

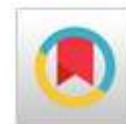


Potentials of the marine microbial enzymes in therapeutics

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Abstract



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About 70 % of the surface of Earth is covered with oceans and hosts an enormous variety of environmental, biological, and chemical standings. The marine environment consists of a comprehensive range of animals, plants, and microorganisms, which have several benefits in the biotechnological developments. This review aimed to investigate the potentials of using the marine microbial enzymes in therapeutics. The marine microbial species were uncultivable but recently, scientists cultivated certain seawater microbes effectively by a metagenomic technique. Several studies on the marine microbiome are undergoing and it can be assumed that approximately 91 % of the microbial species in the oceans are unidentified. The marine surroundings possess an exclusive environment with inimitable features and become a source of microbes fabricating many biocatalysts with no earthbound analog. The oceanic microbial enzymes have recently been found to be eco-friendly, rapid, inexpensive for construction, and can be used in several industries, including food, fabric, cleansers, medications, chemicals, dairy, biodiesel, and cosmetics. Compared with the mesophilic enzymes, the extremozymes execute a wider range of reactions and can act as natural substitutes for the mesophilic enzymes. The most relevant part of the worldwide economy is the therapeutic industry, whose market value is around 1.1 trillion US \$. The enzyme biocatalysis is a prevailing approach that can be implemented in an assortment of industries, and is a more discriminative tool, sustainable, and eco-friendly as compared with the chemical catalysis.

Keywords: Marine microorganisms, Marine enzymes, Natural substitute, Biotechnological developments, Therapeutic industry

1. Introduction

About 70 % of the surface of Earth is covered by oceans, which host an enormous variety of environmental, biological, and chemical standings ([Stincone and Brandelli, 2020](#)). The marine

environment consists of a comprehensive range of animals, plants, and microorganisms, which embraces bacteria ([Mohamed et al., 2021](#)), fungi, viruses, and other microbial species, including archaea,

cyanobacteria, eubacteria, actinomycetes, unicellular yeasts, microalgae, algae, and protozoa ([Beygmoradi and Homaei, 2017](#)). These microbial species have several benefits in the biotechnological developments ([Mohamed et al., 2021](#)). The structure of the oceanic microbial communities fluctuates daily, monthly, and yearly, due to the patterns of the ecological seasons. The factors that alter the microbial existence include nutrient accessibility, temperature, light intensity, eddies, and upwelling events, which regulate the microbial communities that are also predisposed strongly to their activity and growth rates ([Mena et al., 2020](#); [Auladell et al., 2022](#)). The oceanic microbial species were uncultivable, thus they obtained inadequate consideration by the researchers; however, recently, scientists effectively cultivated certain marine microbes using a metagenomic technique ([Kizhakkekalam and Chakraborty, 2019](#)), which is helpful in the study of the sea microbiota as well as exploring the novel enzymes without cultivation ([Rao et al., 2017](#)). When the taxonomic classification commenced, more than 1.2 million of the marine microbial species have already been categorized, and it can be assessed that in the oceans approximately 91 % of the microbial species are still unidentified ([Stincone and Brandelli, 2020](#)).

The marine surroundings possess an exclusive environment with inimitable features and become a source of the microbes fabricating many biocatalysts and bio-macromolecules with no earthbound analog ([Ghanbarzadeh et al., 2018](#)). In 2018, the worldwide market manufactured enzymes at the cost of 5.5 billion \$, which must reach 7.0 billion \$ in 2023, with a 4.9 % of compound annual growth rate (CAGR) for the extent of 2018-2023 ([Global Markets for Enzymes in Industrial Applications, 2018](#)). The extremophilic microbes in the oceanic surroundings can survive under extreme pressure, temperature, and salinity, thus proving their potential for the biotechnological progressions ([Di Donato et al., 2019](#)). The researchers are now attentive to exploring the novel enzymes in industry ([Bhatia et al., 2021](#)), which are more sustainable, eco-friendly, survive in extreme settings,

and substitute the chemical catalysis with the enzymatic processes ([Bhatia et al., 2021](#)). Seawater microbes produce several enzymes, which possess countless biological activities, including protease, xylanase, ligninase, lipase, keratinase, amylase, galactosidase, esterase, superoxide dismutase, phospholipase, fumarase, glucoamylase, pullulanase, gelatinase, luciferase, DNA ligase, chitinase ([Rao et al., 2017](#)), cellulase, agarase, carrageenase, and lyase, etc. ([Wijaya et al., 2021](#)).

The marine origin is testified as a significant source of microbes having pharmacologic implications, like anti-inflammatory, antioxidant, anti-diabetic ([Kizhakkekalam and Chakraborty, 2019](#)), antiviral (HIV), anti-cancerous, and anticoagulant, etc. ([Ellithey et al., 2014](#)). Currently, more than 120 formulations are used medically to treat the communicable diseases, cancer, and organ transplantation ([Kizhakkekalam and Chakraborty, 2019](#)). Industrially, the oceanic surroundings are observed as a possible reserve of huge bioactive metabolites. From marine sources, around 20,000 natural products, nine accredited drugs, and 12 drugs under clinical trials have been documented ([Al-Agamy et al., 2021](#)). An inadequate number of marine enzymes are used for several industrial and research purposes, due to the absence of inexpensive procedures for their large-scale construction ([Kim, 2015](#)). Considerable modifications have been reported between the homologous enzymes produced by the terrestrial and marine microbes, which are attributed to the presence of extreme aquatic environments, such as temperature, salinity, pressure, and lightning settings ([Nguyen and Nguyen, 2017](#)). Compared with the mesophilic enzymes, the extremozymes execute a wider range of reactions and can be considered as natural substitutes for the mesophilic enzymes under the harsh circumstances ([Mesbah, 2022](#)). The enzyme biocatalysis is a prevailing approach that can be executed in a variety of industries and is a more sustainable, ecological, and discriminative tool compared with the chemical catalysis. Marine enzymes can be used in several industries, including food, fabric, cleansers,

medications ([Wijaya et al., 2021](#)), chemicals, dairy, biodiesel, and cosmetics ([Nguyen and Nguyen, 2017](#)). The objective of this review was to explore the use of the oceanic microorganisms and their enzymes in therapeutics.

2. Marine microbial assortment

A previous study conducted by [Petersen et al., \(2020\)](#) reported that across the millennium, the progression of various creatures and biocoenosis have been created with alterations in their emergence, way of living, processing, absorbing, and secretion of the constituents into the atmosphere, which can be found in all the living organisms. Microorganisms play a substantial part in the seawater ecologies, such as the association with macroorganisms, biogeochemical cycles, and established chemical indications, which support the conscription of the oceanic invertebrates ([Zhang et al., 2019](#)). The forms of marine microbial assortment relate to the communities and nearby situations that encompass latitude, depth, and season ([Galand et al., 2018](#)). The marine microorganisms comprise viruses (stereotypically 4×10^{30} cells and 10^7 viruses/ ml), archaea (1.3×10^{28} cells), bacteria (3.6×10^{29} cells), fungi, and microalgae ([Luna, 2015](#)). The marine bacterial biomass spreads into all the maritime bionetwork including tidal areas, seafloors, and brines, etc., which internationally accounts for around 5.4×10^{29} cells ([Di Donato et al., 2019](#)). A previous study conducted by [Rao et al., \(2017\)](#) revealed that more than 98 % of the marine microorganisms have not been cultivated, in addition their enzymes and bioactive compounds are all wasted by the conventional culturing techniques. Metagenomics has been introduced as a tool for analyzing and discovering the novel enzymes from the various environmental sources ([Mendes et al., 2017](#)).

3. Sources of the marine microbial species

Marine water has different areas like coral reefs, mangrove ecologies, deep sea, and extreme settings ([Paulus, 2021](#)). Microorganisms of the marine ecosystem are classified according to these areas

([Baharum et al., 2010](#)). The mucus fabricating bacteria are present in the coral reef areas ([Lee et al., 2016](#)), the nitrogen-fixing and photosynthetic bacteria exist in the mangrove ecologies ([Inoue et al., 2020](#)), the adequate substrate-consuming bacteria live in the deep sea ([Baharum et al., 2010](#)), and the bacteria that survive in the extreme circumstances (extremophiles) are present in the extreme situations ([Schröder et al., 2020](#)). These sources are described below in details.

3.1. Coral reefs

Coral reefs that occupy beneath 0.1 % of the surface of the ocean's biosphere are defined as the most varied creatures on the Earth and are frequently known as the "tropical forest of the sea" ([Li, 2019](#)). Coral reefs are one of the utmost miscellaneous bionetworks, which act as a habitat for an assessed 25 % of the entire identified species of the aquatic system ([Glasl et al., 2018](#)). They offer an environment for a minimum of 1000 coral species, 500,000 multicellular species, and 6000 designated fishes. These faunas are enclosed by various plentiful bacteria, viruses, archaea, and micro-eukaryotes, which are collectively present in the exterior surface microbiota ([Chiarello et al., 2020](#)). The roles of capturing, retaining, and utilizing nutrients and trace elements in the coral reefs are performed by the assorted groups of nonparasitic and host-associated microorganisms, which permit the aquatic ecology to flourish like a desert ([Vanwonterghem and Webster, 2020](#)). A metagenomic study from the forereef sites illustrated that between daytime and nighttime, the composition of the microorganisms is more different when collecting samples from distant reefs. In the daytime, *Psychrobacter* spp. is more plentiful, while at night time, the *Halomonas*, *Alteromonas*, and *Roseobacter* species are present in the coral reefs ([Kelly et al., 2019](#)). Similarly, a genome-centric metagenomic analysis from the inshore coral reefs reported the identification of four bacterial clusters, namely Alphaproteobacteria, Chloroflexota, Bacteroidota, and Firmicutes, which are correlated to the variations in the environment ([Glasl et al., 2020](#)). Another study reported by [Weber and Apprill, \(2020\)](#) has sequenced

the small subunit rRNA genes of the reef seawater, which revealed that *Synechococcus* and *Prochlorococcus* spp. are constantly raised at night. This fluctuates over time concerning the concentration of silicate, nitrite, and temperature, whereas in the daylight, the alpha assortment of archaea and bacteria are notably higher near the coral brine and reef depth.

3.2. Mangrove ecologies

On earth, mangrove forests are the foremost prolific and environmentally significant bionetworks. These are present in the biosphere's tropical and subtropical shorelines, which live in brackish water and are the only woody halophytes ([Jin et al., 2019b](#)). Mangrove forests reside around 0.5 % of the shoreline, store about 10 to 15 % of the worldwide carbon, and are known as “Blue carbon reservoirs” ([Zhang et al., 2019](#)). Mangroves offer substantial roles in the aquatic system, such as sustaining the diversity of the environment, improving the quality of the littoral water, and resisting wave destruction ([Zhao et al., 2019](#)). Later, [Allard et al., \(2020\)](#) added that mangroves also yield treasured facilities for humans, such as plant products (*i.e.*, timber, runoff earthbound filtration, etc.), and territory for the different species of fisheries. As indicated in Table (1), these roles and facilities are performed by the various mangrove microbes (*i.e.*, fungi, protists, archaea, and bacteria).

3.3. The deep sea

According to [Zhang et al., \(2018\)](#), approximately 75 % of the entire oceanic volume is covered by the deep sea, which is the sea with a depth of > 1000 m. The temperature of the deep-sea water is ~1–3 °C (excluding hydrothermal vents), pH is ~7.8–7.9 (examined in most sites), salinity is ~35, absence of sunshine, which exists only at the depth of 250 m of the aquatic water, and the aquatic water pressure is about >1000 atmosphere. The microorganisms present in the deep sea endure in the extreme surroundings by the exclusive biological metabolic pathways. Around 50 years earlier, natural products of > 30,000 from the oceans have been explored, where approximately 2 %

of these products are derived from the deep-sea microorganisms ([Wang et al., 2020](#)). The deep sea is a huge biosphere encompassing half of the sea's microorganisms. Using the non-culture-based techniques, we realized that sediments and water of the deep sea comprise extremely miscellaneous bacteria, as demonstrated in Table (2) ([Zhang et al., 2018](#)).

3.4. Extreme situations

Nearly all parts of the Earth originate life, including the extreme environments categorized by the extreme situations of any abiotic limitation(s). These limitations significantly fluctuated comparatively for a short duration. The examples comprise the oligotrophic oceans, tidal zones, the deep sea, and deserts ([Bang et al., 2018](#)). The extreme settings incorporated a variety of physical limitations, including temperature, salinity, pressure ([Zhu et al., 2020](#)), pH, radiation, metals, oxidative stress, chemicals ([Dalmaso et al., 2015](#)), vacuum, and absence of water ([Di Donato et al., 2019](#)). The organisms that are proficient in the existing specific ecologies, such as temperatures, pH, high pressure, salinity ([Zhu et al., 2020](#)), high ionic strength, UV radiations, and anaerobic surroundings ([Poli et al., 2017](#)), are known as “Extremophiles” ([Zhu et al., 2020](#)).

Numerous aquatic environments originate diverse types of poly-extremophiles, such as the cold seas in the Antarctic or Arctic regions, a few hypersaline lakes of an oceanic origin, shallow vents, the ocean depths, the undersea hydrothermal vents, and the black smokers ([Di Donato et al., 2019](#)). Across the preceding few eras, the extremophiles have gained the fascination of several scientists for the exploration of novel bioactive constituents, like biocides and enzymes (extremozymes), which will be used in the therapeutic, agricultural, nutriment, bioenergy, chemical, cosmetic, and fabric industries of the global economy ([Di Donato et al., 2019](#)). The microorganisms isolated from the marine extreme conditions are presented in Table (3).

Table 1: Isolated microorganisms from the mangrove ecologies

Sample sites	Locations	Techniques	Microorganisms	References
Mangrove and non-mangrove sediment.	Beibu Gulf, South China Sea.	Metagenomics analysis.	Proteobacteria, Bacteroidetes, Firmicutes, Methanosarcinaceae, <i>Vibrio</i> and <i>Dehalococcoides</i> .	(Zhao et al., 2019)
Mangrove sponges.	New Washington, Aklan, Philippines.	Morphological observation.	22 Genera of ascomycetes, 18 genera of asexual morphs, 2 genera of basidiomycetes, 21 morphospecies of <i>Mycelia sterilia</i> , 1 unidentified yeast species, and 11 unidentified hyphomycetes.	(Calabon et al., 2019)
Mangrove sediments.	Southeastern China.	High-throughput DNA sequencing.	Prokaryotic alpha diversity, beta diversity, <i>Gammaproteobacteria</i> , <i>Deltaproteobacteria</i> , <i>Chloroflexi</i> , and <i>Euryarchaeota</i> .	(Zhang et al., 2019)
Mangrove.	Shenzhen, Yunxiao, Zhanjiang, Hainan, Hongkong, Fangchenggang, and Beihai.	16S rRNA gene amplicon sequencing and GeoChip.	<i>Gamma proteobacterium</i> , <i>Woeseia</i> , <i>Neisseria</i> , <i>Ruegeria</i> , <i>Rhodococcus</i> , <i>Desulfotomaculum</i> , <i>Gordonia</i> , <i>Neisseria</i> and <i>Treponema</i> .	(Meng et al., 2022)
Mangrove sediments.	Zhenzhu Harbor, Yuzhouping, Maowei Sea, Qinzhou Harbor, Beihai City, and Shankou along the coastline of Beibu Gulf in Guangxi province, China.	16S rRNA gene sequencing.	<i>Proteobacteria</i> , <i>Bacteroidetes</i> , <i>Chloroflexi</i> , <i>Actinobacteria</i> , <i>Parvarchaeota</i> , <i>Acidobacteria</i> , <i>Cyanobacteria</i> , <i>Desulfococcus</i> , <i>Arcobacter</i> , <i>Nitrosopumilus</i> and <i>Sulfurimonas</i> .	(Gong et al., 2019)

Table 2: Isolated microorganisms from the deep sea

Sample sites	Locations	Techniques	Microorganisms	References
Deep sea surface sediments.	Arctic, South, and North Pacific, South and North Atlantic, Indian, and Antarctic Oceans.	16S rRNA gene sequencing.	<i>Gammaproteobacteria</i> , named “JTB255-Marine Benthic Group” (now the candidate order Woeseiales).	(Hoffmann et al., 2020)
Deep sea sediments.	Northern South China Sea.	Metagenomics.	Phyla TA06 and LCP-89, <i>Lokiarchaeota</i> , <i>Heimdallarchaeota</i> , and a newly described phylum B38.	(Huang et al., 2019)
Deep sea asphalt seeps	Chapopote Knoll, Mictlan Knoll.	Metagenomics and imaging analyses.	Species of sponges, and methanotrophs.	(Rubin-Blum et al., 2019)
Deep sea sediments.	The westernmost Mediterranean.	High-throughput sequencing.	<i>Bacillus</i> , <i>Micrococcus</i> , <i>Planococcaceae</i> , <i>Anaerolineaceae</i> , <i>Planctomycetaceae</i> , <i>Microlunatus</i> , <i>Microbacterium</i> , <i>Propionibacterium</i> , <i>Fictibacillus</i> , <i>Thalassobacillus</i> , and <i>Bacteroides</i> .	(Jroundi et al., 2020)
Deep-sea.	Atlantic Ocean (seamounts and ridges).	16S rRNA gene high-throughput sequencing.	Biofilm forming bacterial and archaeal communities on macro-debris.	(Woodall et al., 2018)

Table 3: Isolated microorganisms from the extreme situations

Sample sites	Locations	Techniques	Microorganisms	References
Shallow-water hydrothermal vents.	Panarea.	Culturing.	Antibiotic and heavy metal-resistant <i>Actinobacteria</i> , <i>Gammaproteobacteria</i> , <i>Alphaproteobacteria</i> , and <i>Firmicutes</i> .	(Arcadi et al., 2022)
Shallow-water hydrothermal vent.	Offshore in northeast Taiwan.	Culturing and 16S rRNA gene sequencing.	Phylum Firmicutes and genus <i>Bacillus</i> .	(Gurunathan et al., 2021)

Deep-sea hydrothermal region.	South Atlantic Ocean.	High-throughput sequencing, gas chromatography-mass spectrometry, and gravimetric analysis.	Oil degrading <i>Pseudomonas</i> , <i>Nitratireductor</i> , <i>Acinetobacter</i> , and <i>Brevundimonas</i> .	(Ma et al., 2021)
Deep-sea hydrothermal environments.	Northwest Indian Ocean.	16S rRNA gene sequence analysis.	<i>Sulfurimonas hydrogeniphila</i> sp. nov.	(Wang et al., 2021)
Shallow-sea hydrothermal vent system.	Panarea Island, Tyrrhenian Sea off the southwestern coast of Italy.	Culturing and 16S rRNA gene sequencing.	<i>Blastopirellula retiformator</i> sp. nov.	(Kallscheuer et al., 2020)
Hypersaline lake.	Aiding Lake, China.	Culturing and 16S rRNA gene sequencing.	Phylum <i>Actinobacteria</i> , <i>Firmicutes</i> , <i>Proteobacteria</i> , and <i>Rhodothermaeota</i> , and Order <i>Actinopolysporales</i> , <i>Alteromonadales</i> , <i>Bacillales</i> , <i>Balneolales</i> , <i>Chromatiales</i> , <i>Glycomycetales</i> , <i>Jiangellales</i> , <i>Micrococcales</i> , <i>Micromonosporales</i> , <i>Oceanospirillales</i> , <i>Pseudonocardiales</i> , <i>Rhizobiales</i> , <i>Streptomycetales</i> , and <i>Streptosporangiales</i> . Predominant phyla included <i>Actinobacteria</i> and <i>Firmicutes</i> , and the predominant genera included <i>Actinopolyspora</i> , <i>Gracilibacillus</i> , <i>Halomonas</i> , <i>Nocardiopsis</i> , and <i>Streptomyces</i> .	(Guan et al., 2020)
Saline-alkaline crater-lake.	Dziani Dzaha (Mayotte, Indian Ocean).	Morphological, ultrastructural, and molecular methods.	<i>Picocystis salinarum</i> , <i>Desertifilum dzianense</i> sp. nov., <i>Sodalinema komarekii</i> gen. nov., sp. nov., <i>Sodaleptolyngbya stromatolitii</i> gen. nov., sp. nov., and <i>Haloleptolyngbya</i>	(Cellamare et al., 2018)

			<i>elongata</i> sp. nov.	
Hypersaline environment.	TuzGözü Lake, Turkey.	Culturing and PCR.	<i>Bacillus megaterium</i> strain CTBmeg1.	(Akçay and Kaya, 2019)
Hypersaline lake.	Aran-Bidgol-Iran.	Morphological, physiological, biochemical testing, and 16S rRNA gene sequencing.	<i>Bacillus</i> , <i>Halomonas</i> , <i>Oceanobacillus</i> , <i>Salinicoccus</i> , <i>Thalassobacillus</i> , <i>Ornithinibacillus</i> , <i>Halobacillus</i> , <i>Salicola</i> , <i>Virgibacillus</i> , <i>Aerococcus</i> , <i>Arthrobacter</i> , <i>Idiomarina</i> , <i>Paraliobacillus</i> , <i>Staphylococcus</i> , <i>Acinetobacter</i> , <i>Aneurinibacillus</i> , <i>Brevibacillus</i> , <i>Brevundimonas</i> , <i>Chromohalobacter</i> , <i>Gracilibacillus</i> , <i>Jeotgalicoccus</i> , <i>Kocuria</i> , <i>Marinilactibacillus</i> , <i>Marinobacter</i> , <i>Microbacterium</i> , <i>Paenibacillus</i> , <i>Paracoccus</i> , <i>Piscibacillus</i> , <i>Pseudomonas</i> and <i>Sediminibacillu</i> .	(Didari et al., 2020)

4. Marine microbial enzymes

The microorganisms that can endure the various extreme settings such as temperature, pH, salinity, or pressure, are known as “Extremophiles” and the enzymes produced by these extremophiles are recognized as “Extremozymes” [\(Zhao et al., 2021\)](#). Compared with the mesophilic enzymes, the extremozymes execute a wider range of reactions and can be natural substitutes for the mesophilic enzymes [\(Mesbah, 2022\)](#). Due to the sophisticated activity and stability beneath the extreme situations, the extremozymes obtained from the deep-sea extremophiles have extensive diverse applications in industries, including pharmacological, nutriment, agriculture, beverage, forage, cleaner, fabric, leather,

biomining, and pulp industries [\(Jin et al., 2019a\)](#). Rendering to their natural habitation, the extremophiles are categorized into halophilic, psychrophilic, xerophilic, acidophilic, barophilic, thermophilic, alkaliphilic, radiophilic, and metalophilic [\(Mesbah, 2022\)](#). A previous study conducted by [Sarmiento et al., \(2015\)](#) reported that genetic engineering or bioprospecting of extreme situations makes it possible to perceive and invent eco-friendly, inexpensive, and sustainable extremozymes compared with chemical catalysis. Due to their substantial capabilities, the extremozymes such as proteinase, xylanase, lipase, cellulase, glucanase, pectinase, chitinase, α -amylase, esterase, pullulanase, mannanase, peroxidase, glucoamylase, and oxidase, can be applied industrially [\(Dumorné et al., 2017\)](#).

Several previous literatures reported that the microbial metabolic and enzymatic potential depends upon a distinction in the structure of the microbial community

([Balmonte et al., 2019](#); [Balmonte et al., 2021](#)). The commercial uses of the marine extremozymes are depicted in Table (4).

Table 4: Commercial uses of the marine enzymes

Sources	Marine enzymes	Commercial uses	References
<i>Bacillus amyloliquefaciens</i> strain S13 isolated from marine brown alga.	Keratinase.	Leather and poultry industry.	(Hamiche et al., 2019)
Clone of a marine metagenomic library.	Laccase.	Dye decolorizing industry.	(Yang et al., 2018)
Marine bacterium <i>Bacillus sp.</i> Alg07.	Alginate lyase.	Production of mannuronic oligosaccharides and polyG blocks from alginate.	(Chen et al., 2018)
Filamentous fungi <i>Geomyces sp.</i> F09-T3-2 isolated from marine sponges.	Pectinase.	Food processing industry.	(Poveda et al., 2018)

5. Potentials of the marine microbial enzymes in therapeutics

The most relevant part of the worldwide economy is the therapeutic industry, which is responsible for investigating ([Milanesi et al., 2020](#)), developing, manufacturing, and advertising several pharmacological medications ([Peña et al., 2021](#)), vaccines, and therapies, to cure the common and sporadic ailments ([Milanesi et al., 2020](#)). Yearly, the worldwide therapeutic market value is around 1.1 trillion US\$, and approximately 35 % of these medications are initiated from the natural products, such as herbs (25 %), microorganisms (13 %), and animals (3 %), which serve as enormous sources for expansion of the novel medications globally ([Calixto,](#)

[2019](#)). Based on the chemical structure of the enzymes, antibodies, peptides, oligonucleotides, small molecules, natural products, and combination of medications categorization, the Food and Drug Administration (FDA) in 2018 permitted the use of about 59 novel medicines, including 17 biological and 42 chemical entities ([de la Torre and Albericio, 2019](#)). In 2019, the US FDA approved 48 novel medicines, including 10 biological and 38 chemical entities ([de la Torre and Albericio, 2021](#)). The marine biosphere is the prime unexplored source for investigation of the innovative natural products that originated the invention of medicines. Meanwhile, nature is also deliberated as the “Primordial Pharmacy,” because it is the source of the innovative products used for the treatment of numerous ailments, such as Acquired

immunodeficiency syndrome (AIDS), cancer, and a huge diversity of bacteriological, mycological, and viral diseases ([Ruocco et al., 2016](#)). Moreover, these products also act as anti-microtubule, anti-tumor, anti-hypertensive, anti-cytotoxic, and anti-proliferative drugs ([Suarez-Jimenez et al., 2012](#)). Enzyme biocatalysis is a predominant approach, which can be implemented in a range of industries for the construction of medicines, biofuel, nutriment, and biochemicals, etc. Furthermore, [Kim, \(2022\)](#) recently added that in contrast to the chemical catalysis, enzyme biocatalysis is a more discriminative, sustainable, and ecofriendly tool. A previous research conducted by [Nguyen et al., \(2021\)](#) highlighted that 4-OH atorvastatin synthesized from atorvastatin by using the bacteriological CYP102A1 peroxidase is useful for treatment of the hyperlipidemia and cardiac diseases. Similarly, [Nam, \(2022\)](#) revealed that a glycosidic hydrolase named lysozyme degrades the bacterial cell wall that is made up of peptidoglycan and is reported as a natural antimicrobial constituent. Chemical nature of the marine water is significantly closer to the blood plasma of humans, which is the reason that the oceanic microbial enzymes are considered suitable for the human therapeutic execution with the least side effects ([Barzkar et al., 2021](#)). The enzymes can be utilized as therapeutic agents for cancer by using different mechanisms, such as decreasing the inflammation in the tumor tissue, preventing cellular death of the carcinoma cells, and averting the contagious pathogens in the cancer tissues, in addition to vital controlling of the catalytic enzyme activity at the site of the tumor, etc. For instance, arginine deaminase and asparaginase can be used effectively in treating liver carcinoma and acute lymphoblastic leukemia, respectively ([Sharifi et al., 2020](#)). A research study reported by [Orabi et al., \(2020\)](#) stated that the extracellular L-glutaminase enzyme obtained from the newly isolated marine *Bacillus subtilis* OHEM11 (MK389501) has anti-cancerous activity against several cell lines, including NFS-60, MCF-7, and HepG-2. The same study verified that L-glutaminase could be implemented in the pharmacological, food dispensation, and many other biotechnological industries. Another study

conducted in Saudi Arabia by [Ameen et al., \(2020\)](#) isolated the L-asparaginase-producing *B. subtilis* from the Red Sea marine sponges and conveyed that this L-asparaginase (partially purified 100 µg/ ml) has presented positive anti-cancerous activities against MCF-7, HepG2, and HCT-116 cancer cell lines. Similarly, researchers of [El-Gendy et al., \(2022\)](#) study have isolated several strains of the marine *Streptomyces* (i.e., *Streptomyces* sp. MORSY 50, 17, 36, 25, 45, and 22) from soft corals of the Red Sea, Egypt. In addition, they reported the production of several enzymes, such as alkaline protease, tyrosinase, L-asparaginase, L-methioninase, and L-glutaminase; with their anti-proliferative effects on the colon and liver carcinoma cell lines, antimicrobial activity against fungi and bacteria, anti-biofilm forming activities on the multidrug-resistant *Pseudomonas* spp. and methicillin-resistant *Staphylococcus aureus*, and antiviral effects on the Hepatitis C virus. The potentials of the marine enzymes in therapeutics are described in Table (5).

6. Scope, significance, and limitations of the marine microbial enzymes

The marine microbial species that flourish in the hostile environment are the probable sources of the enzymes that have a variety of catalytic activities, and are fascinating for several commercial implementations, such as the manufacturing of medicines and biofuels ([Zhang et al., 2021](#)), leather, nutrition, forage, cleansers ([Qeshmi et al., 2020](#)), dairy, cosmetic, fabric ([Nguyen and Nguyen, 2017](#)), paper ([Daniotti and Re, 2021](#)), synthesis of novel polymeric constituents, agrochemicals, and chemicals ([Nguyen and Nguyen, 2017](#)), and as catalysts for bioremediation ([Zhang et al., 2021](#)). The marine enzymes have much significance in the industrial implementations, due to their stability at high temperatures, salinity, and pH, and they have novel chemical and stereochemical possessions ([Dumorné and Severe, 2018](#)). The limitations of exploring the marine ecology include the difficulties in accessing the deep sea, problematic analysis, and the complex

Table 5: Potentials of the marine microbial enzymes in therapeutics

Samples	Sources	Marine enzymes	Therapeutic implementations	References
Water samples from the Mediterranean Sea.	<i>Bacillus subtilis</i> OHEM11.	L-glutaminase.	Anti-cancerous activity against NFS-60, HepG-2, and MCF-7 cancer cell lines.	(Orabi et al., 2020)
Strains isolated from Red Sea, Egypt.	<i>Aspergillus terreus</i> .	L-asparaginase.	Anticarcinogenic activity against HCT-116, Hep-G2, and MCF-7 cell lines.	(Hassan et al., 2018)
Seawater and sediment samples from the Al-Marabi coast, the Red Sea, Saudi Arabia.	<i>Halomonas meridian</i> .	L-glutaminase.	Anticancerous effects on colorectal adenocarcinoma cells, LS 174 T and HCT 116.	(Mostafa et al., 2021)
Sponges from the Red Sea, Saudi Arabia.	<i>Bacillus subtilis</i> .	L-asparaginase.	Anticarcinomic activity against HCT-116, MCF-7, and HepG2 cancer cell lines.	(Ameen et al., 2020)
Sediment samples from the Red Sea, Saudi Arabia.	<i>Bacillus velezensis</i> .	Glutaminase-free L-asparaginase.	Anti-breast cancer activity against MDA-MB-231 cell line.	(Mostafa et al., 2019)
Water samples from the Red Sea off the southwestern coast of Saudi Arabia.	<i>Bacillus licheniformis</i> .	L-asparaginase.	Antineoplastic activity against MCF-7 breast, HCT-116 colon, and HepG human cancer cell lines.	(Alrumman et al., 2019)
Marine sediment samples from Al-Jouf, Saudi Arabia.	<i>Aspergillus terreus</i> .	Chitinase.	Antimicrobial activity against <i>Aspergillus niger</i> , <i>A. oryzae</i> , <i>Penicillium oxysporium</i> , <i>Rhizocotonia solani</i> , <i>Candida albicans</i> , <i>Fusarium solani</i> , <i>Staphylococcus aureus</i> , <i>Salmonella typhi</i> and <i>Pseudomonas aeruginosa</i> .	(Farag et al., 2016)
Water samples from the Red Sea, Saudi Arabia.	<i>Bacillus licheniformis</i> .	L-asparaginase.	Anticarcinogenic effects on MCF-7, HCT-116 cells, and HepG-2 cells.	(Alrumman et al., 2019)
Aquatic sediment samples from	<i>Bacillus subtilis</i> strain JK-79.	L-glutaminase.	Cytotoxic activity on Jurkat, K562, and U932 Leukemic	(Kiruthika and

Parangipettai, India.			cell lines as well as MCF-7, HCA 7, and OV1063 cell lines.	Swathi, 2019
Marine sponge isolates from Egypt.	<i>Bacillus circulans</i> , <i>Bacillus safensis</i> , <i>Bacillus pumilus</i> .	L-asparaginase.	Antineoplastic effects on PC-3, HepG-2, and MCF-7 cell lines.	(Bakeer et al., 2022)
Mangrove water samples from the Red Sea, Egypt.	<i>Bacillus sp. DV2-37</i> .	L-glutaminase.	Antitumor activity against HCT-116, MCF-7, and HepG-2 cell lines.	(Gomaa, 2022)
Sea mud from Beibu Gulf, South China Sea.	<i>Bacillus velezensis</i> Z01.	Velegfibrinase.	Thrombolytic effects on mouse tail thrombosis.	(Zhou et al., 2022)

taxonomic classification. These are in addition to the probable errors that compromise the whole drug discovery procedure, which are attributable to the unreproducible isolation methods following the detection of new bioactive compounds ([Daniotti and Re, 2021](#)).

Conclusion

This review has presented the potential of marine microbial enzymes in therapeutics. The marine microbial enzymes have meaningful advantages in the biotechnological industries and can act as substitutes for the mesophilic enzymes in therapeutics, due to their minimum side effects. The therapeutic industry is the most important part of the worldwide economy and up till now, approximately 35 % of the medicines have originated from natural products. Numerous researchers have explored the marine microbial enzymes obtained from different sample collection sites. They checked their anti-cancerous activities against diverse cell lines in the past seven years (2016-2022), which indicate that these enzymes will be used as anticancer agents in the future, but excessive human trials are urgently needed. The future perspectives include studying the exploration of more novel marine enzymes from the different sites of the oceans,

identifying the innovative and more feasible methods of isolation, and determining their potentials to treat more un-curable diseases.

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Conflict of interest

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