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Antibacterial potential of marine organisms and coastal plants in combating antibacterial resistance: A review

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ABSTRACT

The increasing number of drug-resistant pathogens is a global issue and becoming worse because it has reduced the effectiveness of current antibiotics in the management of infectious diseases. Therefore, this situation highlights the urgency of an action plan to identify and develop novel and potent antimicrobials derived from natural resources. Therapeutic compounds from natural resources can offer novel, straightforward approaches against pathogenic bacteria with the least toxic manifestations and a low risk of acquiring resistance. Marine organisms and coastal plants receive much interest among researchers nowadays for developing new pharmaceuticals because they are rich in secondary metabolites that have various pharmacological effects, such as antibacterial, anti-cancer, antiviral, anti-inflammatory and others. This review's goal is to highlight the phytochemical components of marine organisms and coastal plants that might be accountable for their antibacterial properties that have been scientifically confirmed and can be potential aids in treating infectious diseases caused by multidrug resistant (MDR) bacteria in humans.

Keywords: Antibacterial, antimicrobial resistance, coastal plants, marine organisms, natural products, secondary metabolites

INTRODUCTION

The struggle of humankind against infectious diseases is well known and the discovery of antibiotics in the early 20th century has led to optimism that infections can be controlled and prevented (Kapoor *et al*., 2017). Antibiotics are chemotherapeutic agents that either kill or stop the development of microbial cells. Antibiotics work by attacking the physiology and biochemistry of bacteria or by allowing the body's natural defences to eliminate pathogens (Sengupta *et al*., 2013). Since their discovery and their introduction into commercial use over 70 years ago, modern medicine has depended on the efficacy of antibiotics in treating and preventing numerous illnesses, including urinary tract infections, skin and soft tissue infections, pneumonia and also life-threatening infections such as endocarditis, meningitis and sepsis. Besides, antibiotics are also required for routine and advanced medical procedures such as organ transplants and caesarean sections (Banin *et al*., 2017).

However, the effectiveness of antibiotics that have saved millions of lives is in jeopardy due to the increasing rise of bacteria resistant to various currently available drugs. Antimicrobial resistance (AMR) occurs when bacteria develop the ability to resist the drugs designed to kill them and continue to grow. The primary causes of AMR include the overuse, incorrectly prescribed use and extensive agricultural use of antibiotics that can promote the development of genetic alterations in bacterial pathogens, such as changes in gene expression, horizontal gene transfer (HGT) and mutagenesis (Ventola, 2015). The biochemical resistance mechanisms used by bacteria include limiting drug uptake, altering a drug target, inactivating a drug and active drug efflux (Reygaert, 2018). The emergence of AMR is acknowledged as a global burden since it limits treatment options for patients, increases the cost and length of treatments and significantly increases mortality and morbidity associated with common bacterial diseases (Prestinaci *et al*., 2015). Therefore, the development of new antibiotics or alternative therapies are urgently needed to combat the issue comprehensively.

Oceans encompass 70% of the earth's surface, where an estimated 50-80% of all life on earth resides. Marine organisms and coastal plants are marine resources that have been known for their great potential as a source of

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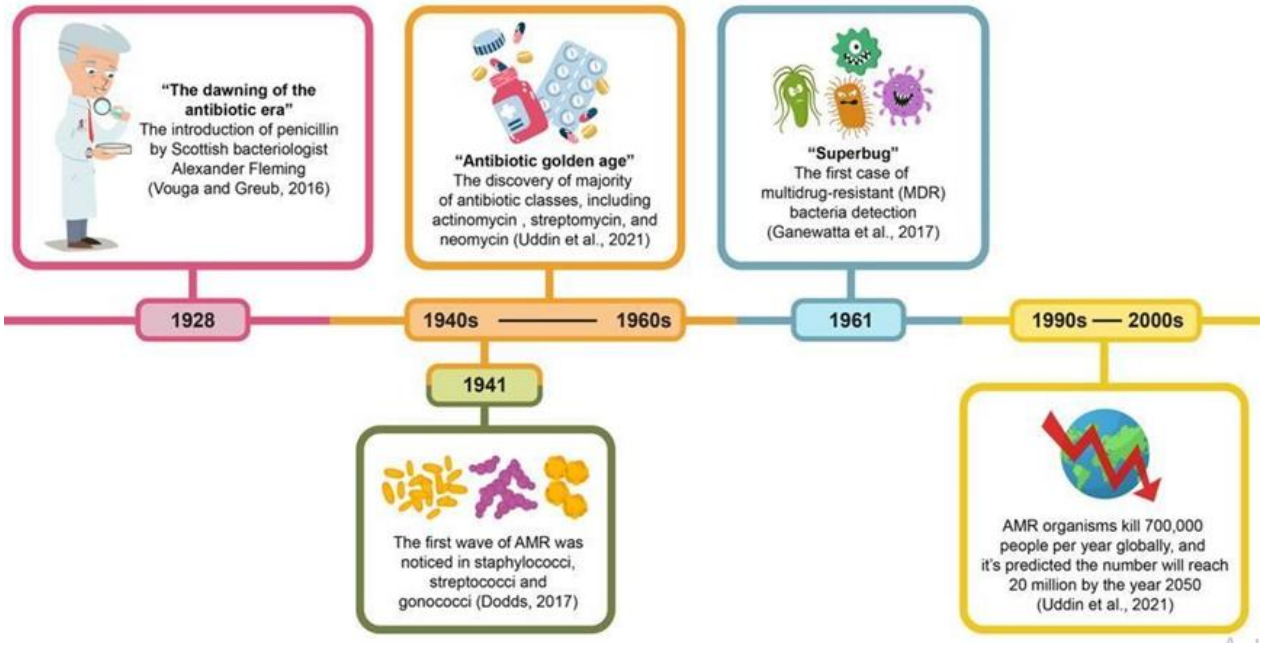

Figure 1: Schematic diagram depicts the history of antibiotic discovery and evolution up to the development of antibiotic resistance (Created using Adobe Illustrator.com).

bioactive compounds that have been found *in vitro*, such as flavonoids, alkaloids, tannins, saponins, terpenoids and glycosides, many of which exhibit various bioactivities including anti-cancer, antibacterial, antifungal, antiviral and antioxidant activities (Hamdillah *et al*., 2019). Marine bioactive compounds came to the attention of the pharmaceutical industry in 1969, when the first anti-cancer drug related to marine species was approved for clinical use. Since then, numerous new bioactive compounds with antimicrobial properties have been discovered, but all of them are still under investigation (Ng *et al*., 2015). According to research conducted in 2022 by Karthikeyan *et al.* (2022), various antibacterial potentials of marine-derived bioactive compounds, including spirotetronate, ansamycin-type polyketide, beta-diketones, tetracenediones, lactones, quinolones, xanthones, peptides, terpenoids, lipopeptides and depsipeptides, which have potential effects on various infectious diseases. Natural products found in marine resources have a variety of structural characteristics that are distinct from those found in terrestrial organisms. Meanwhile, besides protecting the coast from erosion and flooding, coastal medicinal plant communities were frequently used by coastal people to cure several diseases. Prior studies of this marine flora suggest that they may have abundant medicinal properties due to salty adaptation (Prakash *et al.*, 2016). As many know, the mechanism of bioactive compounds from plant-derived antimicrobials could have other target sites than current antibiotics, which might lead to different modes of action against microorganisms (Subramani *et al.*, 2017). There are several mechanisms that underlie the antimicrobial action of natural bioactive compounds, including disrupting microbial membranes or impairing cellular metabolism, controlling biofilm formation, inhibiting bacterial capsule production, attenuating bacterial virulence by controlling quorum-sensing, reducing microbial toxin production and also acting as resistance-modifying agents (RMA) (Ginovyan *et al.*, 2017). Hence, the use of bioactive compounds derived from natural resources plays a crucial role in biomedical research and drug development as a potential replacement for current synthetic antibiotics because they are more effective and safer without toxic side effects and have a low chance of developing resistance. Manufactured drugs have the potential to be poisonous, and prolonged usage in high doses can be harmful or carcinogenic to humans (Yuan *et al.*, 2016). These natural resources are more sustainable and cost-effective since they can be easily found locally or widely cultivated in tropical and subtropical climates.

A BRIEF HISTORY OF ANTIBIOTICS

Antimicrobials refer to a class of medications from natural, synthetic or semi-synthetic origin with the same goal of lowering the risk of infection and sepsis from microorganisms (Nankervis *et al*., 2016). It includes preventing and treating infections from viruses, bacteria, fungi, protozoa and parasites (Di Martino, 2022). As shown in Figure 1, penicillin introduced by Scottish bacteriologist Alexander Fleming in 1928, was the first antibacterial of natural origin to be used in a therapeutic environment. Penicillin is regarded as one of the most important advances in therapeutic medicine and the beginning of the antibiotic era (Vouga and Greub, 2016). The period between the 1940s and 1960s was considered

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Table 1: Common MDR pathogens that pose a danger to human health around the globe.

MDR bacteria	Diseases	Antibiotic	Resistance mechanisms	References
Escherichia coli	Urinary tract infection, Pneumonia, Meningitis, Septicemia, Enteritis	Vancomycin, tetracyclines, phenolics, sulfonamides, trimethoprim and fosfomycin	Intrinsic resistance and alter the drug target	Poirel *et al.* (2018); Mancuso *et al.* (2021); Wu *et al.* (2021); Islam *et al.* (2023)
Pseudomonas aeruginosa	Nosocomial bloodstream infection, Maculopapular pruritic rash, Breast tenderness, Fever, Axillary lymphadenopathy	Carbapenems, Aminoglycosides, Quinolones and β-lactams	Intrinsic resistance, limiting uptake of drugs, active drug efflux and inactivating a drug	Pang *et al.* (2019); Mancuso *et al.* (2021); Wilson and Pandey (2023)
Methicillin-resistant *S. aureus* (MRSA)	Superficial skin abscess, Necrotic pneumonia, Endocarditis	All β-lactam	Alter the drug target	Bitrus *et al.* (2018); Siddiqui and Koirala (2023)
Bacillus subtilis	Bacteremia, Endocarditis, Pneumonia, Septicemia	Lincomycin (Lnc), Norfloxacin, Penicillin, Trimethoprim-sulfamethoxazole, Clindamycin and Tetracycline	Inactivating a drug	Takada *et al.* (2022); Adamski *et al.* (2023); Zhai *et al.* (2023)
Carbapenem-resistant *K. pneumoniae* (CRKP)	Pneumonia, Bloodstream infections, Meningitis, Urinary tract infections	Carbapenems	Alter the drug target, decreased membrane permeability in the cell wall	Bengoechea and Sa Pessoa (2019); Reyes *et al.* (2019)

the “antibiotic golden age” due to the discovery of the majority of the antibiotic classes, including actinomycin, streptomycin and neomycin, that are still utilized in clinical practice today (Uddin *et al*., 2021). However, the first wave of AMR was noticed in staphylococci, streptococci and gonococci; penicillin-resistant strains of *Staphylococcus aureus* emerged shortly after the introduction of penicillin to the general public in 1941. The bacteria produced β-lactamase enzymes, which hydrolyzed the β-lactam bond and prevented the antibiotic from binding to their target (Dodds, 2017). Over the last few decades, repeated exposure of bacteria to different classes of antimicrobials has created a lethal army of MDR bacteria that are known as “superbugs,” which pose a danger to human health around the globe because they are resistant to multiple antibiotics as in Table 1 (Ganewatta *et al*., 2017). As stated in the World Health Organization (WHO) report of 2019, AMR organisms kill 700,000 people per year globally and it's predicted that number will reach 20 million by the year 2050, whereas the financial burden could cost up to US$ 2.9 trillion (Uddin *et al*., 2021). The majority of these cases and deaths occur among adults 50 years of age or older as well as individuals with weakened immune systems, such as those with chronic diseases, including acquired immunodeficiency syndrome (AIDS), cancer, lupus and organ transplant recipients (Ventola, 2015).

Malaysia is not an exception when it comes to the threat of AMR infections. Malaysia has been one of the countries with the highest *E. coli* resistance to aminopenicillin. The majority of tested *E. coli* isolates from patients with urinary tract infections were resistant to penicillin at a rate ranging from 68-100% and 85% for ciprofloxacin and cefuroxime. Numerous studies indicate that the expression of numerous efflux pumps or the intrinsic resistance are the two main factors contributing to the resistance pattern (Naeemmudeen *et al.*, 2021). Moreover, in a study conducted by University Malaya Medical Centre (UMMC) between 1996 and 1998, carbapenems-resistant *Acinetobacter baumannii* (CRAB) was completely resistant to amoxicillin-clavulanate, ampicillin, cefoperazone and cefuroxime and also had 90% resistance rates against gentamicin, ciprofloxacin and cephalosporins (Mortazavi *et al*., 2020). In 2017 and 2018, the highest resistance rate of *A. baumannii* against carbapenems and aminoglycosides varied, along with an average of 93% fluoroquinolone resistance (Naeemmudeen *et al.*, 2021). Next, all 539 MRSA isolates were penicillin-resistant, according to one of the early reports from Hospital Kuala Lumpur (HKL). Up until 2018,

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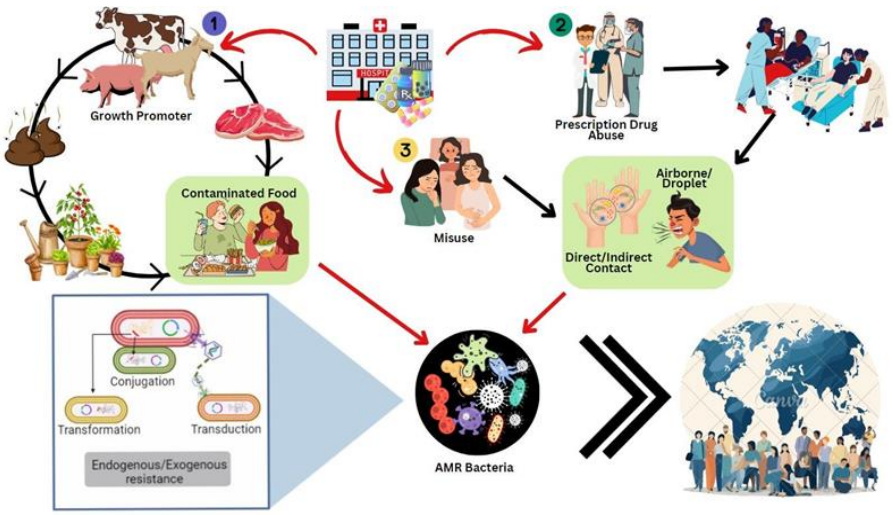

Figure 2: Schematic diagram representation of possible factors that lead to antimicrobial resistance (AMR) and antibiotic resistance spread (Created using Canva.com).

The resistance rates of tested MRSA isolates against oxacillin, cefoxitin and penicillin remained constant at 100% and had 88.8% resistance rates to gentamicin (Bariman *et al.*, 2019). Apart from that, most *Klebsiella pneumoniae* isolates examined between 2010 and 2012 were 97-100% resistant to second and third-generation cephalosporins. The resistance to ampicillin, amoxicillin-clavulanate acid and aztreonam was strong among this species, ranging from 94 to 100% on average (Al-Marzooq *et al*., 2015). Although the Malaysian government has come up with an action plan that calls for raising public awareness to educate communities regarding the health implications of antibiotic resistance, this issue still thrives each year (Naeemmudeen *et al.*, 2021).

ANTIMICROBIAL RESISTANCE

AMR occurs when bacteria develop the ability to resist the drugs designed to kill them and continue to grow (Ventola, 2015). The WHO proclaimed that AMR is among the ten worldwide public health hazards to people in 2019 (Meinen *et al*., 2023). The main contributing factors to the development of AMR, according to the Centers for Disease Control and Prevention (CDC), are the overuse of antibiotics due to their easy availability and the use of antibiotics to treat asymptomatic infections, which make the bacteria more tolerant to the drug's concentration and eventually develop resistance (Mittal *et al*., 2020) (Figure 2). Antibiotics only work against bacteria, not viral infections and increased consumption of antimicrobial drugs by patients without getting a clinical test and physicians' counselling are fuelling resistance to lifesaving drugs (Read and Woods, 2014). Next, improper prescribing of antimicrobial therapy in medical practice has contributed to the growing resistance problem, such as the wrong drug choice, the wrong route of administration, the wrong dose and the wrong frequency or duration of treatment (Tangcharoensathien *et al*., 2018). Moreover, antibiotics are often used as growth supplements in the livestock industry and 80% of the antibiotics sold in the United States are used on animals to increase their general health and produce higher-quality products and greater harvests (Bartlett *et al*., 2013). Nevertheless, livestock transmits the resistant bacteria to humans through meat products and it was noticed 35 years ago when high rates of antibiotic resistance were discovered in the intestinal flora of both farm animals and farmers (Golkar *et al*., 2014).

This condition has the potential to enhance the development of AMR bacteria by encouraging their genetic changes via either vertical gene transfer (endogenous) or horizontal gene transfer (exogenous). Endogenous resistance refers to the phenomenon of a spontaneous mutation that confers more resistance to a certain substance on the bacteria (from its parents to its children) (Patangia *et al.*, 2022). The development of high-level resistance frequently occurs in stages, starting with an initial mutation brought on by antibiotic treatment that enables mutant bacteria to dominate the pathogen population and progressing to later mutations that confer additional survival advantages during subsequent antibiotic treatments (Laws *et al.*, 2019). While exogenous resistance involves the transfer of a resistance gene from a resistant bacterium to a susceptible bacterium (in a community setting), it typically happens between different organisms or different species (Shi *et al.*, 2021). The mechanisms through which it can occur are conjugation, which involves the transfer of resistance (R) plasmids containing antibiotic resistance genes between bacteria through a conjugative pilus, the transformation which involves the alteration of the bacterial genome through the uptake and incorporation of exogenous DNA and transduction which involves the transfer of bacterial DNA as facilitated by a viral vector as shown in Figure 2 (Tao *et al.*, 2022).

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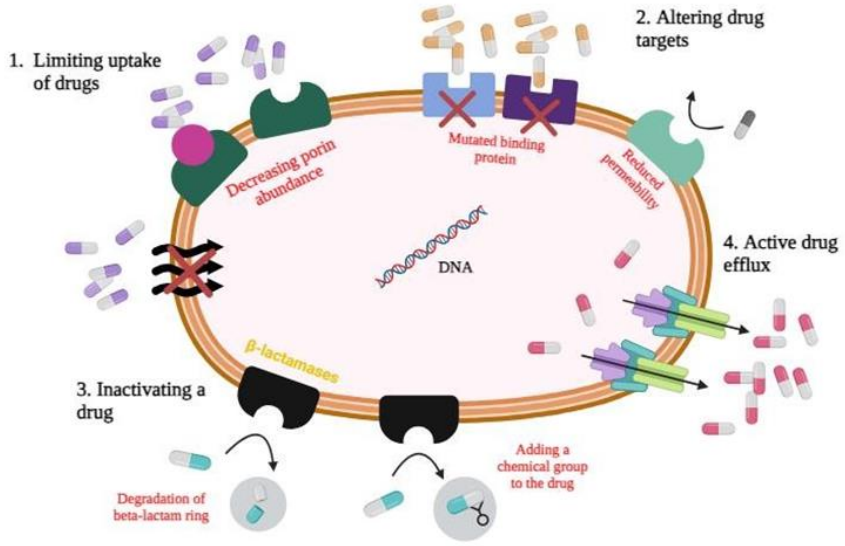

Figure 3: Schematic diagram representing the general antibiotic resistance mechanisms (Created using Biorender.com).

MECHANISMS OF BACTERIAL RESISTANCE TO ANTIBIOTICS

AMR bacteria may be categorized into four main types of mechanisms: (1) limiting uptake of drugs; (2) altering drug targets; (3) inactivating a drug; (4) active drug efflux, which are discussed separately below (Figure 3). The capability of bacteria to restrict the absorption of antimicrobial drugs varies naturally due to the structural variations between Gram-positive bacteria and Gram-negative bacteria have (Chancey *et al.*, 2012). Gram-negative bacteria restrict drug uptake in two ways: by decreasing porin abundance (the Enterobacteraceae family can develop resistance against carbapenems by having fewer porins and sometimes stopping production entirely of certain porins) and by causing mutations that alter the porin channel's selectivity (*Enterobacter aerogenes* have mutations that alter the porin channel, making them resistant to imipenem and certain cephalosporins) (Reygaert, 2018). Recently, Gram-positive bacteria such as *S. aureus* have developed resistance to vancomycin by developing a thicker cell wall as a result of an unidentified process, making it more difficult for the antibiotic to enter the cell and provide intermediate resistance to the drug (Gardete and Tomasz, 2014). Another widely seen phenomenon in bacterial colonization is the development of a thick, sticky biofilm matrix, which contains polysaccharides, proteins and DNA from the residing bacteria and shields them from both host immune system attacks and antimicrobial agents (Mah, 2012).

Second, the bacteria can alter the drug target to confer resistance to certain antibiotics. For example, Gram-positive bacteria can acquire resistance to β-lactams antibiotics by modifying the shape and/or number of PBPs (penicillin-binding proteins) either completely block drug binding or reduce the quantity of medication that can bind to the target (Beceiro *et al.*, 2013). Gram-negative bacteria (with thick lipopolysaccharide layers) can develop intrinsic resistance to many antibiotics, such as vancomycin, that inhibit bacterial cell wall synthesis by generating van genes that change the structure of peptidoglycan precursors and reduce vancomycin's capacity to bind to them (Phukan *et al.*, 2016).

Third, bacteria can inactivate medications in two ways: by actually degrading the drug or by adding a chemical group to the drug. Drug degradation commonly involves β-lactamases, a large group of drug hydrolyzing enzymes and tetracycline is another medication that can be rendered inactive by hydrolysis via the tetX gene (Blair *et al.*, 2015). The most often used chemical groups for drug inactivation through transfer to the drug are acetyl, phosphoryl and adenyl. The most often utilised method is acetylation, which has been shown to be effective against aminoglycosides, chloramphenicol, streptogramins and fluoroquinolones (Ramirez and Tolmasky, 2010).

Lastly, active drug efflux is a common resistance mechanism in a wide range of bacterial pathogens to regulate their internal environment by removing toxic substances, including antimicrobial agents, metabolites, and quorum sensing signal molecules faster than the time required to be diffused (Villagra *et al.*, 2012). Many pathogenic Gram-positive and Gram-negative bacteria, including *S. aureus*, *P. aeruginosa* and *A. baumanii* exhibit antibiotic resistance via mechanisms of the efflux pump (Vaou *et al.*, 2021). There are five main families of efflux pumps in bacteria categorized based on structure and energy source: the ATP-binding cassette (ABC) family, the multidrug and toxic compound extrusion (MATE) family, the small multidrug resistance (SMR)

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family, the major facilitator superfamily (MFS) and the resistance-nodulation-cell division (RND) family (Blanco *et al.*, 2016).

HEALTH AND ECONOMIC BURDEN OF AMR

AMR infections are one of the biggest obstacles for hospitals to provide safe and effective healthcare due to the fact that most AMR patients experience ineffective treatment, an increased risk of severe, recurrent infection and delayed recovery (Llor and Bjerrum, 2014). Currently, there is no specific treatment for AMR infection patients; the basic treatment for them includes having a medical professional provide treatment based on the patient's symptoms, such as combination therapy, which includes the use of two or more antibiotics (which works to increase the approach and access to the target site or enhance the efficacy of primary antibiotics), intravenous fluids to prevent dehydration, surgery to remove unnecessary dead tissue, blood transfusions for patients with severe blood loss or kidney dialysis (Gupta and Datta, 2019).

Continued increases in AMR infection rates combined with the equally rapid decline in the discovery and development of new antibiotics have led to fewer treatment options for patients and an associated increase in morbidity and mortality (Cassir *et al*., 2014). The result is that now we are dealing with infections that are more serious and require significant treatment, and longer courses of illness often require extended hospitalization. This has terrible effects on the healthcare expenses associated with these infections. AMR costs are predicted to range from $300 billion to more than $1 trillion annually by 2050 globally, according to various analyses (Dadgostar, 2019). In the United Kingdom, the extra expense for treating urinary tract infections brought on by resistant *E. coli* at a general practitioner's office was £3.62. Whereas in Thailand, hospitalization expenditures for patients with extended-spectrum beta-lactamases (ESBL) producing *E. coli* infections increased to a median of US$ 528 from US$ 108 (Ahmad, 2019). Next, studies on the expenses of treating MRSA infections alone show that the expenditures are over $18,000 per case in the U.S., close to €9,000 per case in Germany and over 100,000 Swiss francs per case on average in Switzerland (Reygaert, 2018). The world is predicted to face an economic burden due to this issue, where the annual global gross domestic product (GDP) might fall 1% by 2050, with underdeveloped nations seeing losses of 5-7%. According to recent Globe Bank research, antibiotic resistance would have a more significant impact on low-income and middle-income countries, increasing the prevalence of poverty (Dadgostar, 2019).

ANTIBACTERIAL OF MARINE ORIGIN

Researchers have paid more attention to the marine biosphere lately due to their wide range of valuable and distinctive chemicals with a variety of biological properties, including antibacterial, antitumor, anti-cancer, antithrombotic and anti-inflammatory capabilities (Hughes and Fenical, 2010). More than 30,000 natural macromolecules have been reported and identified from life in the ocean (protozoans, jellyfish, anemones, flatworms, roundworms, bryozoans, clams, squid, copepods, annelids, sea stars, sea cucumbers, corals, sponges and algae); however, only small numbers of these macromolecules are currently explored and validated (Nalini *et al*., 2018). Besides, the crude extracts of different parts of medicinal plants, including the root, flower, fruit, twigs and stems have been used as a traditional remedy in the treatment of various diseases since ancient times (Gonelimali *et al*., 2018). Approximately 28,187 different plant species are utilized by humans for medicinal purposes, and over 1340 plants have been identified as having specific antibacterial properties, with more than 30,000 antimicrobial chemicals have been extracted from plants (Vaou *et al*., 2021). Coastal plants were not an exception when it comes to the richness of bioactive compounds to protect themselves from cell and tissue damage because they had to survive in extreme environmental conditions like high salinity areas, direct sunlight exposure and exposure to an abundance of microorganisms (Rahmania *et al*., 2018). The antibacterial activity of common examples of six marine habitats against the human pathogenic microorganisms is summarized in Table 2.

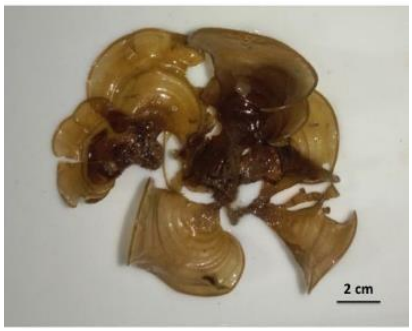

Figure 4: Morphology of *Padina boryana* (Adapted from Arguelles and Sapin, 2022, under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License).

Padina boryana Thivy (Brown algae)

Padina boryana Thivy (Figure 4) is a brown algal with upright fan-shaped blade physics that belongs to the class Phaeophyceae (Wichachucherd *et al*., 2014). These benthic microalgae are dominant in coastal areas of the Indo-Pacific Ocean, where they can be spotted clinging to rocks and dead coral in rocky intertidal zones or submerged reef-like habitats (Jayawardena *et al*., 2020). Even though the *Padina* species are typically consumed as food sources, such as sweet meat that resembles gelatin and seasoning in the form of dry flakes, a previous study has shown that this type of seaweed also exhibits a number of biological properties, including antioxidant,

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Table 2: Antibacterial activity of common examples of marine organisms and coastal plants against human pathogenic bacteria.

Marine organisms	Bacteria											References
	Escherichia coli	*Staphylococcus aureus*	*Bacillus subtilis*	*Bacillus cereus*	*Pseudomonas aeruginosa*	*Staptococcus* sp.	*Klebsiella pneumonia*	*Proteus vulgaris*	*Proteus mirabilis*	*Salmonella typhi*	MRSA	
Padina boryana Thivy	*	*			*		*			*	*	Sangeetha and Poonguzhali (2021); Arguelles and Sapin (2022)
Lautencia papillosa	*	*	*		*				*			Kavita *et al*. (2014); Omar *et al*. (2018)
Sepia sp.	*	*			*	*		*	*			Degiam and Abas (2010); Shanmugam *et al*. (2016); Fitrial and Khotimah (2017)
Sonneratia alba	*	*	*	*	*	*		*	*	*		Milon *et al*. (2012); Saad *et al*. (2012); Sahoo *et al*. (2012)
Bacopa monnieri	*	*					*		*			Fazrul *et al*. (2019); Mehta *et al*. (2022)
Vitex rotundifolia	*	*		*	*						*	Van *et al*. (2020); Azizul *et al*. (2021)

(*) denotes an antibacterial activity of the marine habitats against selected bacterial pathogens.

anti-diabetic, anti-inflammatory, hypoallergenic and antibacterial properties (Salosso *et al*., 2020).

The methanolic extract of *P. boryana* showed a significant antibacterial activity with the minimum inhibitory concentration (MICs) of 125 µg/mL for *Staphylococcus epidermidis* and *Micrococcus luteus*, and 250 µg/mL for *Staphylococcus aureus* and *Aeromonas hydrophila* (Arguelles and Sapin, 2022). In a different investigation, the inhibition zone of *Padina boryana* methanolic extract outperformed ethanol, acetone and aqueous extraction against a variety of bacterial pathogens with a range of 7-26 mm due to the high extractability of methanol to extract more phytochemical compounds compared with other solvents (Sangeetha and Poonguzhali, 2021).

Additionally, a study of *P. boryana* in ethanol and acetone extraction displays a favourable outcome against human pathogenic bacteria, with MICs ranging from 31-250 µg/mL. In the same study, total phenolic content was found to be 21.81 mg/g for ethanol extraction and 15.22 mg/g for acetone extraction, respectively. Total flavonoid content was found to be 13.81 mg/g for ethanol extraction and 12.09 mg/g for acetone extraction, respectively. Thus, the high phenolic and flavonoid content that was reported for these brown algae may be responsible for its antibacterial action (Sameeh *et al*., 2016).

Laurencia papillosa (Red algae)

Laurencia papillosa (Figure 5) is a red seaweed that belongs to the family Rhodomelaceae, with 146 taxonomically recognised species found worldwide, primarily in tropical and subtropical waters (Cabrita *et al*., 2010). Seaweeds are one of the most abundant and potential sources of bioactive primary and secondary metabolites with antimicrobial capabilities because they preferentially absorb Ca, Na, I, K, Mg and Br from the ocean and store them in their thalli (Samar *et al*., 2022). Genus *Laurencia* is acknowledged to produce the greatest variety and quality of secondary metabolites, including antibacterial, anti-inflammatory, antifeedant, antiproliferative, cytotoxic and insecticidal among the red algae (Shaaban *et al*., 2021).

A previous investigation of *L. papillosa* in dichloromethane:methanol (1:1) extract displayed a broad spectrum of antimicrobial action against the pathogens tested, primarily inhibiting the growth of *P. aeruginosa*, *S. aureus*, *C. tropicalis*, *E. coli* and *P. mirabilis* with inhibition zones ranging from 13 to 15 mm (Omar *et al*., 2018). Furthermore, the methanol extract of this red algae demonstrated positive results when tested against *E. coli* ATCC 8739, *P. aeruginosa* ATCC 9027, *S. aureus* ATCC 25923 and *B. subtilis* ATCC 6051, with zones of inhibition of 12.33 mm, 14.33 mm, 13.33 mm and 11.66 mm, respectively. The methanolic extract of *L. papillosa* was tested in the same investigation against patient-isolated bacteria to determine its MIC value and the results show IC_{50} ranging from 0.53 to 1.7 µg/mL and IC_{90} ranging from 1.58 to 3.16 µg/mL (Kavita *et al*., 2014).

In addition, the highest levels of cytotoxicity test of *L. papillosa* ethanol/chloroform extract after 72 h of treatment presents the reducing the percentage cell viability of Jurkat cancer cell line (acute lymphoblastic leukemia) at IC_{50} value of 57.77 µg/mL compared to IC_{50} value of 121.642 µg/mL of ethanol/water extract (Tannoury *et al*., 2017).

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Figure 5: Morphology of *Laurencia papillosa* (Adapted from Shaaban *et al.*, 2021 under the Creative Commons Attribution License).

Figure 6: Morphology of *Sepia* sp. (Adapted from Lawal-Are *et al*. (2018) under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License).

Figure 7: Morphology of *Sonneratia alba*. A) Full-grown form, B) Flower, C) Fruit, D) Leaf (Adapted from Osing *et al.*, 2019, under the Creative Commons Attribution License).

***Sepia* sp.**

Sepia sp. (Figure 6) is a cuttlefish from the phylum Mollusca that inhabits the littoral and benthic to pelagic regions of all oceans on Earth (Ramasamy *et al*., 2011). Among the 100 species of cuttlefish in the world, *Sepia* sp. is the most popular due to its abundance of bioactive compounds contained in their meat and the substantial mineral and protein content in their cuttlebone that benefits human health (Santi *et al*., 2019). Besides the cuttlefish meat consumed by the people, cuttlebone was also used by Indonesian communities as a casting material for carving gold and silver jewellery, as well as a source of minerals for bird and turtle feed (Henggu, 2021).

In 2017, a study conducted by Fitrial and Khotimah (2017) from Indonesia demonstrated that melanin from this cuttlefish ink has the potential to suppress 99.99% of *E. coli* bacteria at a concentration of 10 mg/mL. The antibacterial activity of *Sepia* sp. ink extract is also reported to have potential against *Aeromonas hydrophila* bacteria originating from Jepara Brackishwater Aquaculture Centre in Indonesia, with an MIC of 50 ppm and inhibition zones of 19 mm, 22 mm and 27 mm at concentrations of 250 ppm, 300 ppm and 350 ppm, respectively (Islamy, 2019). The most common types of diseases caused by these freshwater bacteria include gastroenteritis, necrotizing fasciitis and septicaemia in fishes, reptiles, birds, amphibians and even mammals (Semwal *et al.*, 2023). Another study found that, at a dosage of 100 mg/mL, the chitosan of *Sepia* sp. obtained by extracting chitin from the cuttlebone had a robust antibacterial activity with diameters of inhibition zones >16 mm against *Streptococcus* sp., *Vibrio cholera* and *P. aeruginosa*. Meanwhile, the lowest MIC value for this experiment indicated that the chitosan extract of this cuttlefish can inhibit *P. vulgaris* bacteria at a concentration of 50 µg/mL, the same as the MIC value for phosphorylated chitosan against *S. aureus* (Shanmugam *et al*., 2016). According to a prior study, *Sepia* sp. exhibits antibacterial activity against human pathogenic bacteria isolated from the Al-Hussain Teaching Hospital in Iraq with the highest zone of inhibition and a MICs value of 23.6 mm and 10 mg/mL, respectively, against *P. aeruginosa* (Degiam and Abas, 2010).

Moreover, previous cell viability tests of nanohydroxyapatite from the synthesis of lamella bone from *Sepia* sp. indicated that this extract was not toxic, with a cell viability value greater than 80% (Aminatun *et al.*, 2019). Next, *in vitro* assay using sulfated chitosan from this cuttlefish showed that it had avian antiviral properties against the Newcastle disease virus by interacting with the virus's surface receptors and preventing the hemagglutination of avian red blood cells (Karthik *et al*., 2016).

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Malays. J. Microbiol. Vol 20(2) 2024, pp. 244-262
DOI: http://dx.doi.org/10.21161/mjm.230485

Sonneratia alba

Sonneratia alba (Figure 7) also known as “perepat” or mangrove apple by the Malaysian natives, is a mangrove plant that can be found distributed from East Africa and extending to Southeast Asia, northern Australia, Borneo, and the Pacific Islands (Saad *et al.*, 2012). This mangrove is 5-15 meters long and members of the Sonneratiacea family, which is well-known for its high antimicrobial potential due to its abundance of tannin sources (Milon *et al.*, 2012). Perepat has been extensively used in folklore medicine and many studies have revealed its ability to combat diseases that affect humans, animals and plants (Harizon *et al*., 2015).

In earlier work, ethanol extraction of this mangrove leaf demonstrated the highest inhibition zone of 17 mm, 16.7 mm, 15 mm and 10.7 mm against human pathogenic bacteria, including MDR strain, which were *Salmonella typhi*, *Proteus mirabilis*, *Proteus vulgaris* and *Streptococcus* sp., respectively (Sahoo *et al.*, 2012). In a different study, perepat bark in carbon tetrachloride extract demonstrated mild antifungal activity with a 12 mm of inhibition zone against *Shigella dysenteriae* and *Sarcina lutea*, as well as moderate inhibitory activity against a variety of bacteria, including *B. cereus* (10 mm), *B. subtilis* (11 mm) and *P. aeruginosa* (10 mm) (Milon *et al.*, 2012). Furthermore, the antibacterial efficacy of *S. alba* was assessed using the disc diffusion technique, MIC and MBC values in 2 different solvent extractions demonstrated encouraging results against both grams of bacteria, which were *S. aureus*, *B. cereus* and *E. coli* (Saad *et al.*, 2012).

Moreover, the leaf crude extract of *S. alba* in methanolic condition indicated mild toxicity when analyzed using brime shrimp lethality test and the fraction recovered from liquid separation showed a totally not toxic to the brime shrimp larvae (Morada *et al.*, 2016). Meanwhile, the ethyl acetate extract of this apple mangrove leaves was cytotoxic against Hela cell viability with LC_{50} value of 478.63 µg/mL (Suryaningrum, 2021).

Bacopa monnieri

Bacopa monnieri (Figure 8) also synonym as “water hyssop” in English, is a warm wetland coastal plant that is native to Australia and India (Aguiar and Borowski, 2013). This indigenous plant belongs to the family Scrophulariaceae and the entire plant is usually used medicinally by the Indian native people for the treatment of anxiety and epilepsy and to improve human cognitive processes (Kumar *et al.*, 2016). Many studies have claimed that this coastal plant possesses various biological properties, including antioxidant, antimicrobial, epilepsy, skin disorders, antipyretic, analgesic, stress-related disorders and digestive disorders (Jeyasri *et al.*, 2020).

Antibacterial tests of *B. monnieri* leaf extract against 18 different pathogens (including Gram-positive and Gram-negative bacteria) in different solvents demonstrated that ethyl acetate (EtOAc) and methanol

Figure 8: Morphology of *Bacopa monnieri* (Adapted from Ghosh *et al.*, 2021 under the Creative Commons Attribution-Non-commercial 4.0 License).

(MeOH) extracts have the most promising antibacterial properties against most bacteria species possible (15 of each). At a 5 mg/mL concentration, both *B. monnieri* leaf in EtOAc and MeOH extraction have shown more than 14 mm of zone inhibition for most of the bacteria tested (Khan *et al.*, 2010). In a separate experiment, this coastal plant's diethyl acetate was found to have a strong antibacterial effect against *S. aureus* ATCC 25923 (18.36 mm) and an extract of EtOAc demonstrated effects on *E. coli* ATCC 25922 (13.3 mm) during an agar disc diffusion test among the various extracts at a concentration of 300 g/mL (Fazrul *et al.*, 2019). The study conducted in 2022 revealed that the methanolic extract of *B. monnieri* has higher antibacterial properties compared to the ethanolic extract against human pathogenic bacteria that can cause urinary tract infections (*K. pneumonia* and *P. mirabilis*), with zone inhibition ranging from 17 to 25 mm by disc diffusion technique because methanol has a high extractability compared with ethanol (Saad *et al.*, 2012).

Besides, *B. monnieri* is also reported to have anti-cancer properties against breast cancer and colon cancer cell lines. This plant works by decreasing the transcriptional expression of the membrane transport system aquaporin (AQP1) due to the presence of two bioactive compounds, bacopaside I and bacopaside II (Fatima *et al.*, 2022). Furthermore, the *B. monnieri* toxicity test revealed that the high single oral dose (5,000 mg/kg) of this plant extract did not result in Sprague-Dawley rats mortality and the rats displayed normal behavioral patterns (Sireeratawong *et al.*, 2016).

Vitex rotundifolia

Vitex rotundifolia (Figure 9) is a deciduous plant that belongs to the family Lamiaceae mainly found in the coastal areas and commonly known as “Legundi or Lemuni” by Malaysians who are native to the area, or “three-leaf chaste tree” in English (Azizul *et al*., 2021). This plant grows on sand coasts as a coastal defense system for the protection and prevention of erosion and processes of accretion brought by winds, waves and other natural events (Yeh and Kirschner, 2019). Legundi is a Chinese herbal medicine that has traditionally been

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Malays. J. Microbiol. Vol 20(2) 2024, pp. 244-262
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Figure 9: Morphology of *Vitex rotundifolia* (Adapted from Yeh and Kirschner, 2019 Creative Commons Attribution License).

used to treat various diseases, including migraine, inflammation, liver disease, gastrointestinal infections, allergic diseases and asthma (Mu *et al.*, 2019).

Previous investigations have discovered that the essential oils of *V. rotundifolia* was effective against *S. aureus*, *B. cereus*, *P. aeruginosa*, *S. enteritidis*, *S. typhimurium*, *E. coli* with the diameter of the growth inhibition zone in the range of 8.3-27.3 mm, respectively (Van *et al*., 2020). Next, three isolated chemicals from the subterranean part of this coastal plant (vitrofolal C, vitrofolal D and detetrahydroconidendrin) demonstrated the potential against human pathogenic bacteria, which was MRSA with MIC values of less than 64 µg/mL against 8 out of 18 strains (Azizul *et al*., 2021).

MARINE-DERIVED COMPOUNDS

Biologically active substances obtained from natural resources are currently quite popular due to their medical value. Marine species develop complex secondary metabolites, including antimicrobial substances, to enable them to thrive and flourish in intricate communities while interacting closely with one another in ecological pressure conditions, competition for space, predation, and tide changes (Pérez *et al.*, 2016). The sea environment, especially marine organisms and coastal plants is renowned for being a plentiful source of chemical compounds with a variety of advantageous health benefits (Karthikeyan *et al.*, 2022). Table 3 reveals few generic and specific bioactive compounds that contribute to the presence of antibacterial activity in marine organisms and coastal plants.

POSSIBLE MECHANISMS OF ACTION OF NATURAL BIOACTIVE ANTIBACTERIAL AGENTS

The mechanisms of action of these natural bioactive compounds are distinct and consist of disruption at the cellular, structural and molecular levels, including (1) inhibition of nucleic acid synthesis; (2) inhibition of quorum sensing function; (3) modulation of efflux pumps; (4) increase of membrane permeability; (5) inhibition of biofilm formation; (6) inhibition of cell wall synthesis; (7) inhibition of bacteria motility, which are covered individually in Figure 10.

Firstly, the natural bioactive compounds will indirectly interfere with DNA synthesis by targeting the DNA gyrase (a DNA replication-related enzyme) subunit of

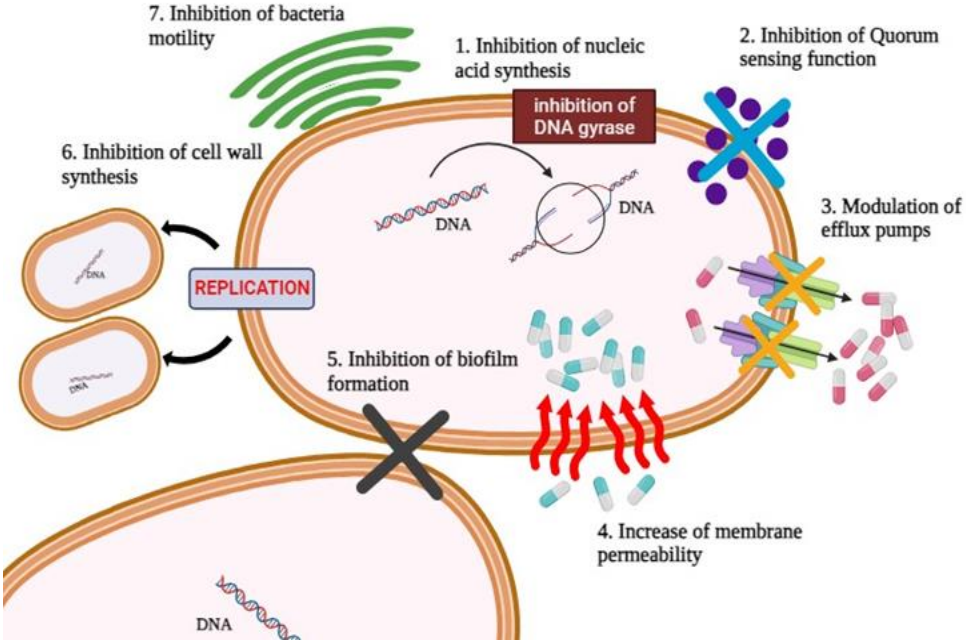

Figure 10: Schematic representation of natural bioactive antibacterial agents (Created using Biorender.com).

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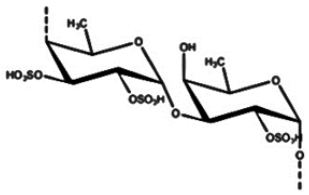
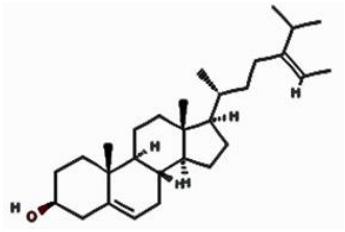
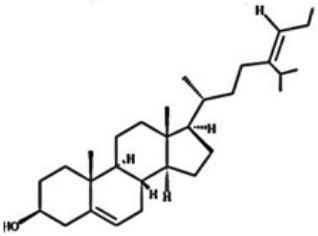
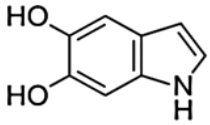
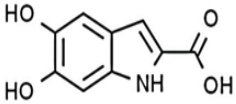
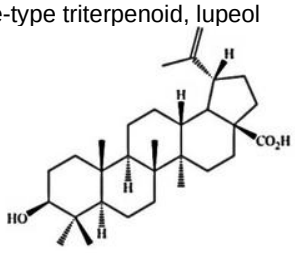
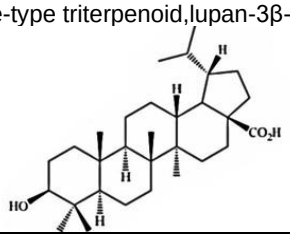
Table 3: Common examples of bioactive compounds of marine organisms and coastal plants.

Organisms	Bioactive compound	Antibacterial agent	References
Padina boryana Thivy	• Flavanoids • Carbohydrates • Phenolics • Tannins • Proteins • Steroids	Fucoidan  Fucosterol 	Ahmed *et al.* (2014); Meinita *et al*. (2021); Rushdi *et al*. (2021); Sonbol *et al.* (2021)
Laurencia papillosa	• Terpenoids • Amino acids • Phenolics • Flavanoids • Cholestrol • Steroids • Phlorotannins • Fatty acids	24-propylidene cholest-5-en-3β-ol 	Kavita *et al.* (2014); Shaaban *et al.* (2021)
Sepia sp.	• Peptide • Depsipeptide • Sterols • Sesquiterpene • Terpenes • Polypropionate • Nitrogen compounds • Fatty acids • Alkaloids	5, 6-dihidroxyindole  5, 6-dihidroxyindole-2-carboxylic acid 	Degiam and Abas (2010); Henggu (2021); Ramasamy *et al*. (2011)
Sonneratia alba	• Alkaloids • Phenolics • Steroids	3β-hydroxy-lup-9(11),12-diene, 28-oic acid 16upine-type triterpenoid, lupeol  16upine-type triterpenoid,lupan-3β-ol 	Harizon *et al.* (2015); Latief *et al.* (2019); Rahmania *et al.* (2018)

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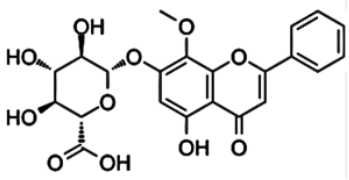
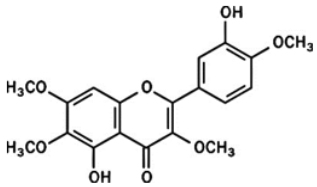
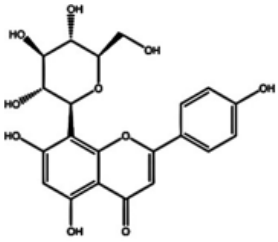
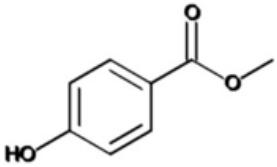
Malays. J. Microbiol. Vol 20(2) 2024, pp. 244-262
DOI: http://dx.doi.org/10.21161/mjm.230485

(Continued)

Organisms	Bioactive compound	Antibacterial agent	References
Bacopa monnieri	• Alkaloids • Nicotine • Herpestine • Saponin • Monierin • Steroids Triterpene • Bacosine • Cucurbitasin • Phenolics	Oroxidin 	Kumar *et al.* (2016); Fatima *et al.* (2022); Mehta *et al*. (2022)
Vitex rotundifolia	• Flavanoids • Phenolic acid • Terpenes • Alkaloids • Saponin • Iridoids • Phenylpropanoids • Terpenoids	Casticin  Vitexin  4-hydroxybenzoic acid methyl ester 	Van *et al.* (2020); Azizul *et al.* (2021); Yan *et al.* (2023)

topoisomerase type II (Santos and Lamers, 2020). The inhibition of DNA gyrase will produce a permanent double-stranded break in the bacteria nucleic acid that will prevent the growth of pathogenic germs (Lobiuc *et al.*, 2023). Next, inhibition of the quorum- sensing function via interfering with the ability of the autoinducer (Ais) molecules that are vital in the process of cell-cell communication within eukaryotic organisms to attach to their receptor (Yada *et al.*, 2015). Anti- quorum sensing action would reduce the pathogenicity and virulence of infectious bacteria by preventing plaque biofilm formation and targeting the efflux pump gene expression (Naga *et al.*, 2023). Moreover, modulation of efflux pumps looks to be a promising strategy to address the issue of drug resistance (Bhardwaj and Mohanty, 2012). The natural bioactive compounds can perform various mechanisms of action in an attempt to inhibit the efflux pumps and allow the compounds to successfully accumulate inside the cells, including by interfering with the genetic regulation of bacteria to down-regulate pump gene expression, preventing the assembly of functional efflux pumps, altering the structure of bioactive compounds that are no longer recognized as substrates and bringing the energy mechanism that powers the efflux pumps to a halt (Sharma *et al.*, 2019).

Furthermore, natural phytochemicals may increase the bacteria's membrane permeability by disrupting their outer membrane. This mechanism can increase the diffusion of antimicrobial substances across the lipopolysaccharide layers of bacteria, especially the large scaffolds, which leads to more substrate binding to the target site (Muheim *et al.*, 2017). In addition, active ingredients from natural resources proved to have significant anti-biofilm formation mechanisms by preventing the colonisation of bacteria phenomenon (Mishra *et al.*, 2020). For example, by impairing the expression of quorum sensing-related genes in the accessory gene regulator (Agr) system in *S. aureus* and downregulating the transcription of the quorum sensing relative gene luxR in *Cronobacter sakazakii* (Liu *et al.*, 2021). Besides, the inhibition of cell wall synthesis is another frequent mechanism of natural bioactive compounds by promoting the inactivation or inhibition of intracellular and extracellular enzyme synthesis to

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Figure 11: Various applications of natural antimicrobials in various sectors (Created using Canva.com).

reduces the cross-linking of peptidoglycan formation during the bacterial replication process (Sarkar *et al.*, 2017). Destruction of bacteria's membrane integrity will result in osmotic imbalance and intracellular component leakage, which can ultimately lead to rapid bacterial mortality (Khameneh *et al.*, 2019). Last but not least, the majority of bacterial cells are motile by swimming, swarming, sliding, twitching or gliding as a means of self-propulsion to escape from harmful environments to develop colonization and biofilm formation (Palma *et al.*, 2022). The natural phytochemical acts by blocking the auto- inducer of the quorum sensing network and also suppressing the expression of a variety of genes involved in biofilm formation indirectly by reducing the bacteria movement (de la Fuente-Núñez *et al.*, 2012).

FUTURE PERSPECTIVE OF NATURAL MARINE ANTIMICROBIAL

The need to learn more about marine-derived bioactive chemicals' intriguing biocatalysts for brand- new and effective potential antimicrobials have increased as a result of recent studies on their powerful therapeutic potential in a number of ailments (Karthikeyan *et al.*, 2022). Besides, these natural bioactive compounds also provide a low risk of side effects and offer high bioavailability to reach the target sites compared to synthetic drugs. Since the occurrence of the epidemiological transition, infectious diseases and pandemics that had previously decimated the population have made people more aware of improved sanitation and public health, in addition to fully relying on vaccines and antibiotics (Gajdács *et al.*, 2021). These days, consumers concern about the use of naturally-occurring antimicrobials from natural resources continues to grow daily, triggered mainly by the increasing awareness about the antibiotic resistance crisis and the risk associated with the use of synthetically manufactured products (Batiha *et al.*, 2021).

Antimicrobial textiles (AT) are one of the latest innovations that help in the eradication or inhibition of microorganisms' growth, including bacteria, fungi and viruses. AT can be defined as a functionally active textile with the ability to either kill or stop the growth of germs. The applications of AT include various sectors such as household, health care, food industries, apparel, commercial and many more as in Figure 11 (Gulati *et al.*, 2022). Next, natural antimicrobials for food preservation are also a popular consumer demand as a replacement for synthetic addictive to inhibit the growth of microorganisms that trigger food deterioration. Bio-preservatives derived from natural resources not only lengthen the useful life of food products but also improve their safety, quality and nutritional values while posing no health risks to consumers (Quinto *et al*., 2019). In addition, the cosmetic industry recently came up with the idea to include natural ingredients with antimicrobial properties in their products to ensure their durability, safety, quality, affordability, improved health and environmental friendliness. Cosmetic products with natural antimicrobial compounds can help prevent the contamination of microorganisms during product manufacturing and also during customer application that may produce serious health effects, such as dermatitis, folliculitis, eye infections, corneal ulcers or phlebitis (Rybczyńska-Tkaczyk *et al*., 2023). However, there are many advantages and challenges in utilizing these natural bioactive agents for the development of new antibacterial medicine, as summarized in Figure 12.

CONSERVATION OF NATURAL MEDICINAL RESOURCES

According to the WHO, the need for clinical development has increased due to the many discoveries of successful clinical trials of drugs derived from natural resources. In 2007, the market for pharmaceuticals made from plants was worth US$ 100 billion, and it is predicted that the number will reach US$ 5 trillion by the year 2050 (Greenwell and Rahman, 2015). Hence, a constant demand for alternative drugs from natural extracts for health products and research purposes has put high pressure on them and threatened their extinction if overexploitation continues, especially for organisms from wild populations (Parveen *et al*., 2013). Therefore, there are few conservation strategies to prevent the loss of natural resources and biodiversity such as harvesting only specific parts of the organisms that are used in treatments (Greenwell and Rahman, 2015). This proper harvesting technique might help to prevent chopping the entire plant, fulfil the requirement of sustainable harvesting, and at the same time, meet the demand for herbal medications all at once (Papageorgiou *et al*., 2020). Next, the application of biotechnical approaches such as the cryopreservation method (to preserve biological material in liquid nitrogen), tissue culture (to propagate plants in sterile conditions and quickly produce mature plant clones of rare species)

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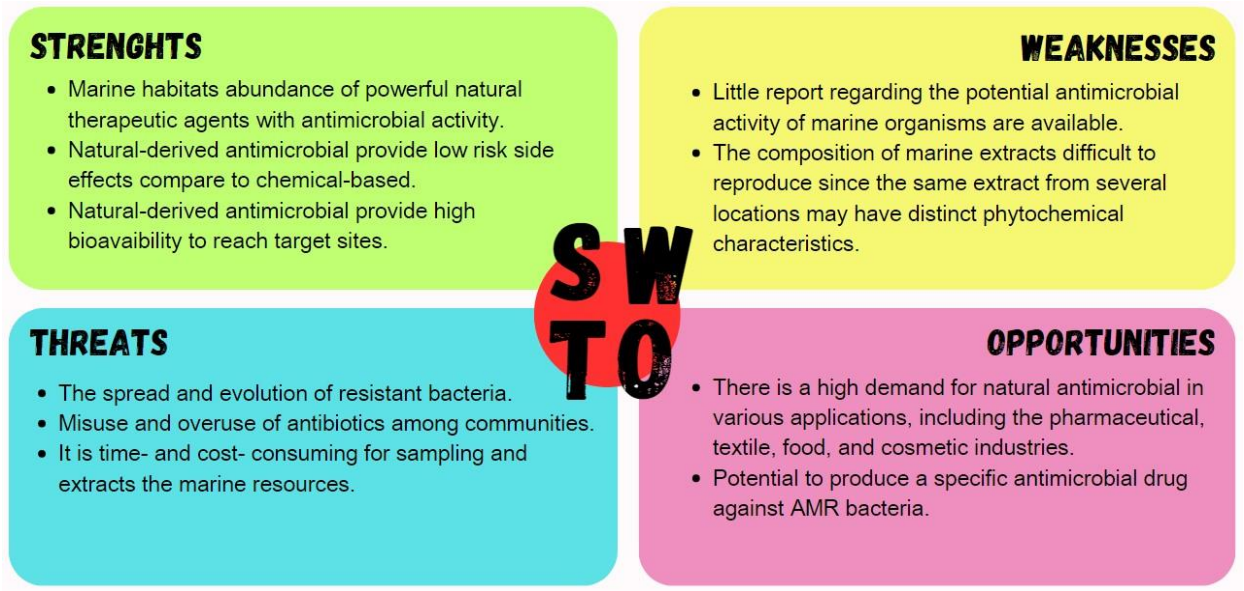

Figure 12: Summarized the various opportunities and challenges in the application of natural antimicrobials (Created using Canva.com).

and also germplasm conservation (by storing viable seeds) are effective practices to stop the loss of plant biodiversity for the use of all plant parts, including leaf, stem, root and bark (Parveen *et al*., 2013). Furthermore, other methods of conservation include genetic engineering approaches such as breeding improvement using molecular marker-based technology and synthetic bioactive compounds to mimic the functions of natural bioactive compounds (Chen *et al*., 2016). Besides, most plant species across the plant kingdom, especially mangrove and coastal plants harbour endophytic bacteria (EB). Endophytic microorganisms live within the plants in a symbiotic relationship and secrete biologically active compounds to protect host plants under adverse conditions (Christina *et al*., 2013). It is strongly believed that plant species with antimicrobial properties are likely to have endophytes that can produce novel antibiotics. Thus, studies on these endophytes from these plants may also have a huge potential for novel antibiotics. Last but not least, expanding research into potential local natural products can help in protecting our own natural resources from the invasion of the foreign pharmaceutical sector on our biodiversity (Neergheen-Bhujun *et al*., 2017).

CONCLUSION

All instances of marine habitats reviewed here represent significant sources of potential antibacterial medicine against clinically relevant human pathogenic bacteria and are able to contribute to managing infectious diseases in people. All the studied marine creatures and coastal plants have substantial biological activities, as shown by the abundance of active compounds from earlier identification and isolation investigations. Further investigations are needed to explore more comprehensive marine resource bioactive compounds because only a small percentage of their antimicrobial properties have been investigated, highlighting their possible contribution to humanity. It is expected that this review will be helpful in the finding of novel antibacterial agents that are more efficient and straightforward methods against infection caused by MDR bacteria.

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