine bacteria are also important natural sources for drug discovery. Exploration of marine-derived compounds has extended the scientific knowledge of potential scaffolds for antibiotic drug discovery, including developing novel antitubercular agents **(Daletos *et al.*, 2016)**.

Types of marine bacteria isolated from *Gracilaria* sp.

Gracilaria sp., a genus of red algae, is known for harboring several bacterial species that interact with the algae in various ways. These bacteria can assist in the growth and health of the algae, aid in the nutrient cycle, or even protect the algae from pathogens (Fig. 1) **(Singh & Reddy, 2014; Liu *et al.*, 2024)**. The findings of marine bacteria isolated from *Gracilaria* sp. are demonstrated in Table (1).

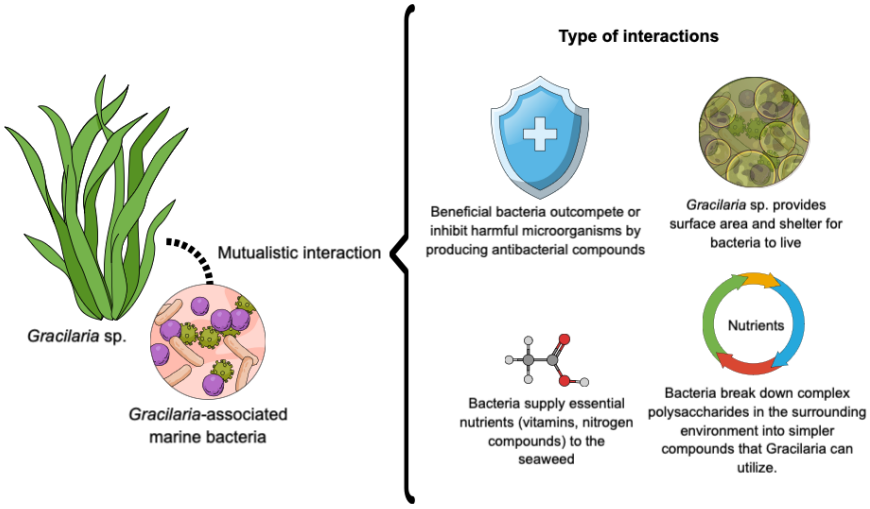

Fig. 1. Interactions between *Gracilaria* sp. and marine bacteria

Table 1. Marine bacteria isolated from *Gracilaria* sp.

Bacterial Species	**Source**	**Reference**
Pseudoalteromonas sp.	*Gracilaria* sp. (Karimunjawa)	**(Lunggani *et al.*, 2020)**
Wenyingzhuangia gracilariae sp. nov.	*Gracilaria vermiculophylla*	**(Yoon *et al.*, 2015)**
Seonamhaeicola algicola sp. nov.	*Gracilaria blodgettii*	**(Zhou *et al.*, 2016)**
Agaribacter flavus sp. nov.	*Gracilaria blodgettii*	**(Yu *et al.*, 2018)**
Crocinitomix algicola sp. nov.	*Gracilaria blodgettii*	**(Shi *et al.*, 2017)**
Marinagarivorans algicola gen. nov. sp. nov.	*Gracilaria verrucose*	**(Guo *et al.*, 2016)**
Agarilytica rhodophyticola gen. nov., sp. nov.	*Gracilaria blodgettii*	**(Ling *et al.*, 2017)**
Bacillus amyloliquefaciens	*Gracilaria corticate*	**(Kooren *et al.*, 2024)**
Staphylococcus equorum *Bacillus tropicus*	*Gracilaria* sp. (Tongkaina)	**(Ginting *et al.*, 2024)**
Vibrio brasiliensis, *Paracoccus zeaxanthinifaciens*, *Alteromonas* sp. *Pseudoalteromonas* sp.(a putative novel) *Bacillus licheniformis*.	*Gracilaria edulis*	**(Umashree *et al.*, 2024)**
Bacillus kokeshiiformis strain SM24 *Nitratireductor kimnyeongensis strain E14* *Brevibacillus agri strain 13*	*Gracilaria edulis*	**(Saravanan *et al.*, 2024)**
Enterobacter cloacae subsp. *dissolvens*	*Gracilaria foliifera*	**(Ezhilarasi and Vanavil, 2023)**
Bacillus endophyticus *Bacillus licheniformis*	*Gracilaria dura*	**(Mathew *et al.*, 2023)**

Bacillus velezensis		
Halomonas sp.	*Gracilaria changii*	**(Muthukrishnan *et al.*, 2023)**
Bacillus sp.	*Gracilaria corticata*	**(Deb *et al.*, 2023)**
Vibrio sp.	*Gracilari* sp. (Yamaguchi)	**(Ito *et al.*, 2022)**
Alteromonas macleodii QZ9-9	*Gracilaria hainanensis*	**(Wang *et al.*, 2022)**
Lysinibacillus odysseyi KC14951	*Gracilaria canaliculata*	**(Karthick and Mohanraju, 2020)**
Marinomonas agarivorans sp. nov.	*Gracilaria blodgettii*	**(Yu *et al.*, 2020)**
Corynebacterium sp. *Bacillus megaterium,* *Klebsiella oxytoca,* *Corynebacterium* sp. *Bacillus pasteurii,* *Bacillus cereus,* *Aeromonas* sp. *Corynebacterium* sp. *Lysinibacillus xylanilyticus,* *Lactobacillus casei,* *Aeromonas hydrophila*	*Gracilaria edulis*	**(Suvega and Arunkumar, 2019)**
Exiguobacterium aestuarii St. SR 101	*Gracilaria corticata*	**(Leela *et al.*, 2019)**
Bacillus sp. *Pseudomonas stutzeri* *Vibrio owensii*	*Gracilaria corticata*	**(Karthick and Mohanraju, 2018)**
Bacillus subtilis	*Gracilaria gracilis*	**(Viszwapriya *et al.*, 2016)**
Lacinutrix gracilariae sp.	*Gracilaria* sp. (Jinjiang)	**(Huang *et al.*, 2016)**
Pseudomonas sp.	*Gracilaria dura*	**(Gupta *et al.*, 2013)**
Bacillus licheniformis *Bacillus pumilus* *Exiguobacterium homiense*	*Gracilaria dura*	**(Singh *et al.*, 2011)**
Bacillus safensis	*Gracilaria* sp. (Mediterranian)	**(Deutsch *et al.*, 2021)**

Functional and metabolic roles of *Gracilaria*-associated bacteria

Marine bacteria isolated from *Gracilaria* sp. exhibit diverse metabolic capabilities. This has been well-described in a number of applications involving producing bioactive compounds, agarose activity, carrageenase activity, polysaccharide degradation, exopolysaccharide production, etc. Marine bacteria, particularly those derived from *Gracilaria* sp., synthesize diverse bioactive chemicals with considerable promise for biological applications. These chemicals demonstrate varied properties, including antibacterial, antioxidant, and anticancer activity, and are also implicated in enzyme formation **(Mulligan *et al.*, 2014)**. *Pseudomonas* sp. isolated from *Gracilaria dura* synthesizes an extracellular exo-β-agarase capable of hydrolyzing agar into neoagarobiose and galactose, indicating its potential for the bioconversion of marine red algal polysaccharides into energy feedstock **(Gupta *et al.*, 2013)**. Additionally, *Agarilytica rhodophyticola*, a novel species isolated from *Gracilaria blodgettii*, showed

agarolytic characteristics **(Ling *et al.*, 2017)**. Furthermore, the metabolic capabilities related to carrageenase activity were also noted in *Vibrio* sp. strain NJ-2, extracted from decaying red algae such as *Gracilaria* sp., which produces κ-carrageenase, capable of depolymerizing κ-carrageenan into oligosaccharides, beneficial for diverse biological applications **(Zhu & Ning, 2016)**. Streptomyces sp. ALG-5, extracted from seaweeds such as *Gracilaria* sp., degrades alginate into disaccharides, trisaccharides, tetrasaccharides, and pentasaccharides, underscoring its function in polysaccharide degradation. In addition certain bacterial strains can degrade polysaccharides and produce exopolysaccharides. *Enterobacter cloacae* subsp. dissolvens, extracted *from Gracilaria foliifera*, is recognized for producing curdlan, an important exopolysaccharide characterized by distinctive thermo-gelling capabilities. Curdlan's unique gelation properties and broad commercial applications underscore its potential for various industrial uses **(Ezhilarasi & Vanavil, 2023)**.

The isolated marine bacteria from *Gracilaria* sp. have a symbiotic role to its host. Specific bacteria associated to *Gracilaria* sp. can enhance its growth. *Halomonas* sp. isolated from *Gracilaria changii* has been demonstrated to stimulate bud formation and synthesize indole-3-acetic acid (IAA), a growth hormone that facilitates the seaweed's growth **(Muthukrishnan *et al.*, 2023)**. Moreover, the metabolic connections between *Gracilaria* sp. and its bacterial community are crucial for nutrition exchange. Bacteria supply vital elements that seaweed cannot independently produce, including vitamins and nitrogen compounds, which are important for its growth and resilience to stress **(Walker & Crossman, 2007; Kim *et al.*, 2024)**. The bacterial population linked to *Gracilaria* sp. is essential for disease prevention. Beneficial bacteria can surpass pathogenic species, thereby safeguarding the seaweed against diseases that may result in degradation and subsequent financial losses **(Liu *et al.*, 2024; Zeb *et al.*, 2024)**.

Identified Antibacterial Compounds in *Gracilaria*-associated Bacteria

Marine bacteria are known to produce a wide array of antibacterial compounds. These include, but are not limited to, polyketides, terpenoids, nitrogenous compounds, peptides, alkaloids, bile acids, phenolic compounds, and derivatives of fatty acids **(Kim *et al.*, 2007; Qi *et al.*, 2009; Choi *et al.*, 2015; Murniasih *et al.*, 2022)**. The specific antibacterial compounds of marine bacteria isolated from *Gracilaria* sp. are given in Table 2.

Table 2. Antibacterial compounds in marine bacteria isolated from *Gracilaria* sp.

Marine Bacteria	Host macroalgae	Bioactive compounds	Inhibited microorganisms	Molecular Mass (kDa)	Reference
Pseudoalteromonas sp.	*Gracilaria* sp. (Karimunjawa)	2,3,5,7-tetrabromobenzofuro[3,2-b]pyrrole	methicillin-resistant *Staphylococcus aureus* (MRSA)	1.93 (±0.05)	**(Fehér *et al.*, 2010)**
		4,4′,6-tribromo-2,2′-biphenol		2.19 (±0.08)	

Bacillus amyloliquefaciens	*Gracilaria corticata*	hexahydro-41-hydroxy-macrobrevin-31-acetate	Vancomycin-resistant *Enterococcus faecalis, Methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa Klabsiella pneumoniae.*	NR[a]	**(Chakraborty *et al*., 2022a)**
Staphylococcus equorum	*Gracilaria* sp. (Tongkaina)	Bis(2-ethylhexyl) phthalate (DEHP)	*Bacillus subtilis Escherichia coli*	0.39	**(Murniasih *et al*., 2023)**
		Stigmasta-3,5-diene (Sterol)		0.40	
		3-benzylhexahydropyrrolo[1,2-A] pyrazine-1,4-dione		0.24	
		Hexadecanoic acid		0.26	
Bacillus tropicus	*Gracilaria* sp. (Tongkaina)	NR[a]	Multi-drug resistant *Bacillus cereus* Multi-drug resistant *Escherichia coli*	NR[a]	**(Ayuningrum *et al*., 2019)**
Bacillus licheniformis	*Gracilaria edulis Gracilaria dura*	Bacitracin/Ayfivin	*Mycobacterium tuberculosis*	1.42	**(Shleeva *et al*., 2023)**
		Proticin		0.56	
		Peptide A12-C		0.77	
		Licheniformins		3.8 – 4.8	
		Amoebicins d13-A, d13-B, and d13-C		1.87	
		Lichenicidin		3.25	
Bacillus velezensis	*Gracilaria dura*	Amylocyclicin	NR[a]	NR[a]	**(Wang *et al*., 2024)**
		ComX1			
		LC (Bacteriocin)			
Lysinibacillus odysseyi KC14951	*Gracilaria canaliculata*	Furan	*Klebsiella pneumoniae, Shigella flexneri*	NR[a]	**(Karthick and Mohanraju, 2020)**
		Diazene			
		Lupenol			
Lysinibacillus xylanilyticus	*Gracilaria edulis*	N-acyl homoserine lactone like compound	*Xanthomonas oryzae* pv. oryzae.	66	**(Suvega and Arunkumar, 2019)**
Bacillus megaterium	*Gracilaria edulis*	7,7-bis(3-indolyl)-p-cresol	*Vibrio vulnificu Vibri parahaemolyticus Bacillus cereus Micrococcus luteus Trichophyton mentagrophytes*	0.34	**(Cuong *et al*., 2014)**
		cyclo-(S-Pro-R-Leu)		0.21	
		cyclo-(S-Pro-R-Val)		0.20	

Pseudomonas stutzeri	*Gracilaria corti cata*	4b-methyl-5, 6, 7, 8 tetrahydro-1 (4b-H)- phenanthrenone	*Staphylococcus aureus, Salmonella typhi*	NR[a]	**(Uzair *et al.*, 2008)**
Bacillus safensis	*Gracilaria* sp. (Mediterranian)	NR[a]	*Photobacterium damselae Streptococcus iniae Aeromonas salmonicida*	NR[a]	**(Deutsch *et al.*, 2021)**

[a]NR, not reported

Antibacterial mechanism

The antibacterial efficacy of these substances typically entails the disruption of bacterial cell walls, inhibiting protein synthesis, or interfering with DNA replication. Compounds such as anthracimycin and kocurin have broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria by targeting critical bacterial activities **(Schinke *et al.*, 2017).**

Bacillus licheniformis is a marine bacteria isolated from *Gracilaria edulis* and *Gracilaria dura*. The antibacterial mechanisms of *B. licheniformis* primarily involve targeting the bacterial cell membrane, nucleic acids, and cell wall. Compounds such as lichenicidin, subtilin, and lipopeptides interact with lipid constituents of the bacterial membrane, including Lipid II or the lipid bilayer, resulting in pore formation and breakdown of membrane integrity. Due to membrane rupture, this leads to membrane depolarization, ion influx, and cell death. Another process involves enzymes such as NucB and antimicrobial compounds (AMS) that degrade or inhibit the synthesis of bacterial nucleic acids (DNA and RNA). This inhibition disrupts essential activities such as mRNA and peptide synthesis, compromising biofilm development and cellular functions, ultimately leading to bacterial death. Furthermore, agents such as bacitracin, ppABP, and chitinases affect the bacterial cell wall by obstructing peptidoglycan production or degrading chitin, resulting in cell wall disintegration. The compromised cell wall leads to the release of cellular components, culminating in bacterial lysis. Together, these processes provide a comprehensive strategy for antibacterial activity, effectively incapacitating bacterial cells through multiple targets **(Shleeva *et al.*, 2023)**.

Potential for drug development for tropical diseases

Marine bacteria represent a promising avenue for discovering new antibiotics, thanks to their unique compounds that often feature different mechanisms of action, effectively targeting various pathogens, including those resistant to existing treatments **(Bérdy, 2012)**. These compounds typically exhibit lower toxicity to human cells and have less overlap with current antibiotics, which reduces the risk of cross-resistance **(Stien, 2020)**. Moreover, many marine-derived antibiotics display potent bioactivity at low concentrations and can enhance the effectiveness of traditional treatments through synergistic effects **(Nweze *et al.*, 2020b)**. As renewable resources, marine bacteria

provide sustainable alternatives for drug development, making them crucial in addressing the growing global health challenge of antibiotic resistance **(Wibowo *et al.*, 2023a)**.

Marine bacteria-derived antibiotics present notable benefits in combating antibiotic resistance due to their distinct chemical compositions and innovative mechanisms of action. These compounds frequently target bacterial pathways that differ from those affected by traditional antibiotics, making them effective against pathogens that have become resistant to existing treatments **(Penesyan *et al.*, 2015)**. Furthermore, many of these marine-derived antibiotics demonstrate lower toxicity to human cells, improving their safety profiles **(Bérdy, 2012)**. The variety of bioactive compounds marine bacteria produce offers a valuable resource for discovering new antimicrobial agents. It minimizes the risk of cross-resistance, as these unique compounds can bypass the resistance mechanisms employed by conventional antibiotics **(Nweze *et al.*, 2020b)**. This combination of efficacy and safety underscores the importance of marine bacteria in addressing the growing global health crisis of antibiotic-resistant infections.

Combating antibiotic resistance

Marine bacteria have been recognized as abundant sources of new bioactive chemicals with considerable antibacterial activity. *Bacillus* sp. DK1-SA11, extracted from coastal ecosystems, exhibits extensive antibacterial efficacy, particularly against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Candida albicans* **(Khan *et al.*, 2015)**. Moreover, marine-derived microorganisms have been recognized as sources of efficient chemicals against multidrug-resistant (MDR) infections. *Bacillus amyloliquefaciens*, linked to sea algae, demonstrated inhibitory effects against MRSA, vancomycin-resistant *Enterococcus faecalis*, and other antibiotic-resistant bacteria **(Chakraborty *et al.*, 2022b)**. Marine microorganisms have demonstrated the ability to create antibiofilm compounds, which are essential for combating biofilm-associated infections caused by multidrug-resistant bacteria. Proteins released by marine *Priestia* sp. markedly reduced biofilm formation by *Staphylococcus aureus* **(Ribeiro *et al*., 2024)**. A significant discovery in the research is the identification of *Bacillus licheniformis*, isolated from *Gracilaria dura* and *Gracilaria edulis*, as a promising antibacterial agent against *Mycobacterium tuberculosis* **(Shleeva *et al.*, 2023)**.

Synergistic Effects with Existing Antibiotics

Marine bacterial compounds exhibit extensive antibacterial properties, including the suppression of biofilm development, which is essential for combating chronic illnesses. Particularly, certain compounds including polyketide derivatives, amino acid derivatives, and terpenoids synthesized by marine bacteria have shown effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) **(Rahman *et al.*, 2010; Dinarvand *et al.*, 2020; Wibowo *et al.*, 2023b)**.

Epiphytic bacteria associated with *Gracilaria canaliculata*, including *Lysinibacillus odysseyi*, exhibit significant antibiotic efficacy against pathogens such as *Escherichia coli* and *Klebsiella pneumoniae*, suggesting their potential for bioactive chemical production **(Zainuddin *et al.*, 2019)**. Bacteria isolated from *Gracilaria verrucosa*, including genera such as *Vibrio*, *Chromobacterium*, and *Flavobacterium*, have been recognized for their diverse metabolic capabilities, underscoring their potential as sources of novel bioactive metabolites, although not directly associated with antibiotic synergy **(Karthick & Mohanraju, 2020)**.

CONCLUSION

Marine bacteria associated with *Gracilaria* sp. have emerged as a promising source of novel antibacterial compounds for combating tropical diseases. These bacteria produce a wide array of bioactive compounds, including polyketides, terpenoids, nitrogenous compounds, peptides, alkaloids, bile acids, phenolic compounds, and derivatives of fatty acids, which exhibit antibacterial activity through various mechanisms such as disrupting bacterial cell walls, inhibiting protein synthesis, or interfering with DNA replication. Notably, *Bacillus licheniformis* isolated from *Gracilaria* sp. has demonstrated significant antibacterial efficacy against pathogens relevant to tropical diseases, including *Mycobacterium tuberculosis*. The unique chemical compositions and innovative mechanisms of action of these marine-derived antibiotics offer advantages in combating antibiotic resistance, as they target bacterial pathways distinct from those affected by traditional antibiotics and exhibit lower toxicity to human cells. Furthermore, the synergistic effects of these compounds with existing antibiotics highlight their potential in enhancing the effectiveness of current treatments. The identification of bioactive substances and the extensive potential of marine bacteria associated with *Gracilaria* sp. underscore their promise as sources for developing novel antibacterial drugs to address the challenges posed by tropical diseases.

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