



New Perspectives of Antimicrobials from Marine Environment in the Treatment of Non-Healing Foot Wounds of Diabetics

BHAVNA MADHUSHI RAKHAL¹, ABDULWAHED FAHAD ALREFAEI²,
KUNHIRAMAN CHANDANADUKKAM RAJESHKUMAR³, NADEEM NAZURALLY⁴,
RAJESH JEEWON^{1,2*}

¹Faculty of Medicine and Health Sciences, Department of Health sciences,
University of Mauritius, Reduit, Mauritius.

²College of Sciences, Department of Zoology, King Saud University, Riyadh, Saudi Arabia.

³National Fungal Culture Collection of India (NFCCI), Department of Biodiversity and Palaeobiology
(Fungi) Group, Agharkar Research Institute, Pune, India.

⁴Faculty of Agriculture, Department of Agricultural and Food Science,
University of Mauritius, Reduit, Mauritius.

Abstract

Diabetes mellitus is a persisting disorder with increasing prevalence all over the world with 280,442 cases in Mauritius. Type 2 diabetes mellitus is the outcome from the synergy of genetic and environmental factors which trigger insulin resistance, followed by severe health complications including non-healing foot wounds, gangrene, amputation, among others. Microbes either have a symbiotic balance with mankind or exist as pathogens causing internal harm to the body. *Proteus* species, *Enterococcus* species, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella* species, *Bacillus* species, *Acinetobacter* species, *Serratia marcescens*, *Enterobacter* species, *Morganella morganii*, *Citobacter koseri* and *Pseudomonas aeruginosa* have been isolated from non-healing wounds. While ensuring the wellbeing of the population, pathogen adversaries previously led to the discovery and presently the overuse of antibiotics due to their pharmaceutical properties. Scientists have been motivated to search for new bioactive compounds with novel mode of action since lately, commonly used synthetic antibiotics are no longer effective against microorganisms which have led to antimicrobial resistance. Despite several strategies, drug evolution continues to fail which have triggered the thought that the streamline of drugs is overseen. Indigenous and traditional



Article History

Received: 27 January
2025

Accepted: 22 April 2025

Keywords

Antimicrobial Resistance;
Diabetes Mellitus;
Marine Environment;
Non-Healing Foot Wounds;
Pharmaceutical Properties.

CONTACT Rajesh Jeewon ✉ r.jeewon@uom.ac.mu 📍 Faculty of Medicine and Health Sciences, Department of Health sciences,
University of Mauritius, Reduit, Mauritius.



© 2025 The Author(s). Published by Enviro Research Publishers.

This is an  Open Access article licensed under a Creative Commons license: Attribution 4.0 International (CC-BY).

Doi: <https://dx.doi.org/10.12944/CRNFSJ.13.2.5>

medicine, composed of considerable natural products and plant derivatives are widely used throughout the world as they have been validated to confer therapeutic benefits in clinical trials. Similarly, oceans nurture a wide variety of organisms which are biologically and chemically diverse, with several metabolic activities as they possess phenolic compounds, sulphated polysaccharides, organic acids and phytochemicals. Alongside, coastal greens have not only demonstrated effective de-novo synthesis in hypoglycaemic activities but also represent a potential for antimicrobials. Due to this assortment and molecular complexity of marine organisms, structure-tissue exposure-activity relationship (STAR) is suggested in terms of novel drug design instead of currently used structure-activity-relationship (SAR) for drug optimisation in the future. Also, the synergy of the biomolecules of aquatic creatures with commonly used drugs could be considered to treat actual treatment failures of non healing wounds while alleviating the burden of antimicrobial resistance. Though oceanic organisms have enormous health prospective in terms of a wide array of drug discovery, there is a gap remaining in the academic research of their extracts. This review has as objective to bring forth an extensive knowledge on the marine environment community and their challenges to the synthetic organic chemist by assembling research work and review articles (from 2015 to 2024). It also has as intention to discuss antimicrobial resistance of common antibiotics and the benefit of antimicrobials from selected marine organisms in the fight against non-healing foot wounds.

Abbreviations

		MIC	Minimum Inhibitory Concentration
		<i>M. morganii</i>	<i>Morganella morganii</i>
ACE	angiotensin-converting enzymes	MDR	multidrug resistance
A. marina	Avicennia marina	MRSA	Methicillin resistant
AMPK-6-2	adenosine monophosphate-dependent kinase		Staphylococcus aureus
AMR	Antimicrobial resistance	NP	natural products
<i>B. cereus</i>	<i>Bacillus cereus</i>	NHFW	non healing foot wounds
<i>B. subtilis</i>	<i>Bacillus subtilis</i>	<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
<i>B. rasmose</i>	<i>Barringtonia Racemose</i>	PABA	p-amino-benzoic acid
<i>B. sexangular</i>	<i>Bruguiera sexangular</i>	PBDE	Polybrominated diphenyl ethers
CRISPER	Clustered regularly interspaced short palindromic repeats	PPAR γ	Peroxisome proliferator activated receptor gamma
DFU	Diabetic foot ulcer	PTP1B	Protein tyrosine phosphatase 1B
DM	diabetes mellitus	<i>R. mucronate</i>	<i>Rhizophora mucronata</i>
DNA	deoxyribonucleic acid	ROS	Reactive oxygen species
<i>E. coli</i>	<i>Escherichia coli</i>	SAR	Structure activity relationship
<i>E. faecalis</i>	<i>Enterococcus faecalis</i>	<i>S. aureus</i>	<i>Staphylococcus aureus</i>
<i>E. agallocha</i>	<i>Exoecaria agallocha</i>	Spp.	Species
GLASS	Global Antimicrobial Resistance Surveillance System	<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
HPN	benzene-1-2,diol	STAR	Structure tissue activity relationship
IDFA	International Diabetes Federation Atlas	WHO	World Health Organization
<i>K. pneumoniae</i>	<i>Klebsiella pneumoniae</i>	<i>X. granatum</i>	<i>Xylocarpus granatum</i>

Introduction

Pathophysiology of Diabetes mellitus

The escalating prevalence of diabetes mellitus (DM) remains a challenge in the medical field. The World Health Organization (WHO) report on the ascending resistance in microorganisms and the Global Antimicrobial Resistance Surveillance System (GLASS) report predict a critical future for humankind.¹ Similarly, the International Diabetes Federation Atlas (IDFA) previously estimated a population of greater than 425 million with DM including 4 million deaths annually² while the report of 2022 and 2023 highlight further complications of DM leading non healing foot wounds among others. The American Diabetes Association (ADA) in 2024 estimated 643 people to have diabetes by 2030 if left untreated.³ DM may not only have devastating effects but represent consequent economic burden universally.⁴ Several microorganisms namely, *Acinetobacter* species, *Bacillus* species (*Bacillus* sp.), *Candida albicans*, *Enterococcus* sp., *Escherichia coli* (*E. coli*), *Klebsiella* sp., *Morganella morganii* (*M. Morganii*) *Pseudomonas aeruginosa* (*P. aeruginosa*), *Proteus* sp., *Staphylococcus aureus* (*S. aureus*), among others have been detected as invasive microbiota of foot ulcers.⁵⁻⁸ It should be noted that microvascular complications of DM lead to retinopathy⁹ and neuropathy diseases while macrovascular complications lead to coronary diseases and cerebrovascular diseases.¹⁰ The limited volume of epidermal growth factors in non-healing foot wounds (NHFV) contribute to chronic foot ulcers (25%), which blend in treatment failures, lower limb amputation notably 85% of all amputations, poor quality of life and shortly premature death.⁵

Treatment; Currently used Antiseptics

The disordered physiological process that causes DM is yet to be considered as formerly distinguished medicines like insulin-sensitizing biguanide, also known as metformin and thiazolidinedione (rosiglitazone and pioglitazone) aim at hindering single molecules, such as adenosine monophosphate-dependent kinase (AMPK)-6-2 enzyme and peroxisome proliferator activated receptor gamma (PPAR γ) 96-3¹¹ also known as the reverse insulin receptor. However, due to health complications such as lactic acidosis resulting from derivatives of the above, phenformin and buformin are no longer used in various countries.¹² Topical antiseptics

are praiseworthy as they act on bacteria, fungi, viruses, with minimal side effects unlike several drugs that have restricted targets.¹³ They also allow movement of keratinocyte into wound site to start the re-epithelisation, and eventually wound healing, Timolol has been currently the choice of topical in the treatment of foot ulcers.¹⁴ Sponges, hydrogels, films, hydrocolloids and hydrofiber mats have been simultaneously used as innovative dressings due to their ability to provide safe and suitable environment while distributing active ingredients to wound site to ease the healing process.¹⁴ Other commonly used antiseptic compounds include alcohol, iodine, biguanides, halophenols, bisphenols, silver, gold and zinc nanoparticles¹⁵ hydrogen peroxide. However, owing to the distinctive biological and the complex system of tissue repair, new effective and targeted cures are constantly required.¹⁴ A more recent technique to better understand the microbiota of organisms colonising NHFW is the 16s-ribosomal DNA sequencing, which helps limit inflammatory process thus aid in the healing process.¹⁶ Hence, this review paper highlights the potential therapeutics for chronic wounds infections in terms of antimicrobials from the marine environment.

Traditional Herbs and Freshwater Algae as Antimicrobials

In addition to antimicrobial properties, plants contain anti-inflammatory substances due to their phytochemical constituents that lighten human pain by reducing swelling¹⁷ while traditional herbs are often recognized to mimic drugs, known as phytopharmaceuticals¹⁸ which eventually help in recovery of wounds. Moreover, there are about 2.7- 4 million species of endophytes residing in plants¹⁹ which rather than harming their internal tissues, develops similar bioactive substances as the host plants and endophyte richness is especially observed among tropical plants. The discovery of novel antibiotics in terms of fungal endophytes is a promising substitute to overcome drug resistance by pathogens ever since Alexander Fleming was credited with the discovery of penicillin in 1928 and may be supported by their antibacterial, antiparasitic and antifungal properties and their accessibility.²⁰ *Ficus religiosa*, from the family of Moraceae, has been reported to be effective against DM as its constituents have similar effect as enzymes α -glucosidase and α -amylase, that degrade polysaccharide into glucose.²¹ Phytochemicals in

green algae exhibit antimicrobial properties.²² For instance, chlorellin derived from freshwater green microalgae *Chlorella*, inhibits human pathogens isolated from NHFW.²² Similarly, *Dunaliella salina* and freshwater *Pseudokirchneriella subcapitata* microalgae have bactericidal properties against *S. aureus*, *P. aeruginosa*, *E. coli*, and *Klebsiella* sp.²³ which are the most common pathogens isolated from NHFW.

Aspects of Common Antibiotics and Antimicrobial Resistance

Men and microbes have been forever co-existing and co-evolved. Antibiotics have been widely used for healing purposes¹ and for increasing human life expectancy as infections with resistant organisms lead to several diseases and death in men. Antibiotics should have selective toxicity, either be bactericidal, that is they completely kill bacteria or bacteriostatic, that is they inhibit the growth of bacteria.²⁴ Satisfactory antimicrobials should also be able to hinder the growth of organisms regardless of the affected area with minimal side effects on the host; should reach the target at effective concentration; have tolerance residue and should have a defined Minimum Inhibitory Concentration (MIC). The spectrum activity, economic aspect and availability are key elements that should be considered on selection of antibiotics.²⁵ The overuse, inappropriate prescribing, incorrect dosages and duration of treatment has progressively led to antimicrobial resistance (AMR);²⁶ one of the major drawbacks in the treatment of long-term complications of DM. AMR arises when bacterial pathogens evolve to mutate; that is acquire new genes in a way to decrease or annihilate the potency of antibiotics.²⁷ In this way, the antibiotics is less effective, which permit bacteria to thrive.²⁸ The comprehension of the biochemical and genetic basis of AMR is of paramount importance as antimicrobial selection may differ according to the two resistance mechanism.²⁵ In the intrinsic resistance mechanism, there is inhibition of cell wall synthesis and permeability through it as well as inhibition of protein synthesis while in the acquired resistance mechanism, the function of nucleic acids is hampered by mutations.²⁵

Resistance According to Classes Of Antibiotics And Multidrug Resistance

Multidrug resistance (MDR) is the resistance of microorganisms to the administered antimicrobials

despite previous sensitivity to them. MDR organisms have emerged from both the hospital environment and community settings²⁸ by bacterial adaptation. A report published by WHO stated that infections are generated by resistant pathogens such as *E. coli* against broad spectrum antibiotics namely cephalosporin and fluoroquinolones, *Klebsiella pneumoniae* (*K. pneumoniae*) against cephalosporin and carbapenems, *S. aureus* against narrow spectrum methicillin and *Streptococcus pneumoniae* (*S. pneumoniae*) against penicillin.²⁵ Organisms secrete several enzymes including beta-lactamase that often break down drugs resulting in beta lactamase antibiotic resistance.²⁹ Tetracyclines group of antibiotics, widely used in several treatment prevent the attachment of aminoacyl-tRNA to the ribosomal acceptor and operate by inhibiting protein synthesis. The three main modes of action of resistance to tetracyclines are: 1) efflux of the antibiotics; 2) ribosome protection and 3) modification of the binding sites.³⁰ Aminoglycosides, another group of antibiotics exert their activity by irreversible binding of ribosomes and inhibiting protein synthesis.³⁰ The mechanisms of aminoglycoside resistance include: 1) Decreased permeability or reduced uptake by cell membrane modification; 2) alterations at ribosomal binding sites through mutations and 3) production of aminoglycosides modifying enzymes.^{30,31} Fourth group of antibiotics, Fluoroquinolones antimicrobial activity is due to interference with deoxyribonucleic acid (DNA) replication and transcription in bacteria through inhibition of certain bacterial topoisomerase enzymes.³⁰ The two mechanisms of resistance to fluoroquinolones include 1) modification in drug target enzymes; 2) changes that decrease penetration of the drug to the site.³⁰ Macrolides, a fifth group of antibiotics meddles with amino acid during protein synthesis. The mechanisms of resistance to macrolides are 1) post-transcriptional modification; 2) the presence of efflux proteins and 3) enzymatic inactivation.³² Glycopeptides, the sixth group, achieve bacteriostatic effect by interfering with D-alanyl-D-alanine side chains. Resistance mechanism to glycopeptide is by the production of innovative genes which promote regeneration of the peptidoglycan side chain.³³ Sulfonamides, the seventh group of antibiotics proceed by competitively blocking the p-amino-benzoic acid (PABA) which is a chief compound in bacterial folic acid synthesis. Also, constantly evolving genes render organisms

resistant to Sulfonamides, as the latter fail to bind and attack the new structure of microbials.³⁴ Eighth, the oxazolidones interfere with the 80S initiation complex at the P site and prevent protein biosynthesis. Resistance to oxazolidone drugs is generally due to mutations in the six domains V of 23S, nucleotide long component ribosomal ribonucleic acid (rRNA) of the organisms. Fortunately, owing to the presence of multiple copies of redundant rRNA genes in bacterial genomes, resistance to oxazolidones hardly occurs and develops steadily.²⁵ The search for new antibiotics remains vital for a better management of public health.³⁵

Benefits of the Marine Environment

The marine environment is associated with wide range of thermal pressure, has vast surfaces which receive sunlight as well as aphotic zones, with a wide range of nutrients and low oxygen zones which are about 300m to 700m deep down.³⁶ The ocean therefore comprises of several living organisms including plants and algae, among others, that produce extensive secondary metabolites to safeguard themselves against other species such as marine herbivores, for reproduction purposes as well as to keep pace with competitors for survival.³⁷ By evidence, marine organisms constantly evolve to adapt themselves in harsh environmental conditions.³⁷ As contrast to terrestrial organisms, various organic products are derived from marine organisms due to the elaborated living diversity of species and hence have more powerful biodiversities.³⁸ Sponges, molluscs, tunicates and macroalgae are the common marine organisms.³⁹ Algae are neither plants nor animals but rather belong to a group of living things called protists. Seaweed comprises of species of macroscopic, multicellular algae sticking to rocks and found along the seashore in abundance in every ocean.⁴⁰

New Sources of Therapeutics in the Marine Environment

There have been several controversies surrounding the responsiveness of existing drugs. Despite vigorous attempts from the whole world to enhance knowledge and tackle AMR, since July 2017, only eleven new drugs, most associated with pre-existing classes with restricted clinical benefits have been approved.⁴¹ The marine organisms produce several residues by break down of their natural components that could be used to fuel the futered

discovery pipeline of drugs which are currently less explored.⁴² During the period 1998-2008, initially the global marine pharmaceutical analysis included 806 chemicals which expressed antibacterial, antifungal, among others, with actions on the cardiac, hormonal and sense organs.⁴³ By 2022, there has been a huge increase in seawater pharmaceuticals as around 37, 542 novel natural products have been recorded and authorized for official use in the market as pharmaceuticals.⁴⁴ Eminent marine drugs are derived from marine species of bacteria, virus, algae, fungi and sponge,³⁷ which have been modified to fight against competitive organisms by showing defence mechanisms against those that swallow them, plants that grow on them for support and organisms that pollute the surrounding with excrement.⁴⁵ The possible rationale for the enhancement of antibiotic production in microorganisms in terms of bacteria is due to their fierce competition for space, nutrient and potential to kill competitor bacteria in their environment.³⁸ One of the major side effects of NHFW is of inflammation and amphichopyrones A, a marine fungus derived component has been shown to reduce inflammatory effects by inhibiting nitric oxide production.⁴⁴ Phomoxanthone A, another marine fungus derived natural product, was seen to have cytotoxic effects by aiming at the inner mitochondrial membrane of cancer cells, hence having a specific target.⁴⁴ Also, advanced technology like CRISPER (Clustered regularly interspaced short palindromic repeat) gene editing technique can be used to alter the host plant genomes to achieve the goal.⁴⁶ The above could hence be implemented in genome mining of coastal greens to hamper the regulatory hurdles in diabetic foot treatment and enhance existing therapies. The various species of microorganisms indigenous to the sea that portray antimicrobial is noticeable, hence isolation and identification of specific antibiotics have been attempted, but few of them are in preclinical and clinical trials.⁴⁷ Exploring the marine microbials for their coaction with existing drugs is therefore worthwhile.⁴⁵

Mangroves and Algae

Mangroves are shrubs or trees that grow mainly in coastal areas and brackish water in tropical regions, which also adapt in harsh costal conditions⁴⁸ during climate change. Mangroves are distributed over an area of 152,000 km² globally.⁴⁹ 84 mangrove species are known worldwide, while 80 of them

considered true mangroves and the other 14 are semi-mangrove.⁵⁰ The inhabitants of the coastal regions have acknowledged the benefits of mangroves as the latter have been used as alternatives to drugs for a plethora of diseases.⁵¹ Flavonoids, saponins, alkaloids and phenolics are the bioactive constituents of *Excoecaria agallocha*, whose methanolic extracts displayed antibacterial activity.⁵² Other mangroves used in the medical field to treat hypoglycemic activities include *Acanthus ilicifolius*, *Avicennia marina*, *Rhizophora apiculata*, *Bruguiera gymnorhiza* and *Rhizophora mucronatae*, *Xylocarpus granatum*, *Xylocarpus moluccensis*, *Xylocarpus granatum*, *Sonneratia species*.⁵²

Seaweeds (macroalgae) possess fat, water soluble vitamins, essential minerals and other bioactive agents to combat attributes of the ecosystem such as UV photo damage, high sodium chloride, oxygen toxicity, and stress caused by bacterial colonization.⁵³ Previous studies demonstrated that methanolic extract of *Halimeda* species, part of the green macroalgae family inhibited the growth of *Bacillus subtilis* (*B. subtilis*), *Bacillus cereus* (*B. cereus*) and *S. aureus*⁵⁴ while methanolic extract of *Sargassum polycystum*, a brown macroalgae inhibited *E. coli*, *Proteus vulgaris*, *K. pneumoniae* among others.⁵⁵ Literature review revealed that green algae have higher potential to inhibit gram positive bacteria than gram negative bacteria.⁵⁴ *Prorocentrum* isolates, which forms part of the microalgae family, have been previously identified to have desirable antagonistic effects against Methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis* (*E. faecalis*), among others.⁵⁶ Marine structures are grouped into different chemical classes that is alkaloids, polyketides, peptides, shikimates, sugars and terpenes.⁵⁷ Chemical substances from biologically active seaweeds have been assessed in tissue repair by increasing the feasibility of collagen fibrils or by preventing cell degeneration, or by enhancing DNA synthesis while the brown algae were described as anti inflammatory agent.⁵⁸

Impact of Coastal Greens on Public Health and Economy

Our public health policy is to elevate the health status of our citizens and at the same time guarantee that health goals are met. Thus, the merit of use of marine

herbs in routine use, is to mitigate antimicrobial resistance with the intention to provide medications to patients in a brief delay as they are easily and freely available in several countries. Using coastal greens as drugs are presumed to be sustainable as they will be constantly available and reproducible, with a minimum cost to pharmaceutical companies. Some countries found using traditional herbs for the treatment of DM highly decrease the burden of the cost of conventional medicine as they are easily available and reproducible despite climate change as native plants adapt to their surroundings.⁵⁹ WHO predicted 10 million of deaths on a yearly basis by 2050 due to AMR⁶⁰. Since AMR is a global issue, several pharmaceutical companies may have an increased turnover by business interaction with foreign companies owing to production of drugs with their unique biodiversity of marine herbs. On the other hand, harvesting marine herbs may be laborious in bad weather conditions and their extensive exploitation may lead to their depletion^{60,61} and may hence cause an imbalance of the natural habitat of the oceans leading to deaths of marine organisms. Restoring the damage and caused to the ecosystem might take considerable time and be costly.

Review Methodology

Relevant literature and representative case reports were collected by scrutinising scientific electronic database namely EBSCO, PubMed and Science Direct from the year 2015 to 2024. Keywords marine drugs, traditional drugs, antihyperglycemic, pharmaceutical properties and pharmacological activities were used. Article assemblage was accomplished based on a search strategy. Primarily, a generalised search was executed in the above-mentioned databases, following a screening of the papers which led to their inclusion in this study. Inclusion criteria were based on diversity of marine organisms, their sustainability and availability, their antimicrobial properties and their use in the future to relieve the burden of AMR. Also, genome mining and other novel technologies using bioinformatic analysis for identifying the structure of marine organisms were searched for reproducibility. Data was then gathered and compiled as appropriate as shown in the flow diagram below.

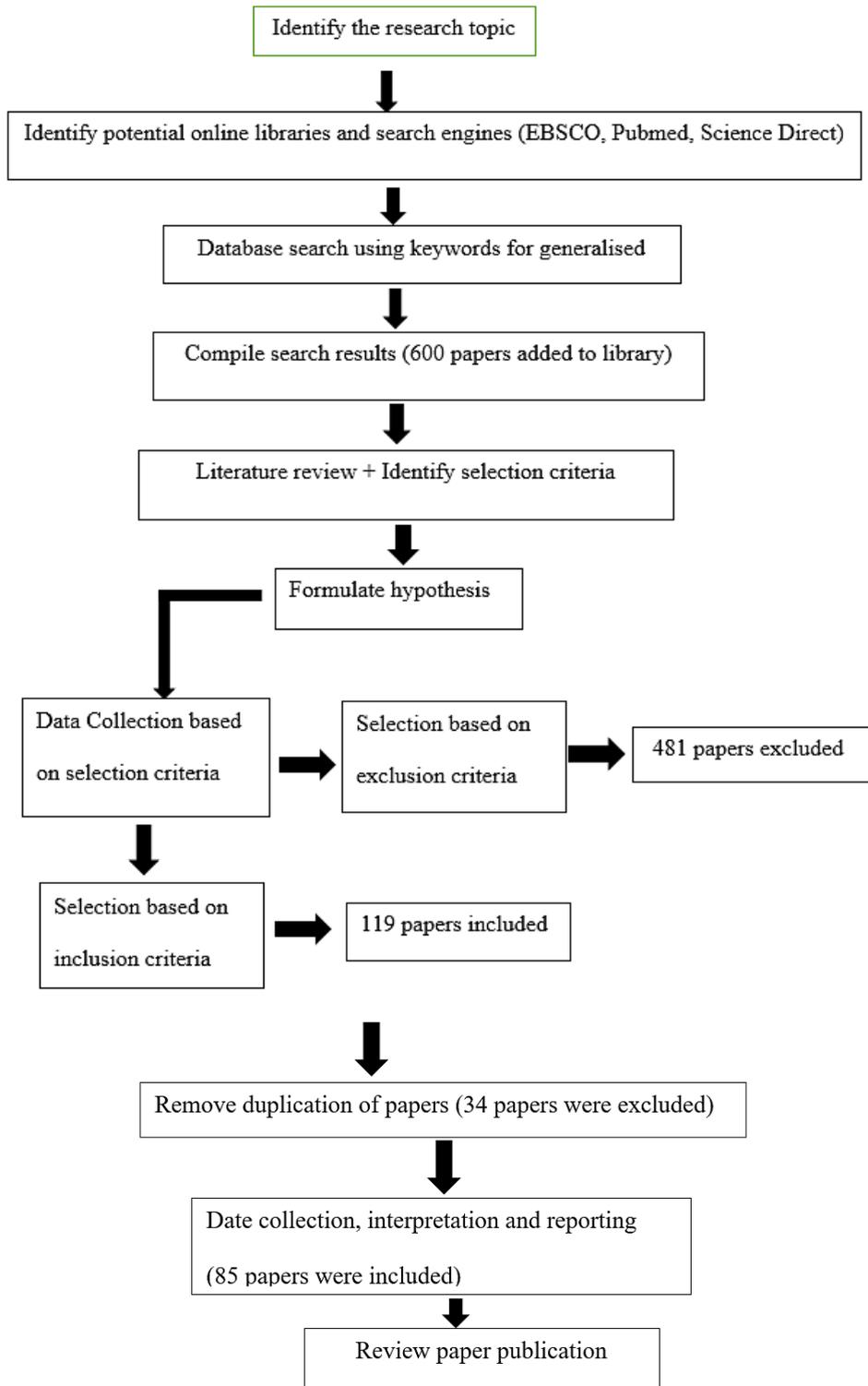


Fig. 1: A flowchart showing the methodology of the review paper

Discussion

Diabetes mellitus forms part of the major universal health pathophysiology's of the current era. There is an undeviating link between family history, increased mechanization, sedentary lifestyle, weight gain, education level, dietary pattern and prevalence of DM². Diabetic foot ulcer (DFU) is defined as the presence of diabetic foot pathologies such as neuropathy and ischaemia, Neutrophils and macrophages are inflammatory cells that play a part in cleanup the wound of pathogens, cell debris and damaged extracellular matrix, and are therefore favourable and vital for restoring damaged skin.⁶² Excessive inflammation rate hampers the typical formation of new cells that migrate and multiply in infected sites, which eventually leads to compromised wound healing.⁶³

Evolving ailments have overburdened the existing drug resources and led to AMR and as the pursue for novel drugs proceeds, confrontation to known drugs continue to rise.⁴⁷ Accumulated evidence from another study of suggest that the highly impermeable cell wall of gram-negative bacteria may significantly contribute to AMR.⁶⁴ For instance, penicillin was primarily used to treat *S. aureus* infections, followed by methicillin, which has now changed to vancomycin.⁶⁵ These researchers also enumerate that resistance to macrolide classes of antibiotics is due to mutations in the ribosomal proteins and enzymatic modification of ribosomal target during drug binding. Hence, treatments to reach specific targets need to be updated in different ecological niches.

About 500,000 natural compounds have been describe globally, among which, 80,000 are bacterial and fungal-derived compounds; 29% of which is derived from actinomycetes⁶⁶. Roughly 80% of the antibiotics used from 1950 to 1980 were isolated from actinomycetes from the genus *Streptomyces*, by 1980, at most eleven actinomycetes genera were disclosed, subsequently one hundred genera by 2005 and two hundred and twenty genera by 2010.⁶⁶ From the same study, it was shown that out of thirty new antibiotics launched worldwide since 2000, two were natural products (NP), twelve were NP-based and sixteen were synthetic.⁶⁶ A category of organisms adjusts exceptionally in salty environments and gravitational pressure exerted by the ocean due to anthropogenic activities,

hence the assortment of microorganisms in marine habitats is quite remarkable.⁶⁷ Reactive oxygen species (ROS) are end products of biochemical pathways of metabolism, which upon excess accumulation prevents the body to clean these free radicals, thus causing aerobic damage, which leads to further diabetic complications.⁵³ Chemical compounds from oceanic sources inherit altered shapes in the foundation or side chain in contrast to human origin, which make them the design of choice for drugs. The peptides taken from ascidians, sponges, as well as mollusks also provide huge great stability from enzymatic degradation as well as thermal conditions.⁴⁴ A wide selection of bioactive peptides are the end products of the association that links microorganisms and the marine creatures.⁶⁸

Moreover, cephalosporins, usual drugs were refined from the marine fungus *Cephalosporium acremonium*.³⁷ Other antibiotics from saltwater fungi include Penicidametizine A and B from *Penicillium adametzioides* in addition to other *Penicillium* spp. from sponges associated, mangroves associated, and marine algae associated.⁶⁹ Since then, extended investigation has been conducted to reveal the bioactivity of marine microbes such as bacteria, fungi, actinomycetes and microalgae-cyanobacteria and the results have been fruitful as antibiotics. The active components derived from several marine organisms and their corresponding antimicrobial effect on common pathogens isolated from NHFW are listed in Table 1. The mechanisms of action of each strain or bioactive compound have not been documented and the marine organisms have been collected from several coastlines globally.

Since the exploration of species not formerly cultivated, could relieve the pressing demand to resistance against currently used antibiotics⁶⁶, ethnomedicines have been recognized by WHO as successful therapeutic agents with application to aquaculture due to the loss of antimicrobial efficiency and the struggle of pathogens to antibiotics.⁵⁰ In line with the above, seaweeds are classified according to their pigments content, structure and physiological attributes in a trio namely red algae (*Rhodophyceae*), brown algae (*Phaeophyceae*) and green algae (*Chlorophyceae*).⁵³ The bactericidal activity of the seaweed extracts seems to be restrained to associates of *Phaeophyceae* and partly among the species of *Rhodophyceae* and *Chlorophyceae*.⁷³

Table 1. Some bioactive compounds isolated from marine organisms.⁷⁰⁻⁷²

Organisms isolated from	Marine organisms	Bioactive compound	Coastal region	Antimicrobial activity against	Reference
Bacteria	Alteromonas spp.	strain 1, strain 6	Rameswaram and Pudhumadam	<i>S. aureus</i>	[70]
	<i>Pseudomonas</i> spp.	Strain 20 Strain 4, strain 5, strain 13, strain 24, strain 25		<i>S. aureus, E. coli</i> <i>S. aureus</i>	[70] [70]
	<i>Pseudomonas</i> spp.	Strain 18		<i>S. aureus, E. coli</i>	[70]
	Marinobacter spp.	Strain 8		<i>S. aureus</i>	[70]
	Marinobacter spp.	Strain 14		<i>E. coli</i>	[70]
	<i>Bacillus</i> spp.	Strain 16		<i>S. aureus, E. coli</i>	[70]
	<i>Bacillus</i> spp.	Bogorol		MRSA, vancomycin resistant <i>Enterococcus</i> (VRE)	[70]
	<i>Pseudomonas bromoutilis</i>	2,3,4-tribromo-5(1'hydroxy, 2',4'- dibromophenyl)	Puerto Rico	<i>S. aureus</i>	[71]
	<i>Pseudomonas</i> spp.*	Pyrone-I		MRSA, VRE	[71]
	Hahella spp.	prodigiosin	Nagasaki Prefecture, Japan	<i>S. aureus</i>	[72]
	<i>HaloBacillus litoralis</i> YS3106 strain	halolitoralins A		<i>C. albicans</i>	[72]
	<i>Pseudomonas</i> UJ-6	1-acetyl-beta-corboline		<i>S. aureus</i>	[72]
	<i>S. arenicola</i>	Salinaphthoquinones		<i>S. aureus, E. faecalis</i>	[72]
	<i>Bacillus</i> spp.	Bacicyclin	mussel <i>Mytilus edulis</i>	<i>S. aureus, E. faecalis</i>	[72]
	<i>Pseudoalteromonas</i> s.	Heat tolerant cell-free culture supernatant	Coral (<i>Platygyra</i> sp.)	<i>B. cereus, S. aureus</i>	[72]
	<i>S. sampsonii</i> -SCSIO 054	Julichrome Monomers	Mollusk <i>Batillaria zonalis</i>	<i>S. aureus</i>	[72]
	<i>B. flexus</i> EED 15 and <i>S. lienomycini</i> EED 16		Seagrasses (<i>Cymodocea</i> sp., <i>Enhalus acoroides</i> , <i>Syringodium</i> sp., and	<i>E. coli, S. aureus</i>	[72]

		<i>Thalassia hemprichii</i>	
Actinomycetes	<i>Nocardioopsis dassonville</i>	kahakamides A	Hawaii B. subtilis [71]
	<i>Nocardioopsis dassonville</i>	N-(2-hydroxyphenyl)-2-phenazamine	Hawaii Candida albicans [71]
	<i>Micromonospora</i> spp.	Tetroarcin	Toyama Bay, Japan B. subtilis, S. aureus [72]
Streptomyces	Streptomyces**	RM80 strain	S. aureus, C. albicans [71]
	Streptomyces spp.	1492 Strain	S. aureus, A. baumannii [72]
	Streptomyces MU5C 135T	bacitracin A	S. aureus [72]
	Streptomyces CTF9	Indole-3-lactic acid, phenylacetic acid	C. albicans [72]
	Streptomyces B8080	chalconmycin	Mangrove sediment in Pohoiki, Hawaii S. aureus, B. subtilis, E. coli [72]
	Streptomyces spp.	Aborycin	Deep-sea sediments of the South China Sea S. aureus [72]
	Streptomyces SMS806	albonoursin	deep-sea sediments in the South China Sea S. aureus [72]
Cyanobacterium	<i>Hormoscilla</i> spp.	anaephenes A-C	S. aureus [72]
sponges	<i>Holothuria tubulosa</i>	peptide fractions	Surface adherent <i>Staphylococci</i> , <i>P. aeruginosa</i> [71]
	<i>Xestospongia testudinaria</i>	diethyl ether fraction	S. aureus, E. coli, K. pneumoniae, P. aeruginosa [71]
	<i>Ageles clathrodes</i>	ethanoic extract	S. aureus, E. coli [71]
	<i>Phyllospongia lamellose t</i>	Phyllospongin D, phyllospongin E,	S. aureus [71]
	<i>Phyllospongia lamellose t</i>	12 α -acetoxy-13 β , 18 β cy -clobutan-20,24-dimethyl-24oxoscalar-16-en-25 β -ol	B. subtilis, S. aureus [71]

Hertios erectus				<i>B. subtilis</i>	[71]
Suberea mollis	Subereamollines A, Subereamollines B, Subereaphenols B, and C	Latrunculin T	Red sea	<i>S. aureus, Paeruginosa, K. pneumoniae</i>	[71]
Negombata magnifica				<i>S. aureus, B. cereus, C. albicans</i>	[71]
Amorphinopsis spp.	<i>Eutypella species, Lasiodiplodia theobromae, Fusarium solani</i>		Indonesia mangrove	ESBL <i>E. coli</i>	[71]
Aplysina aerophoba	<i>cyclic lipopeptides from Bacillus species</i>		Mediterranean Sea	<i>C. albicans, S. aureus, E. coli</i>	[71]
Fungus	<i>Penicillium minioluteum</i>	Purpurides E and F	Red sea	MRSA, <i>E. coli, C. albicans</i>	[71]
Soft Coral		Gorgosten-5(E)-3 β -ol, Sarcoalosterol A.		<i>B. subtilis, S. aureus, E. coli</i>	[71]

*The mechanism of action of the Pyrone-I targets the bacterial cell membrane

** RM80 strain acts on the N-acetylglucosamine

The methanolic extract of red algae *Grateloupia lithophila* Boergesen (*G. Lithophila*) showed biocidal effect against *E. coli*, *P. aeruginosa* and *S. aureus*.⁷³ Compounds found in *Sphaerococcus coronopifolius* has been shown to have antibacterial activity against *S. aureus*.⁷⁴ *In vitro* analysis showed that the bromophenol 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-ethoxymethyl benzyl) benzene-1,2-diol, derived from the red algae *Rhodomela confervoides* along with its synthetic analog 3,4-Dibromo-5-(2-bromo-3,4-dihydroxy-6-isopropoxymethyl benzyl) benzene-1,2-diol (HPN), have convincing Protein tyrosine phosphatase 1B (PTP1B); a significant protein target in the treatment of T2DM.⁷⁵ PBDE (Polybrominated diphenyl ethers) compounds comprising of bromophenol was isolated as well from the Indonesian aquatic sponge *Lamellodysidea herbacea* which is known to exhibit antibacterial effect against *K. Pneumoniae* and *E. Coli*.⁷⁶ Though extensive research on antibacterial activity has been done on *Symphycladia latiuscula*, a phenolic compound isolated from another red algae *Symphycladia linearis* inhibited *S. aureus* and had an MIC of 280 µg/mL alongside *B. Cereus*, with an MIC of 1,024 µg /mL extract.⁷⁷ The mass of the brown algae breed is exposed to extensive study owing to their potentials as active ingredients in pharmaceutical leads and nutraceuticals.⁷⁸ Phlorotannins have shown *in vitro* to act differently by blocking the enzyme site by prohibiting the enzymes such as α -amylase, α -glucosidase, angiotensin-converting enzymes (ACE), aldose reductase, dipeptidyl peptidase-4, and PTP 1B enzyme.⁷⁸ *Ecklonia Stolonifera* Okamura forms part of the algal family *Lessoniaceae*, and its methanolic extract is rich in the bioactive compound phlorotannins which is familiar with strong inhibition effect on enzymes present in tissues that develop diabetic conditions both in rat lenses and human.⁷⁹ Phlorotannins from *Ecklonia kurome* Okamura simultaneously had capacity to inhibit α -glucosidase and α -amylase activities *in vitro* and decreased blood glucose levels after meals *in vivo*. Corresponding activity was also shown by dichloromethane fraction squeezed from *Saccharina japonica* and fucoxanthin removed from *Eisenia bicyclis* and *Undaria pinnatifida*.⁸⁰ The methanolic, ether, aquatic and phenolic extracts of *Colpomenia sinuosa* seaweeds, have been identified as antimicrobials against gram positive organisms, namely *B. subtilis*, *E. coli*, *K. Pneumoniae*, *Ps. aeruginosa* and *S. aureus*.⁸¹

Likewise, there is scope for green algae to screen for antidiabetic compounds since there is at present a terpene (Dysidine), derived from the sponge *Dysidea villosa* that forms part of experiments in search of the cure of diabetes.⁷⁵ Another study outlined that *Spirulina* had antihyperglycemic effect in clinical trials which could maintain euglycemia.⁸² The green microalgae *Chlorella* species and diatom *Nitzschia laevis* showed the maximum obstructive action against the development of total advanced glycation end-products (AGEs), especially pentosidine and Ne-Carboxymethyllysine.⁷⁵ AGEs are the principal process whereby toxic compounds are made when protein or fat amalgamate with sugar in the blood circulation. In the same study, they enumerated that *Cladophora rupestris* have been investigated to suppress α -glucosidase and α -amylase *in vitro* while *Derbesia marina* inhibits PTP1B *in vitro*.⁷⁵

Alongside, phytochemical screening showed that mangroves such as *Avicennia marina*, *Rhizophora apiculate* and *Sonneratia alba* exhibit antibacterial effect against the human pathogen *S. aureus*.⁸³ Also, *Xylocarpus granatum* contain the alkaloids *xylogranatinin*, *granatoin*, *acanthicifoline* and *trigonelline*, which has glucose lowering properties by reinforcing the hormones from the islets of Langerhans or by increasing the flow of blood glucose level to the peripheral tissue.⁵² The same researchers also mentioned that *Avicennia marina* (*A. marina*), *Xylocarpus granatum* (*X. granatumand*) and *Bruguiera sexangula* (*B. sexangula*) are known to possess phytochemicals namely quercetin, kaempferol, catechin, epicatechin and rutin, which aid in stopping β -cell necrosis, encouraging β -cell propagation and insulin flow, thus amplifying insulin activity.⁵² Triterpenoid, referred to as saponin, is a glucose lowering activity and found in *A. marina* and *Barringtonia Racemose* (*B. rasnose*) and may have phenolic compounds that might induce hypoglycemia by promoting insulin levels, raising the responsiveness of tissues to glycaemic action, encouraging glucose exploitation and restraining the action of α -amylase.⁵² *Rhizophora mucronata* (*R. mucronata*) and *A. marina* have likely been referred to as insulin inhibitors.⁵⁰ Studies showed that mangrove plant extracts inhibited *Staphylococcus* sp., *E. coli* and *Pseudomonas* sp.⁸⁴ Similarly, petroleum ether, chloroform, ethyl acetate, ethanol and sterilized water extracts was used to test for the antimicrobial activity of *A. marina*, *Exoecaria*

agallocha (*E. agallocha*) and *B. sexangula* against *S. aureus*, which showed considerable results. Ethanolic extract of *Acalypha indica* (100mg/ml) and *Datura metel* (100 mg/ml) had highest antimicrobial activity against *P. aeruginosa*, *E. coli* and *B. subtilis* and least bactericidal activity against *S. aureus*, while the ethyl acetate extract of the plants showed similar effects against *E. coli*. It should also be noted that the above plants restrained the growth of fungal pathogens.⁸⁵ *Phyllanthus amarus*, also inhibited the growth of *S. aureus*, *E. coli*, *Enterobacter* spp.; *E. faecalis*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, among others. *Mangifera indica* hampered the growth of *K. pneumoniae*, *S. aureus*, *P. mirabilis*, *P. aeruginosa* and *E. coli*.⁸⁵ One hundred and sixty-eight endophytic fungi were isolated from the greenery of *Acanthus ilicifolius* var. *Xiamenensis*, out of which, twenty-eight fungal strains showed bacteriostatic activity against *E. coli*, *B. subtilis*, *S. aureus*, *C. albicans* in one of the various studies conducted in this line.⁵¹ From the above it can be concluded that screening for antimicrobials in the marine environment has been in the limelight. The combination of the extracts of several plants as antimicrobials in topicals can be taken into consideration for future investigations.

It should be noted that new technologies with genome mining could be implemented for more specific target of marine organisms instead of only conventional ethanolic or methanolic extracts in drug design. Also, the structure of marine organisms can be defined using nuclear magnetic resonance spectroscopy and single X-ray diffraction.⁷⁶

Challenges in using Marine Derivative Organisms as Microbials.

Attempts have been previously made to validate the use of marine sources using *in vitro* and *in vivo* models, however under reporting lead to underestimation of their scientific importance. The microbes in the marine basement are assumed to be up to ten percent of the total living biomass carbon in the biosphere, however, the microorganisms use these compounds for their own defence mechanisms and hence not many of them have been explored for their pharmaceutical potential.⁴⁷ Unlike terrestrial actinomycetes, some unusual marine actinomycetes demand unique growth conditions, hence it has been observed that many bacterial cells in environments are viable but not culturable (VBNC),

as approximately only 1% of bacterial cells can grow on isolation media by traditional methods has been mentioned in a study.⁶⁶ Antibiotic production is altered both qualitatively and quantitatively by nature of culture medium, low nutrient media may be used to imitate the low nutrient content of deep-sea environments. Sampling difficulties are the main challenges in understanding marine metabolites as most organisms inhabiting these sites are obligate piezophiles, sensitive to shifts in atmospheric.

The fact that some secondary metabolites found in *Rhodophytae* (Red algae) are poisonous is a major drawback for their use. Manaucalide and polycavernoside found in Pacific members of *Gracilariaceae* do have antiviral effects but at the same time are known to have tumour promoting activities.⁵² Depending upon their dissolvability and polarity, solvents show a range of antimicrobial activity, so it is vital to optimize each antibacterial activity by selecting the best solvent system.⁵³ However, low marketing value, non culturability, laborious isolation, large scale production and purification procedures, long term clinical trials, high toxicity of the active compounds, environmental consequence on natural territory and inadequate investment by pharmaceutical companies³⁹ are among the cause of underutilization of red algae, despite their potent benefits.

Most studies of mangroves are limited to muddy regions as only few species like *Pemphis acidula* are growing only in coral sand substrates.⁸⁴ Each mangroves species may vary in their salinity tolerance and adaptative mechanisms may be vital to maintain proper growth and competitive dominance.⁸⁴ Moreover, due to growing human population, land conversion, overharvesting and pollution, the equilibrium of mangroves is under pressure.⁴⁸

Though the mentioned bioactive compounds from marine organisms have not yet been totally linked as antibiotics for the treatment of pathogens isolated in NHFW, they have been identified to inhibit pathogens like those found in NHFW. Their synergy with commonly used antibiotics can be used at uncovering antimicrobials with favourable outcomes like Chevalone E, derived from the fungus *Aspergillus milianensis* exhibited favourable synergism with the drug oxacillin against MRSA.⁴³

Similar models could be in trial *in vivo* as *S. aureus* is one of the commonly used pathogens isolated in NHFW. However, animal disease models are used during pre-clinical testing, and though these models are known to copy human conditions, finding the best animal model remains a challenge.⁸⁵ The equilibrium of drug exposure in disease targeted tissues as compared to healthy tissue is overseen which mislead the selection of drugs in terms of toxicity and dose efficacy further leading to failed trials.⁸⁵

Future Perspectives

Other technologies such as bioinformatic analysis, gene knockout and heterologous expression should be implemented in clinical practice to elucidate the genome of aquatic plants and conduct *in vivo* studies to validate the efficacy of their identified bioactive compounds. The merit of technologies includes harvesting specific organisms in a small quantity to keep a balance in the ecological system. This paper provides supplementary scientific data for selection, essential insights and offers support for the sustained research of new feasible drugs for human therapeutics from cultured marine species.

Conclusion

There is a desperate need to develop new risk-free drugs to treat the pathophysiology of DM. Owing to their rich biodiversity, low toxicity and precious natural wealth the marine environment is a vast pool of unique species in terms of chemical structure, biological activity, eco-friendly, bio-friendly, cost effective with relatively untapped sources for new bioactive therapeutics. The progress in biological therapy and the substantial improvements in modern multitarget drug design manufacturing has made discovery of marine drugs a feasible goal. Recent advances in genome mining and biosynthetic pathways of natural components of oceanic fungi are an important source of pharmaceuticals.

Acknowledgement

The University of Mauritius is thanked for research and administrative support to Ms B. M Rakhal during her studentship. Rajesh Jeewon would also like to thank the DSFP programme of King Saud University,

Riyadh, Saudi Arabia. RajeshKumar KC also thanks the Director, MACS Agharkar Research Institute, Pune, for motivation in our work.

Funding Sources

The authors received no financial support for the research, authorship and publication of this review paper.

Conflicts of Interests

The authors declare no conflicts of interest.

Data Availability Statement

This statement does not apply to this review paper.

Ethics Statement

This review paper did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This review paper did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This review paper does not involve any clinical trials.

Permission to Reproduce Material from Other Sources

Not Applicable.

Author Contributions

- **Bhavna Madhushi Rakhal:** Methodology, Writing, Data Collection, Original Draft
- **Abdulwahed Alrefaei:** Supervision and Project Administration
- **Nadeem Nazurally:** Correction of initial and final Drafts
- **Kunhiraman Chandanadukkam Rajeshkumar:** Writing, and editing different versions of manuscript
- **Rajesh Jeewon:** Supervision, Project Administration Original Draft, Review, Editing and submission.

References

1. Santos JD, Vitorino I, Reyes F, Vicente F, Lage OM. From ocean to medicine: pharmaceutical applications of metabolites from marine bacteria. *Antibiotics*. 2020; 9(8):1–30. doi:10.3390/antibiotics9080455
2. Seifu Y, Tsegaw D, Haji Y, Ejeso A. Prevalence and associated factors of diabetes mellitus among adult population in Hawassa Zuria Woreda, Sidama Region, Ethiopia. *Diabetes Metab Syndr Obes*. 2020; 13:4571–4579. doi:10.2147/DMSO.S280230
3. Tiwari D, Aw TC. The 2024 American Diabetes Association guidelines on standards of medical care in diabetes: key takeaways for laboratory. *Explor Endocr Metab Dis*. 2024; 1:158–166. doi:10.37349/eemd.2024.00013
4. Lee JW, Wang JH, Teo SS. Antidiabetic effect of *Kappaphycus alvarezii* extracts on streptozotocin-induced type II diabetic ICR mice. *Open Access*. 2017; 2(5): 1–5. Accessed January 26, 2025. <https://www.remedypublications.com/open-access/antidiabetic-effect-of-kappaphycusalvarezii-extracts-on-streptozotocin-induced-type-ii-diabetic-icr-mice-1108.pdf>.
5. Gangawane AK, Bhatt B. Skin infections in diabetes: a review. *Diabetes Metab*. 2016; 7(2):1–4. doi:10.4180/2155-8080.1000804
6. Morsli M, Salipante F, Magnan C, Dunyach-Remy C, Sotto A, Lavigne JP. Direct metagenomics investigation of non-surgical hard-to-heal wounds: a review. *Ann Clin Microb Antimicrob*. 2024; 23(1):39, 2–17. doi:10.1186/s12941-024-00698-z
7. Gunasekaran P. Assessment of major microorganisms involved in diabetic foot infection which delays wound healing. *Int Arch Integr Med*. 2017; 4(8):87–90. Accessed January 26, 2025. <http://iaimjournal.com/>
8. Palani H. View of non-Anthrax *Bacillus* species association in non-healing diabetic foot ulcers and their drug susceptibility. *NVEJ*. 2023; 8(6):5883–5890. Accessed January 26, 2025. <https://www.nveo.org/index.php/journal/article/view/5000/4001>
9. Ansari P, Tabasumma N, Snigdha N, Siam N, Panduru R, Azam S, Hannan JMA, Abdel-Wahab Y. Diabetic retinopathy: an overview on mechanisms, pathophysiology and pharmacotherapy. *Diabetology*. 2022; 3(1):159–175. doi:10.3390/diabetology3010011
10. Mezil SA, Ahmed B. Complication of diabetes mellitus. *Ann Rom Soc Cell Biol*. 2021; 25(3):1546–1580. Accessed 20 January 2025. https://www.researchgate.net/publication/351438082_Complication_of_Diabetes_Mellitus
11. Vieira I, Barros LM, Baptista F, Rodrigues DM, Paiva IM. Recommendations for practical use of metformin, a central pharmacological therapy in type 2 diabetes. *Clin Diabetes*. 2022; 40(1):97–107. doi:10.2337/cd21-0043
12. Bailey CJ. Metformin: therapeutic profile in the treatment of type 2 diabetes. *Diabetes Obes Metab*. 2024; 26(3):3–19. doi:10.1111/dom.15663
13. Hoang TPN, Ghori MU, Conway BR. Topical antiseptic formulations for skin and soft tissue infections. *Pharmaceutics*. 2021; 13(4):558, 1-31. doi:10.3390/pharmaceutics13040558
14. Menezes JVF, Senthamizhan S. Utility of topical timolol in the management of chronic non-healing foot ulcers. *Int Surg J*. 2023; 10(4):806–807. doi:<https://doi.org/10.18203/2349-2902.isj20230980>
15. Negut I, Grumezescu V, Grumezescu A. Treatment strategies for infected wounds. *Molecules*. 2018; 23(9):2392. doi:10.3390/molecules23092392
16. Baig MS, Banu A, Zehravi M. An overview of diabetic foot ulcers and associated problems with special emphasis on treatments with antimicrobials. *Life*. 2022; 12(7):1054. doi:10.3390/life12080054
17. Krishna Freddy IK, Yerragopu AK, Chamarthi SK. A review on plants having anti-inflammatory activity. *J Pharm Res*. 2020; 4(4):1–5. doi:10.23880/oajpr-16000217
18. Alves ASS, Nascimento CCHC, Barreto AS, Stephens PRS, Saranraj P, Dire GF. The role of medicinal plants on drug development: a biotechnological overview. *Int Acad J Multidiscip Res*. 2020; 6(4):2098–2102. doi:10.22192/iajmr.2020.6.4.5
19. Sikarwar V, Ranawat MS. Endophytes: an

- overview. *Pharm Chem J.* 2023; 10(1):21–32. Accessed January 20, 2025. www.tpcj.org
20. Muhammad N, Liaqat I. Endophytes: potential source of antimicrobial and antibiofilm agents. *Nova Publishers.* 2021:17–60. doi:10.52305/OETH8715
 21. Tiwari P, Mahalingam G. Antidiabetic activity of endophytic fungi isolated from *Ficus religiosa*. *Asian J Pharm Clin Res.* 2017;10(4):80. doi:10.22180/ajpcr.2017.v10i4.14808
 22. Little SM, Senhorinho GNA, Saleh M, Basiliko N, Scott JA. Antibacterial compounds in green microalgae from extreme environments: a review. *Algae.* 2021; 36(1):80. doi:10.4490/algae.2021.36.3.6
 23. Otolorin I, Osuala OJ, Chinyere C, Ezemba AS, Etikudike V. Antimicrobial activities of green algae on microbial isolates. *Electron J Stat.* 2020; 1:37–43. Published online January 1, 2023. doi:10.2139/ssrn.4435239
 24. Etebu E, Arikekpar I. Antibiotics: classification and mechanisms of action with emphasis on molecular perspectives. *ResearchGate.* 2016; 4:90–101. Accessed January 26, 2025. https://www.researchgate.net/publication/319881509_Antibiotics_Classification_and_mechanisms_of_action_with_emp
 25. Fomnya H, Ngulde J, Amshi SI, Bilbonga G. Antibiotics: classifications and mechanism of resistance. *Appl Microbiol Biotechnol.* 2021; 9(3):38–50. doi:10.33500/ijambr.2021.09.004
 26. Giacomini E, Perrone V, Alessandrini D, Paoli D, Nappi C, Degli Esposti L. Evidence of antibiotic resistance from population-based studies: a narrative review. *Infect Drug Resist.* 2021; 14:849–880. doi:10.2147/IDR.S289801
 27. Hanrahan D. Combatting resistance: federal efforts to reduce overuse, curb misuse, and incentivize the development of antibiotic drugs. *Ann Health Law.* 2017; 26:67–91. Accessed January 26, 2025. <https://lawcommons.luc.edu/annals/vol26/iss1/5>
 28. Munita JM, Arias CA. Mechanisms of antibiotic resistance. *Microbiol Spectr.* 2016; 4:1–25. Accessed December 5, 2024. https://www.researchgate.net/publication/303808080_Mechanisms_of_Antibiotic_Resistance
 29. Ahmed DA. Beta-lactamases enzymes: mechanism and classification. *Biochem Cell Arch.* 2021; 21(1):1903–1916. Accessed November 17, 2024. https://www.researchgate.net/publication/354208804_Beta-Lactamases_Enzymes_Mechanism_and_classification
 30. Dowling A. Antibiotics: mode of action and mechanisms of resistance. *Microbiol Spectr.* 2017; 4:1–694. Accessed September 2, 2024. https://www.researchgate.net/publication/318081480_Antibiotics_Mode_of_action_and_mechanisms_of_resistance
 31. Garneau-Tsodikova S, Labby KJ. Mechanisms of resistance to aminoglycoside antibiotics: overview and perspectives. *Med Chem Commun.* 2016; 7(1):11–27. doi:10.1039/c5md00344j
 32. Miklasińska-Majdanik M. Mechanisms of resistance to macrolide antibiotics among *Staphylococcus aureus*. *Antibiotics.* 2021; 10(11):1406. doi:10.3390/antibiotics10111406
 33. Kang HK, Park Y. Glycopeptide antibiotics: structure and mechanisms of action. *J Bacteriol Virol.* 2015; 45(2):80. doi:10.4180/jbv.2015.45.2.80
 34. Venkatesan M, Fruci M, Verellen LA. Molecular mechanism of plasmid-borne resistance to sulfonamide antibiotics. *Nat Commun.* 2023; 14(1):4031. doi:10.1038/s41467-023-39778-7
 35. Stonik VA, Makarieva TN, Shubina LK. Antibiotics from marine bacteria. *Biochemistry (Moscow).* 2020; 85(11):1380. doi:10.1134/s0008098020110080
 36. Stramma L, Schmidtke S. Oxygen and nutrient trends in the tropical oceans. *Ocean Sci.* 2021; 17(3):833–847. doi:10.5194/os-17-833-2021
 37. Navgire TD. Study of marine drugs. *Int J Creat Res Thoughts.* 2021; 9:729–736. Accessed January 26, 2025. <https://ijcrt.org/papers/IJCRT2109294.pdf>
 38. Pimpliskar M, Pagare P, Jadhav R. Antagonistic activity of marine bacterial isolates on common human pathogenic bacteria. *Prog Biomed Eng.* 2017; 1(2):81–88. doi:10.29280/pbb2017.v1i2.18
 39. Jaspars M, De Pascale D, Andersen JH, Reyes F, Crawford AD, Ianora A. The marine biodiscovery pipeline and ocean medicines of tomorrow. *J Mar Biol Assoc U K.* 2016; 96(1):151–180. doi:10.1017/

- s0025315415002106
40. Ismail GA, Gheda SF, Abo-Shady AM. In vitro potential activity of some seaweeds as antioxidants and inhibitors of diabetic enzymes. *Food Sci Technol.* 2020; 40(3):801. doi:10.1590/fst.15619
 41. Fleury Y. Marine antibiotics 2020. *Mar Drugs.* 2021; 19(6):351. doi:10.3390/md19080351
 42. Tortorella E, Tedesco P, Palma Esposito F. Antibiotics from deep-sea microorganisms: current discoveries and perspectives. *Mar Drugs.* 2018; 16(10):355. doi:10.3390/md18000355
 43. Liu Y. Renaissance of marine natural product drug discovery and development. *J Mar Sci Res Dev.* 2012; 2(2):106. doi:10.4172/2155-9910.1000e106
 44. Han C, Song A, He Y, Yang L, Chen L, Dai W, Wu Q, Yuan S. Genome mining and biosynthetic pathways of marine-derived fungal bioactive natural products. *Front Microbiol.* 2024; 15:1-28. doi:10.3389/fmicb.2024.1520446
 45. Pérez M, Falqué E, Domínguez H. Antimicrobial action of compounds from marine seaweed. *Mar Drugs.* 2016; 14(3):52. doi:10.3390/md14030052
 46. Tang J. Research and prospect of CRISPR system in marine biological system. *Highlight Sci Eng Technol.* 2023; 36:132-138. doi:10.54097/hset.v36i.5652
 47. Nweze JA, Mbaoji FN, Huang G. Antibiotics development and the potentials of marine-derived compounds to stem the tide of multidrug-resistant pathogenic bacteria, fungi, and protozoa. *Mar Drugs.* 2020; 18(3):145. doi:10.3390/md18030145
 48. Biswas PL, Biswas SR. Mangrove forests: ecology, management, and threats. *Encyclopedia of the UN Sustainable Development Goals.* Published online July 4, 2019:1–14. doi:10.1007/978-3-319-71065-5_26-1
 49. Palacios OA, Adame-Gallegos JR, Rivera-Chavira BE, Nevarez-Moorillon GV. Antibiotics, multidrug-resistant bacteria, and antibiotic resistance genes: indicators of contamination in mangroves? *Antibiotics.* 2021; 10(9):1103. doi:10.3390/antibiotics10091103
 50. Morales-Covarrubias MS, García-Aguilar N, Puello-Cruz AC. *Biopotentials of mangroves. Int J Agric Environ Biotechnol.* 2019; 4(5):280–281. doi:10.35410/ijaeb.2019.4445
 51. Sadeer NB, Zengin G, Jeewon R, Mahomoodally MF. Fungal endophytes associated with mangroves – chemistry and biopharmaceutical potential. *S Afr J Bot.* 2020; 134:1–26. doi:10.1016/j.sajb.2019.12.016
 52. Das SK, Samantaray D, Patra JK, Samanta L, Thatoi H. Antidiabetic potential of mangrove plants: a review. *Front Life Sci.* 2015; 9(1):75–88. doi:10.1080/21553769.2015.1091386
 53. Emer S, Abu-Ghannam N. Seaweeds as nutraceuticals for health and nutrition. *Phycologia.* 2019; 58(5):563–577. doi:10.1080/00318884.2019.1640533
 54. Wan R, Ross R, Farinna N, Rahim A, Khairul Adzfa. Antimicrobial activity of marine green algae extract against microbial pathogens. *Malays J Biochem Mol Biol.* 2018; 2(2):42–46. Accessed January 20, 2025. https://www.researchgate.net/publication/328073921_Antimicrobial_activity_of_marine_green_algae_extract_against
 55. Kousalya M, Rao GMN. Antimicrobial activity of marine algae. *J Algal Biomass Util.* 2015; 6(1):80–87. Accessed January 26, 2025. https://www.researchgate.net/publication/280518024_Antimicrobial_activity_of_Marine_algae
 56. Mussai P, Larsen J, Abdulwahed FA, Jeewon R. Ribosomal DNA sequence-based taxonomy and antimicrobial activity of *Prorocentrum* spp. (Dinophyceae) from Mauritius coastal waters, South-West Indian Ocean. *Mar Drugs.* 2023; 21(4):216. doi:10.3390/md21040216
 57. Mayer A, Rodríguez A, Tagliatela-Scafati O, Fusetani N. Marine pharmacology in 2009–2011: marine compounds with antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous systems, and other miscellaneous mechanisms of action. *Mar Drugs.* 2013; 11(7):2510–2803. doi:10.3390/md11080510
 58. Premarathna AD, Wijesekera SK, Jayasooriya AP. In vitro and in vivo evaluation of the wound healing properties and safety assessment of two seaweeds (*Sargassum ilicifolium* and *Ulva lactuca*). *Biochem Biophys Rep.* 2021;

- 26:100986. doi:10.1016/j.bbrep.2021.100986
59. Salehi B, Ata A, Sharopov F, *et al.* Antidiabetic potential of medicinal plants and their active components. *Biomolecules*. 2019; 9(10):551. doi:10.3390/biom9100551
60. Bharathi D, Lee J. Recent advances in marine-derived compounds as potent antibacterial and antifungal agents: a comprehensive review. *Mar Drugs*. 2024; 22(8):348. doi:10.3390/md22080348
61. Domanski A, Lavery AL. Ecosystem-service scaling techniques to evaluate the benefits of marine debris removal. *Environ Manage*. 2022; 70(1):64–78. doi:10.1007/s00267-022-01636-5
62. Rohl J, Zaharia A, Rudolph M, Murray RZ. The role of inflammation in cutaneous repair. *Wound Pract Res*. 2015; 23(1):8–15. Accessed December 16, 2024. Cambridge Media Journal PDF
63. Lin TK, Zhong L, Santiago J. Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. *Int J Mol Sci*. 2018; 19(1):70. doi:10.3390/ijms19010070
64. Udhav SB, Sivagurunathan MS. Antibiotic susceptibility testing: a review on current practices. *Int J Pharm*. 2016; 6(21):11–17. Accessed January 26, 2025. Academia.edu PDF
65. Gherardi G. Staphylococcus aureus infection: pathogenesis and antimicrobial resistance. *Int J Mol Sci*. 2023; 24(9):8182. doi:10.3390/ijms24098182
66. Subramani R, Sipkema D. Marine rare actinomycetes: a promising source of structurally diverse and unique novel natural products. *Mar Drugs*. 2019; 17(5):249. doi:10.3390/md17050249
67. Isaac A. An essay on the special adaptations of organisms to the estuarine environment. *ResearchGate*. 2021:1–6. doi:10.13140/RG.2.2.32276.83843
68. Youssef FS, Ashour ML, Singab ANB, Wink M. A comprehensive review of bioactive peptides from marine fungi and their biological significance. *Mar Drugs*. 2019; 17(10):580. doi:10.3390/md170100580
69. Wang C, Tang S, Cao S. Antimicrobial compounds from marine fungi. *Phytochem Rev*. 2020; 20(1):85–117. doi:10.1007/s11101-020-09805-5
70. Jeganathan P, Rajasekaran KM, Karuppusamy S. Antimicrobial activity and characterization of marine bacteria. *Indian J Pharm Biol Res*. 2013; 1(4):38–44. doi:10.30750/ijpbr.1.4.8
71. Alahmari AN, Hassoubah S, Alaidaroos BA. Sponges-associated marine bacteria as sources of antimicrobial compounds. *Novel Res Microbiol J*. 2022; 6(5):1802–1807. doi:10.21808/nrmj.2022.280424
72. Srinivasan R, Kannappan A, Shi C, Lin X. Marine bacterial secondary metabolites: a treasure house for structurally unique and effective antimicrobial compounds. *Mar Drugs*. 2021; 19(10):530. doi:10.3390/md19100530
73. Ponmudi P, Shanthi N, Kotteswari M, Subbiah M. Antibacterial activity of marine red alga *Grateloupia lithophila* Boergesen. *Int J Pharm Biol Sci*. 2018; 8(3):1125–1129. Accessed January 26, 2025. *International Journal of Pharmacy and Biological Sciences PDF*
74. Rodrigues D, Alves C, Horta A. Antitumor and antimicrobial potential of bromoditerpenes isolated from the red alga *Sphaerococcus coronopifolius*. *Mar Drugs*. 2015; 13(2):713–726. doi:10.3390/md13020713
75. Lauritano C, Ianora A. Marine organisms with anti-diabetes properties. *Mar Drugs*. 2016; 14(12):220. doi:10.3390/md14120220
76. Hanif N, Ardan MS, Tohir D, Setiawan A, de Voogd NJ, Farid M, Murni A, Tanaka J. Polybrominated diphenyl ethers with broad spectrum antibacterial activity from the Indonesian marine sponge *Lamellodysidea herbacea*. *J Appl Pharm Sci*. 2019; 9(12):1–6. doi:10.7324/JAPS.2019.91201
77. Lee JM, Yim M, Kim HS. Antioxidant, anti-inflammatory and antibacterial activities of a 80% ethanol-Symphyclocladia linearis extract. *Fish Aquat Sci*. 2022; 25(11):806–809. doi:10.48053/fas.2022.e52
78. Gunathilaka TL, Samarakoon K, Ranasinghe P, Peiris LDC. Antidiabetic potential of marine brown algae—a mini review. *J Diabetes Res*. 2020; 2020:1230218, 1-13. doi:10.1155/2020/1230218
79. Kumari A, Bharadvaja BN. A comprehensive review on algal nutraceuticals as prospective therapeutic agent for different diseases. *3 Biotech*. 2023; 13(2):44. doi:10.1007/s13205-022-03454-2

80. Remya RR, Samrot AV, Kumar SS. Bioactive potential of brown algae. *Adsorpt Sci Technol.* 2022; 2022:9104835, 1-13. doi:10.1155/2022/9104835
81. Omar FM, Godeh MM, Said AA. Study the effectiveness of different seasons of extracts *Colpomenia sinuosa* (Mertens ex Roth) Derbes et Soler against some types of human pathogenic bacteria. *EPH Int J Appl Sci.* 2019; 5(4):15–19. doi:10.53555/eijas.v5i4.109
82. Metwally NS, Maghraby AS, Farrag EK, El A, Rawi SM. Efficiency of the algae *Spirulina platensis* as antidiabetic agent. *World J Pharm Res.* 2015; 4(11):18–54. Accessed January 26, 2025. https://www.researchgate.net/publication/283480217_Efficiency_of_the_Alga_Spirulina_Platensis_as_Antidiabetic_Agent
83. Baldevia JH, Acanto RB, Conlu MT, Langcoy MG, Lirazan S, Mario J. Phytochemical screening and antibacterial activity of the selected species of mangroves. *JPAIR Multidiscip Res.* 2022; 49(1):65–80. doi:10.7719/jpair.v49i1.640
84. Saranraj JP. Mangrove medicinal plants: a review. *Am Eurasian J Toxicol Sci.* 2015;7(3):146–180. Accessed October 16, 2024. https://www.researchgate.net/publication/280385348_Mangrove_Medicinal_Plants_A_Review
85. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it. *Acta Pharm Sin B.* 2022; 12(7):3049–3062. doi:10.1016/j.apsb.2022.02.002