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REVIEW

Blue Economic Potency of Marine Invertebrates for Bio-drug Discovery

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Abstract

In terms of focus, promising results obtained from extensive investigations showed that the biodiversity of marine invertebrates has been documented. This poses the marine ecosystem as a hopeful resource in the discovery of novel compounds, with an ideal starting point in scaffolding additional screening of marine natural products (MNPs), especially to face the rise in the burden of diseases and treatment failure. A wide range of antimicrobial, antiviral, anticancer, anti-inflammatory, antiparasitic, neuroprotective, analgesic, antimalarial and other agents of marine origin have been pursued in the control and management of diseases. In the current review, we will focus on figuring out drugs from well-known marine species within invertebrates (e.g., sea stars, sea sponges, sea cucumbers, sea urchins, sea worms, soft corals, sea hares, and sea worms). Moreover, we will discuss the current status and challenges being faced in the marine drug discovery field, the investment in the marine bio-drug sector, and how it provides the market with novel products for treating numerous human diseases.

Keywords: Bio-drugs, Invertebrates, Mangrove, Mollusks, Sea cucumber, Sea hares, Sea star, Sea urchins, Sea worms, Seaweeds, Soft corals, Sponge

1. Introduction

Natural products (NPs) account for more than half of all pharmaceuticals, particularly anti-infective and anticancer therapies. So far, over 400,000 NPs have been discovered, with 10 % originating from marine creatures or their microbial symbionts. Marine molecules have a faster pace of chemical innovation, with almost fourfold the potential to become medications as their terrestrial counterparts. Despite the brief history of research, roughly 15 marine NP-based medicinal products have been licensed and are in clinical use. However, the marine discovery process is lengthy, dangerous, and expensive, with chronic underfunding; thus, the oceans stay neglected for biomedical research (Sigwart et al., 2020).

Antibiotic resistance represents a key concern for harmful bacterial infections (Shaaban et al., 2020). As a result, the quest for new antimicrobial substances from alternative sources, particularly nanoparticles (NPs), has become critical (Abouelkheir et al., 2016; Ibrahim et al., 2020a). Furthermore, different illnesses with various clinical damage (such as viral attacks, malignancy, and so on) must be regulated by NPs to minimize negative consequences (Zhang et al., 2018). Cancer is still one of the most fatal illnesses in the world. New medicines with unique mechanisms of action are desperately needed. As a result, substantial research for new

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anticancer medications from natural sources, including plants, microorganisms, and aquatic creatures, has been done (Khalifa et al., 2019).

The aquatic ecosystem is a vast storehouse of biodiversity and a valuable source of chemical substances (such as tannins, polysaccharides, fatty acids, terpenes, peptides, polyphenols, pigments, and so on), some of which have significant economic worth. In the desperate search for new pharmaceuticals, marine-based drug development has advanced considerably over the last several decades, and there are now several approved marine natural products (MNPs) to treat a variety of tumors (renal, mammary, lung, bladder, melanoma, prostate, osteosarcoma, and lymphoid) and pain, with an additional collection of promising leads in clinical trials (Papon et al., 2022). Maritime invertebrates, in specific, have been classified into more than thirty phyla. They constitute the majority of the macroscopic life in the oceans. Arthropoda, Porifera, Mollusca, Platyhelminthes, Nematoda, Cnidaria, Annelida, and Echinodermata are the primary invertebrate phyla (Karleskint et al., 2012). There has been a rise in study on marine crustaceans, mollusks, and echinoderms throughout the past two centuries, with a focus on secondary metabolites with attractive biological features (Ibrahim et al., 2020a, 2020b, 2020c, 2020d).

Drug demand and supply are critical issues for the medical industry, which may be addressed by new advances in pharmaceutical research centred on marine species. More than 20,000 chemicals have been obtained in various aquatic creatures over the previous five decades (Pandey, 2016). The discovery and supply of MNPs with poor bioavailability and complicated structure, as well as their production for preliminary and clinical research and commercialization, are connected with high prices, unsustainable practices, and serious environmental issues (Papon et al., 2022). All of the preceding considerations illustrate why investing in the aquatic biodrug sector as a blue economy is critical. This investment offers novel and effective pharmaceuticals to the drug market that benefit human health by tackling numerous essential diseases and chronic disorders (Sruthi et al., 2020; MBMOR, 2022). Fortunately, several companies have participated in this industry. Furthermore, significant firms are active in strategic alliances with companies that complement their product portfolio, such as product authorizations, deals, and partnerships (Marine Biotechnology Market MBM, 2022).

Therefore, the main objective of the current review is to focus on the of bio-drugs (such as antimicrobial, antiviral, antimicrobial, anticoagulant, anti-angiogenic, antitumor, anticancer, antihypertension, anti-inflammatory, antioxidant, antithrombotic agents, etc.) obtained from various marine species within invertebrates (sea stars, sea sponges, sea cucumbers, sea urchins, soft corals, sea hares, sea worms, etc.). It will also go over the economic importance of marine creatures in the biodrug investment area.

2. Biodiversity of marine ecosystem and drug discovery

An aquatic environment is essentially an ecological niche for a wide range of living species with varying physiologies and adaptability to their surroundings (Malve, 2016). In fact, the globe's seas are the epicenter of the world's biodiversity, including 34 of the 36 phyla of life. In comparison, only 17 phyla occupy the land. Considering this fact, drug development should have started in the seas' diverse environment. The macroscopic creatures and plants that became accustomed to all of the world's oceans (polar, temperate, and tropical) account for a large portion of this diversity. On coral reefs, diversity of species reaches extremely high densities, occasionally exceeding 1000 species per square meter (Carter, 2002).

The oceans hold over 80 % of the world's diverse plant and animal species. Bioactive chemicals (e.g., oils and cosmetics) are found in marine species such as sponges, tunicates, fishes, soft corals, nudibranchs, sea hares, mollusks, echinoderms, bryozoans, prawns, shells, sea slugs, and marine microbes. Fish oils are a classic example of a sea-derived product that has been used for centuries. Bergmann formally reported the first biologically active MNPs in late 1950 (Bergmann and Stempien, 1957).

Given that the marine environment is an exceptional repository of novel bioactive NPs with structural and chemical properties not found in earth-based NPs, aquatic creatures represent an extensive supply of nutritional supplements and possibly suitable candidates for the medical treatment of a variety of human illnesses (Sruthi et al., 2020). The ocean offers huge prospects for new compound discovery because it has approximately 13,000 molecules described, 3000 of which have significant characteristics (Vignesh et al., 2011). MNPs are secondary metabolites in general. They are not produced by biological or typical metabolisms and serve no primary function in a species' growth, development, or proliferation (Martins et al., 2014). 63 % of all novel medications are naturally derived (that is, modified NP, unmodified NP, or synthetic

molecule having an NP as a pharmacophore). From 1981 to 2008, around 68 % of all anti-infection medications (including antibacterial, antiviral, antiparasitic, and antifungal substances) and 63 % of anticancer drugs were naturally derived (Malve, 2016).

It was discovered in the late 1970s that maritime plants and animals are genetically and biochemically distinct. Approximately 15,000 such distinctive natural substances have been identified, with sponges accounting for 30 % of these compounds (Murti and Agrawal, 2010). Imhoff et al. (2011) provided the first evidence that naturally occurring nucleosides might include sugars other than ribose and deoxyribose. It has been demonstrated that chemicals from the sea can be taken by humans with little modifications (Vignesh et al., 2011).

Microbes are the current target of marine biodrugs. This involves the identification of novel pharmacological possibilities derived from marine microorganisms (Mayer et al., 2010). Some studies have been published on the antibacterial activity of marine macroorganisms gathered from the Indian coastline. *Streptomyces* sp. has been the most extensively researched microbial species from Indian coastal waters as an antibiotic source. The richness of microorganisms in sponges capable of creating novel pharmacologically active compounds (Anand et al., 2006).

Polyphenols, polysaccharides, alkaloids, peptides, and terpenoids represent a number of potentially beneficial metabolites obtained from different marine organisms that display an array of antioxidant, antitumor, and immunostimulatory activities (Khalifa et al., 2019), as well as other crucial illnesses in humans (Choudhary et al., 2017).

3. Marine invertebrates

About 7000 MNPs were discovered from aquatic invertebrates: 33 % from sponges, 18 % from coelenterates (sea whips, sea fans, and soft corals), and 24 % from participants of other invertebrate phyla such as ascidians (tunicates), opisthobranch mollusks (nudibranchs, sea hares, etc.), echinoderms (starfish, sea cucumbers, etc.) and bryozoans (moss animals) (Periyasamy et al., 2012).

In order to defend themselves from predators, marine invertebrates develop special chemical compounds in their surroundings. These kinds of secondary metabolites are currently thought to be effective medications for illness treatment. Some have already hit the market, like Prialt (ziconotide; powerful analgesic) and Yondelis (trabectedin or ET-743; anticancer), while others, such as alpidin and kahalalide F, are in clinical studies (Ebada et al., 2010). Grosso et al. (2014) highlighted the neurological potential of marine invertebrates, notably neurotoxins and neuroprotective medicines.

There are around 30 phyla allocated to invertebrates in general. Porifera (which includes the earliest invertebrates: sponges), cnidaria (which includes sea anemones, corals, sea pens, jellyfish, box jellies, and so on), platyhelminthes, nematoda, mollusca/mollusks (squid, cuttlefish, octopuses, and bivalve mollusks), annelida (worms), arthropod (insects, arachnids, and crustaceans), and echinodermata (sea stars, sea urchins, sea cucumbers, sea lilies, and feather stars) (Thuy and Stöhr, 2016; WoRMS, 2018; Wu et al., 2018). Fig. 1 shows a gallery of some of the most well-known marine creatures. In brief, we will concentrate on the well-known species located within the most studied phylum as valuable sources of bioactive compounds and biodrugs.

3.1. Marine sponges

Marine sponges are thought to be a potential arena for the discovery of new medicinal products to treat a variety of essential illnesses, including malignancy, malaria, microbial, viral, and numerous inflammatory disorders (Hu et al., 2015). Many bioactive chemicals found in diverse sponge species have been found to be useful in the creation of novel antibiotics and antibacterial medicines (Shen et al., 2012). While the sponges release these toxins, they can utilize them selectively without self-destruction (Perdicaris et al., 2013).

Because of their massive manufacturing of chemically varied chemicals, sponges are regarded the chemical factory in aquatic environments. These chemicals have exceptional bioactivities in addition to their chemical diversity. Particularly, sponge extracts were found to have antibacterial properties by various researchers. *Spongia officinalis* (Abou-Elela et al., 2009), *Spongia* sp., *Cinachyrella* sp., *Ciocalypta penicillus*, *Axinella verrucosa*, *and Plakortis simplex* are a few examples (Ibrahim et al., 2018). Mayefis et al. (2020) tested sponge extracts extracted from Natuna Water in the Riau Islands for antibacterial and antifungal activity. Pech-Puch et al. (2020) discovered a chemical called Bromoageliferin, which shown substantial efficacy against the *P. aeruginosa* strain CIP A22. Youssef et al. (2013) isolated three novel alkaloids from Red Sea sponges with antibacterial, antioxidant, and anticancer properties.

These extracts contained fatty acids and their esters (hexadecanoic acid and octadecanoic acid), betulin and betulinic acid, carotenoids, terpenoids, and

Fig. 1. Gallery of several famous marine invertebrates (modified from Abou-Elela et al., 2009; Abd El Hafez, 2018; Allam et al., 2021).

steroids with antibacterial and antifungal properties (Ibrahim et al., 2012). According to Yasuda and Tada (1981), sea sponges are also a good source of uncommon sterols with antibacterial effects. Terpenoids, on the other hand, are abundant in sponges and have varying degrees of bioactivity. Clark et al. (1998) extracted cyclicdipsipeptide cyclolithistide from the marine sponge *Theonella swinhoei*, whereas Otero-González et al. (2010) discovered a promising novel use of antimicrobial peptides from the marine sponge *Discodermia kiiensis* that could be an effective drug in both human and veterinary medicine based on their potential traits.

3.2. Soft corals

Coral reefs are among the most biodiverse and biologically productive of all aquatic ecosystems (Harder et al., 2003). Corals, particularly soft-bodied corals, are proper sources of numerous secondary metabolites with intriguing biological functions. However, the specific group of coral metabolic products that demonstrate substantial anticancer properties on the order of the substances stated above is currently minimal (Yan et al., 2021). *Sarcophyton glaucum*, for instance, produces the diterpenoids sarcophytol A, that exhibit tumor-inhibiting biological activity (Cock, 2011). Cembrane terpenes are abundant in soft corals of the genus *Sarcophyton* (family Alcyoniidae). Furthermore, from the Red Sea soft coral *S. glaucum*, three new and two recognized cembranolides were extracted and chemically analyzed (Hegazy et al., 2012). Sarcophine is an MNP isolated from *S. glaucum* that has shown significant anti-cancer potential for skin (Fahmy et al., 2006). Soft corals, astonishingly, synthesize a wide

range of sesquiterpenoids and diterpenoids. Guaiazulene from the gorgonian *Euplexaura erecta*, for example, displayed antibacterial action against *P. aeruginosa*. Muricins are four new esterified aminogalactose saponins produced by *Muricea* species such as *M. californica* and *M. fruticosa* (Soergel et al., 1992). *Clavularia* contains a lot of bioactive terpenoids, porstanoids, and steroids. Stoloniferones A-D, produced by the coral *Clavularia viridis*, is cytotoxic steroid. It also contains three novel cytotoxic prostanoids, claviridenone E-G, and stolinferone E-G, all of which originated from methylene chloride solubility (Chang et al., 2008).

Furthermore, *Xenia* genus is abundant in terpenoids and steroids. Six novel sesquiterpenoids, xenitorins A-F, have been extracted from *X. peurtogalera* and tested for cytotoxicity towards cancer cells. *Cespitularia's* cembrane and neadolabellame skeletons have yielded diterpenes. *C. hypotentaculata* extract, in particular, shown cytotoxicity to human colon and lung adenocarcinoma, and mouse lymphocytic leukaemia cell cultures via four novel cytotoxic diterpenes: cespitularins A-D, cesputularin, cespitularins F–H, and cespitularane. Eleutherobin, a chemical discovered from *Eleutherobia* sp. and *Erythropodium caribaeorum*, has tentative anticancer activities (Naaz et al., 2019).

Sinularectin 3 is a norcembrane identified from the Kenyan soft coral *Sinularia erecta* (Rudi et al., 2006). Grote et al. (2008) found that furanocembranoids isolated from *Sinularia asterolobata* and *Litophyton arboretum* have remarkable antiproliferative behaviors towards cell lines and modest cytotoxic effects on HeLa cells. Furthermore, the genus *Nephthea* contains a high concentration of terpenoids and steroids (Abdelhafez et al., 2021). Human lung and colon adenocarcinoma, and mouse lymphocytic leukaemia were all significantly susceptible to the toxicity of *Nephthea armata* extract. El-Gamal et al. (2004) identified these compounds as nardosinane sesquiterpenoids, armatins A-E, lemnal-1, ene 2, 12-dione, and armatinols.

3.3. Sea urchins

Because of their medical, nutritional, and ecological relevance, sea urchins are one of the most important organisms in marine study. They are good examples of model organisms that can be used in a variety of biotechnological studies (Ibrahim et al., 2020a). Sea urchin rich in vitamins, minerals, proteins, fatty acids, sphingoid, glycolipids, phospholipids, and polysaccharides (Sibiya et al., 2021). Because they include amino acids, vitamin B complex, vitamin A, minerals, omega-3 and omega-6 fatty acids, some sea urchins are often used as an alternative source of healthy food. The shells of sea urchins have recently been recommended as a source of antibacterial compounds (Hadinoto et al., 2017). As well as, the sea urchins guts contain bioactive compounds that were recognized as; carotenoids, polyphenols and polyunsaturated fatty acids (Ahmadifar et al., 2021).

In focus, *Diadema setosum* is one of the most extensively dispersed sea urchin species (Lessios et al., 2001). Earlier research found that their gonads are high in beneficial components such as polyunsaturated fatty acids and β -carotene (Dincer and Cakli, 2007). *D. setosum* has also been shown to secrete antibacterial chemicals against a variety of harmful bacteria (Marimuthu et al., 2015). Most of these compounds' antifungal and antibacterial properties have been demonstrated (Ibrahim et al., 2018).

Salmaa et al. (2016) reported that *D. setosum* gonad extract has intriguing antibacterial properties against *S. typhi* and *E. coli* bacteria via steroids, flavonoids, and saponin. Hadinoto et al. (2017) discovered that *D. setosum* shell extract was antibacterial agent against *Salmonella* sp., *E. coli*, and *Bacillus cereus*. El-Sayed et al. (2020) discovered that *D. setosum* extract had particular detrimental impacts on various bacterial strains (*E. coli*, *P. aeruginosa*, *S. typhimurium*, *Staphylococcus aureus*, *A. hydrophila*, and *V. damsela*). It was also effective against various fungi, including *F. solani*, *A. niger*, and *R. solani*. Organic and fatty acids and their derivatives, as well as steroids, terpenoids, amino acids, esters, and benzene derivatives, were found in their extracts.

Recently, Ferrario et al. (2020) observed that the shells of sea urchins possess fibrillar glycosaminoglycan-rich collagen, which amazingly produce bilayer collagen-based skin-like scaffolds. Marzorati et al. (2021) have suggested the presence of antioxidant compounds (spironochromes) in the *Paracentrotus lividus* shells extract. Furthermore, Moreno-García et al. (2022) reviewed the potential pharmacological benefits of various sea urchin species [*Diadema antillarum* (Philippi, 1845), *Echinometra mathaei* (de Blainville), *Evechinus chloroticus* (Valenciennes), *Mesocentrotus nudus* (Agassiz, 1863), *P. lividus* (Lamarck, 1816), *Scaphechinus mirabilis* (Agazzis, 1863), *Stomopneustes variolaris* (Lamarck, 1816), *Tripneustes depressus* (Agassiz, 1863), and *Tripneustes ventricosus* (Lamarck, 1816)] as anti-fungal, anti-parasitic, anti-inflammatory, hepatoprotective, antiviral, anti-diabetic, anti-lipidemic, and gastro-protective anti-cardiotoxic agents. However, the results of Chamika et al. (2021) suggested that the

processing sea urchin extracts has potential application to the food and pharmaceutical industries.

3.4. Sea stars

Sea stars are benthic, autonomous echinoderms that have developed with abundant bioactive metabolites like anthraquinones, steroidal glycosides, alkaloids, steroids, glycolipids, and phospholipids (Molinski et al., 2009). The most common metabolites in sea stars are steroidal glycosides and related compounds, which have a wide range of biological actions including antineoplastic, cytotoxicity, hemolysis, antifungal, ichthyotoxicity, repellent, antimicrobial, antiviral, and anti-inflammatory properties (Schumacher et al., 2011).

Astropecten genera, in particular, have the most species within sea stars, and their members are found worldwide, occupying soft-bottom environments ranging from polar to tropical waters and from intertidal zones to the deep sea (Thuy and Stöhr, 2016). *Acanthaster planci*, a starfish, has been found to be high in polar steroids. Kicha et al. (2014) identified three novel polyhydroxylated steroidal biglycosides plancisides A-C from *A. planci*. Lee et al. (2014) discovered that the butanol fraction of *A. planci* reduced the multiplication of human malignant melanoma A375.S2 cells. Later, Datta et al. (2015) revealed that *A. planei* included asterosaponins as well as many thymine deoxyriboside, cerebrosides, pyrimidine nucleosides, and uracil deoxyriboside. Abd El Hafez (2018) also isolated three novel steroids from *A. planci* obtained from the Egyptian Red Sea, which demonstrated antibacterial action towards *P. aeruginosa* and *S. faecalis*. Thao et al. (2014) identified six biologically relevant chemicals from Asterosaponins, Astrosteriosides A-D, Psilasteroside, and Marthasteroside B from *Astropecten monacanthus*. Popov et al. (2016) isolated a novel asterosaponin from *Aphelasterias japonica*, aphelasteroside F, as well as the previously known ophidianoside F. These chemicals suppressed cell proliferation marginally in malignant melanoma cell lines. Organic acids and their derivatives, as well as organic alcohols, steroids, and terpenoids, were found in the *Astropecten spinulosus* extracts (Ibrahim et al., 2018).

Ma et al. (2010) also extracted 11 polyhydroxysteroid glycosides from *Anthenea chinensis*, which showed inhibitory action towards human leukaemia and glioma cells. Peng et al. (2010) discovered that polyhydroxy sterol ester obtained from *Asterina pectinifera* was cytotoxic. Yang et al. (2011) demonstrated that steroids derived from *Archaster typicus* extract have anticancer activity against colon cancer cells. In addition, Thao et al. (2013) discovered anticancer steroids from *Astropecten polyacanthus* versus human cancer cells from leukaemia, prostate, and colorectal.

Other species exhibited evident biological activities as well. Kicha et al. (2003), for instance, synthesized steroid glycosides from *Patiria pectinifera* and displayed hemolytic and cytotoxic action. Malyarenko et al. (2012) described the chemical structures of three asterosaponins derived from the same starfish, namely thornasteroside A, regularoside A, and asteropsiside A. Later, Layson et al. (2014) discovered that *Linckia laevigata* and *Oreaster nodusus* have significant antibacterial action towards *E. coli*. In addition, several polyhydroxylated steroids derived from the starfish *Leptasterias ochotensis* shown antibacterial and cytotoxic activity (Malyarenko et al., 2015). Furthermore, Prabhu and Bragadeeswaran (2013) discovered substantial potency in their extracts of *Ophiocnemis marmorata* as antibacterial agents. Abd El Hafez (2018) isolated two antibacterial chemicals from the brittle star, *Ophiocoma dentate*. Senthikumari and Revathi (2018) isolated antibacterial substances from *Ophiomastrix annulosa* and *Ophiocoma erinaceus* extracts regarding bacterial infections.

3.5. Sea cucumbers

Asians have long utilized sea cucumbers as dietary supplements due to their important bioactive components. *Holothuria scabra*, for example, was used to make high-protein biscuits and jam (Thuy and Stöhr, 2016). Triterpene glycosides are significant secondary metabolites in sea cucumbers (Pandey, 2016).

Antimicrobial substances identified from sea cucumbers include steroidal glycosides, peptide antibiotics, polyhydroxylated sterols, naphthoquinone pigments, lysozymes, and others (Palaniveloo et al., 2020). Antiviral, antibacterial, anticoagulant, antiangiogenic, antitumor, anticancer, antihypertension, anti-inflammatory, antioxidant, antithrombotic, and wound healing effects have been reported to numerous sea cucumber taxa (Althunibat et al., 2009).

Jawahar et al. (2002) investigated the antibacterial and antifungal properties of alcoholic extracts of *holothurian* species from the Tamil Nadu Coast, including *Actinopyga echinites*, *A. miliaris*, *H. atra*, and *H. scabra*. Antibacterial activity was found in extracts from numerous tissues of the sea cucumber, *Cucumaria frondosa*, but primarily in coelomocyte and body wall extracts, according to Haug et al. (2002). *C. frondosa* gastrointestinal organs and eggs showed

relatively significant antibacterial activity. Clearly, Mokhlesi et al. (2011) discovered that *Bohadschia marmorata* has antibacterial and antifungal properties. All of these findings, however, point to marine echinoderms as a possible source of new antibiotics. Ibrahim (2012) discovered antibacterial substances in three sea cucumber species (*H. scabra*, *H. leucospilota*, and *H. atra*) against human and fish diseases. The author explained that the carotenoids in the extracts were responsible for this activity.

Furthermore, several additional researchers discovered that the biological activities of sea cucumbers were associated with the presence of a diverse range of bioactive chemicals. Triterpene glycosides (saponins), chondroitin sulphates, glycosaminoglycan, sulfated polysaccharides, sterols, phenolics, cerberosides, lectins, peptides, glycoproteins, glycosphingolipids, terpenoids, and essential fatty acids are examples of these substances. Organic acids, organic esters, aldehydes, carotene and its derivatives, phenolic compounds, steroids, terpenoids, and other bioactive compounds were detected in extracts of many sea cucumber species (*H. polii*, *H. scabra*, *H. tubulosa*, *H. leucospilota*, *H. atra*, *H. moebi*, *H. pervicax*, *C. frondosa*, and *C. japonica*).

3.6. Sea hares

Sea hares (also known as sea slugs) are a mollusc category that contains numerous genera and several species (Ibrahim et al., 2020d). For defense and communication, all sea hares use a chemical combination (Palaniveloo et al., 2020). When disturbed or assaulted, sea hares squirt ink and swim away using their broad wing-like flaps, or parapodia. Instead of being synthesized, their ink is taken from their algal food (Zsilavecz, 2007). The sea, on the other hand, chemically defends itself to prevent being eaten by predators by detecting chemicals emitted, known as alarm signals, which are and have been observed in many species (Ibrahim et al., 2020d).

Aplysia fasciata, sometimes known as the 'mottled sea hare,' is a species of sea hare that belongs to the Aplysiidae family (Kamiya et al., 2006). Yamazaki (1993) isolated novel antimicrobials from numerous sea hares, including *Aplysia kurodai*, *A. juliana*, and *Dolabella auricularia*, early on. They are known as aplysianins, julianins, and dolabellanins, in that order. Furthermore, he discovered that the factors were active for Gram-positive and Gram-negative bacteria, as well as some fungi, and that their impact was cytostatic rather than cytocidal. Aplyronines are a class of bioactive peptides and macrolides identified from Japanese sea hares that have anticancer action. Surprisingly, the active principles in *Aplysia* species and *D. auricularia* have been identified as L-amino acid oxidase (LAAO), which is responsible for antibacterial and cytotoxic activity (Kamiya et al., 2006). Iijima et al. (2003) successfully extracted a new antibacterial peptide from the sea hare, *D. auricularia*. They and other researchers (Derby et al., 2018) discovered that *Aplysia* species contained biologically active compounds such as antibacterial agents, poisons, and chemical defense chemicals.

Kiyoyuki and Hideo (1997) described the bioactive chemicals extracted by nature from sea hares, primarily from two genera: *Aplysia* and *Dolabella*. These substances are classed as polyketides, terpenes, peptides, and depsipeptides. The chemistry of the derived cytotoxic chemicals, such as aplyronines and dolastatins, is given special attention. Many of the bioactive chemicals found in sea hares are terpenoids, including sesquiterpenoids and diterpenoids, as well as organic acids and their esters (Bornancin et al., 2017). Furthermore, Datta et al. (2019) discovered that the proteinogenic amino acid tyrosine was a powerful antibacterial agent against *Shigella flexneri* 2a and methicillin-resistant *S. aureus*. Furthermore, Sannasiddappa et al. (2017) stated that the bioactive compounds detected in the crude extract of *A. fasciata* were organic acids and their derivatives, as well as many other organic alcohols, steroids, and terpenoids. Most of these compounds' antibacterial actions, however, have been demonstrated (Hussein et al., 2016; Ibrahim et al., 2018).

Glycoproteins derived from *A. fasciata* and *A. kurodai* shown substantial anticancer activity in mice against some human tumors (Takamatsu et al., 1995). Furthermore, anti-cancer dolastatins from *D. auricularia* have been identified (Nocchi et al., 2017). Several bioactive compounds can be identified in ink alone, some in opaline alone, and others only when ink and opaline are co-secreted and combined in the mantle cavity (Derby et al., 2018).

3.7. Sea worms

Platyhelminthes, Nematoda, Annelida (segmented worms), Chaetognatha, Hemichordata, and Phoronida are among the phyla that contain marine worms (Zhang et al., 2017). Few researches have been conducted on marine worms, particularly polychaetes, as a source of bioactive compounds. Benkendorff (2001), for example, discovered that four polychaetes have significant antibacterial action against human pathogenic bacteria: *E. coli*, *S. aureus*,

and *P. aeruginosa*. Based on his findings, the author concluded that, a wide variety of invertebrates use chemical defense to protect their early-stage eggs against bacterial infection. Arenicin-1 and -2 were isolated from coelomoycytes of the polychaete *Arenicola marina* by Ovchinnikova et al. (2004). Perinerin, isolated from the polychaete *Perinereis aibuhitensis* homogenates, is a highly cationic, hydrophobic peptide with antifungal and antibacterial action against Gram negative and Gram positive bacteria (Pan et al., 2004). Later, Ibrahim and Abd-Elnaby (2010) taxonomically identified five marine polychaete species that demonstrated antibacterial and antifungal activity (*Nereis falsa*, *Perinereis nuntia*, *Pseudonereis anomala*, *Halla parthenopeia*, and *Hydroides elegans*). Organic acids and their derivatives were the most abundant constituents found in polycha ete extracts.

Common polychaete worms naturally create brominated and organobromine chemicals such as brominated indoles, 2, 3, 4-tribromopyrrole, and brominated phenols (Kicklighter et al., 2004). Antifungal activity of bromoindoles and its derivatives has been demonstrated (Liu and Gribble, 2002). Many biogenic organobromine compounds have been proposed to have antibacterial or other biologic properties. This explains why marine worms live in sediments, implying that they need an antibacterial approach to survive (Ibrahim and Abd El-Naby, 2010). Furthermore, brominated phenols and indoles are thought to cause both lethal and non-lethal abnormalities (Kammann et al., 2006). *Perinereis vancaurica* myoactive peptides were identified by Matsushima et al. (2002). The peptide was a pentadeca peptide with an amino acid sequence comparable to that of earthworm excitatory peptides and leech excitatory peptides, and it displayed my activity in *P. vancaurica*'s isolated esophagus.

4. Classification of bio-drugs from marine invertebrates

Recently, drug discovery programs have turned their focus to uncommon sources such as marine invertebrates (mollusks, sponges, sea cucumbers, and so on), in the hope of discovering more effective therapeutic instruments with new chemical structures and distinctive mechanisms of action (Nocchi et al., 2017). There are many examples of commercially available marine-derived drugs that have been successful, such as cytarabine (Cytosar-U), isolated from sponges for acute myelocytic leukaemia (Malve, 2016), trabectedin (Yondelis), isolated from a sea squirt for ovarian cancer (He et al., 2019), Eribulin (Halaven), isolated from Japanese sponges for metastatic breast. These breakthroughs, as well as the countless marine-derived drugs under clinical trials, are undoubtedly the motors that will propel the industry forward. In general, marine bio-drugs may be categorized based on their effects as follows:

4.1. Antibacterial agents

Three novel bromotyrosine analogues, ianthelliformisamine A-C, were discovered from the sponge *Suberea ianthelliformis*, along with the known aplysamine I and araplysillin I. Only ianthelliformisamines A and C were shown to have antibacterial action against the Gram-negative bacterium *P. aeruginosa*, whereas C was found to have activity against *S. aureus* (Xu et al., 2012; Ancheeva et al., 2018).

4.2. Antifungal agents

Seven novel chemicals were identified from an Okinawan sea sponge, *Suberites* sp., including six new aaptamine alkaloids. Among the pure compounds, nakijinamine A has shown antifungal efficacy against *Candida albicans*, *Candida neoformans*, and *Trichoderma mentagrophytes*, as well as antibacterial activity against *S. aureus*, *B. subtilis*, and *Micrococcus luteus*. Nakijinamines B and F were shown to be antifungal against *C. albicans* (Takahashi et al., 2012; Ancheeva et al., 2018).

4.3. Antiviral agents

High-molecular-weight exo-polysaccharides isolated from the *Celtodoryx girardae* (French maritime sponge) and its associated symbiotic bacteria have been revealed to have anti-herpes simplex virus-1 (HSV) action (Rashid et al., 2009).

4.4. Anti-inflammatory agents

An in vivo investigation on a rat model of carrageenan-induced paw edoema using extracts and other sections of a Mediterranean sponge species, *S. officinalis* (Dellai et al., 2010).

4.5. Antiparasitic agents

Extracts of *Sarcotragus* sp., also known as Tunisian sponge, produced in dichloromethane have exhibited in vitro antileishmanial efficacy by displaying related morphological abnormalities in leishmania major promastigotes (Ben Kahla-Nakbi et al., 2010).

4.6. Anticancer agents

Bryostatin is largely derived from the bryozoan *Bugula neritina*, while it has also been isolated from sponges and tunicates. Sorbicillin-derived alkaloids sorbicillactone A and its 2′, 3′-dihydro analogue sorbicillactone-B have showed anti-leukemia efficacy without cytotoxicity. Sorbicillactone-B was synthesized from a salt-water culture of the bacterial strain *Penicillium chrysogenum*, which was isolated from the Mediterranean sponge *Ircinia fasciculata* (Bringmann et al., 2007). Keyhole limpet hemocyanin (KLH), a copper-containing extracellular respiratory protein discovered in *Megathura crenulata*, a marine Gastropod species found in vast numbers along the Pacific coast of California and Mexico, is another potential anticancer medicine utilized as an immunotherapeutic agent. KLH has two isoforms: KLH1 and KLH2 (Harris and Markl, 1999).

4.7. Analgesic agents

Ziconotide was the first medicine of marine origin to be approved by the United States Food and medicine Administration (USFDA) in 2004 to treat pain. It was first derived from the sea snail *Conus magus* and is also known as Prialt. Animal studies showed that ziconotide has a function in inhibiting N-type calcium channels on spinal cord main nociceptive nerves (Skov et al., 2007).

4.8. Antimalarial agents

Antimalarial compounds in isonitrile were isolated from the Japanese sponge *Acanthella* sp. The identified molecules are members of the kalihinane diterpenoids family, which includes antifungal, antihelmintic, and antifouling chemicals (Miyaoka et al., 1998).

5. Examples of approved marine bio-drugs

Since sponge metabolites were first found in the 1950s, practically all antiviral medications currently in use can be linked back to them (Sigwart et al., 2020). The focus of these activities then changed to possible biomedical uses of novel chemicals discovered in sponges and related colonial marine invertebrates in the middle of the 1980s. More than 2500 different compounds with different structural properties have been discovered in marine plants and animals as a result of this technique, and several of these compounds have been successfully adapted for use in the pharmaceutical sector (Carter, 2002). Two of the therapeutic molecules produced from marine sources that have been approved are ziconotide and trabectin. Ziconotide received approval for use as a painkiller in the US and EU in 2004. Trabectedin was later authorized as an anticancer medication in Europe in 2007 (Fajarningsih, 2012).

More than 13 substances are now being tested in various stages of clinical trials as marine pharmaceuticals, and there are many more marine-derived compounds and molecules in various stages of preclinical research. Cytarabine (Cytosar-UW, DepocytW), Vidarabine (Vira-AW), and Ziconotide (PrialtW) are the three FDA-approved medications made from marine sources that are now utilized in the United States (Mayer et al., 2010). Along with these medicines, further preclinical products are also in development (Marine Biotechnology Market MBM, 2022). In particular, a large number of biodrugs made from marine invertebrates have received worldwide approval for use in humans, so we will discuss in the following text.

5.1. Cytarabine

Cytarabine, also known as cytosine arabinoside or arabinosyl cytosine ara-C, is a synthetic pyrimidine nucleoside that was primarily obtained from the Caribbean sponge *Tethya crypta*. It is generated from spongothymidine. It is FDA-approved and primarily used in the treatment of various leukemias, such as acute myelocytic, lymphocytic, meningeal, and blast crisis stages of chronic myelogenous leukemia (Malve, 2016).

5.2. Vidarabine

Vidarabine, also known as adenine arabinoside, ara-A, or arabinofuranosyladenine, is a synthetic purine nucleoside that was derived from spongouridine and was first discovered in the Caribbean sponge *Tectitethya crypta*. It is currently available from the bacterium *Streptomyces antibioticus*. Its usage has been authorized by the FDA for the treatment of acute kerato-conjunctivitis, recurrent epithelial keratitis caused by HSV types 1 and 2, and superficial keratitis (Mayer et al., 2010).

5.3. Ziconotide

Ziconotide is a synthetic compound that mimics v-conotoxin MVIIA, a natural 25-amino acid peptide. It was initially taken from the venom of the fish-hunting sea snail *C. magus* and purified from it. The new mode of action of ziconotide has demonstrated

its potential as an analgesic. According to Safavi-Hemami et al. (2019), the FDA has given it analgesic approval.

5.4. Trabectedin

The tunicate species *Ecteinascidia turbinata*, which typically inhabits the Mediterranean and Caribbean Seas, is used to make trabectedin (Yondelis), also known as ecteinascedin. The first anticancer chemical of marine origin to receive EU authorization for use in the treatment of soft-tissue sarcoma and in relapsed cases of platinum-sensitive ovarian cancer was trabectedin, a tetrahydroisoquinoline class alkaloid (Malve, 2016).

5.5. Eribulin mesylate (Halaven Eisai Inc)

The modified synthetic equivalent of halichondrin B known as eribulin mesylate (Halaven) was created from a Japanese aquatic sponge known as *Halichondria okadai* (Barud et al., 2014). It became accessible in 2010 with the intention of using irreversible mitotic inhibition to treat metastatic breast cancer. According to studies (Dyshlovoy and Honecker, 2019), it is useful in the treatment of liposarcoma.

5.6. Pseudopterosins

These substances were initially identified from the soft coral *Pseudopterogorgia elisabethae* and are tricyclic diterpene glycosides. Additionally, a pharmaceutical business has granted them a licence for use as anti-inflammatory medications in medicine. At least one of the pseudopterosins has been the subject of a preclinical application for an investigational new drug (IND) to the FDA. A pseudopterosin extract has entered the non-pharmaceutical market in a line of cosmetic skin care products from Estée Lauder as an additive to prevent skin irritation. Anti-inflammatory and analgesic pseudopterosins have been found in a soft coral species from the Bahamas (Alice and Elegbede, 2016).

5.7. Enfortumab vedotin

It was extracted from mollusks, and the FDA granted expedited approval for Padcev in December 2019. According to Rabet et al. (2017), it is recommended for patients with metastatic and locally advanced bladder malignancies who have previously received treatment with a programmed cell death ligand 1 inhibitor.

5.8. Lurbinectedin

The FDA approved the alkaloid analogue lurbinectedin (Zepzelca) in June 2020 as an orphan medication for the second-line treatment of small-cell lung cancer in adults with a tolerable safety profile and acceptance. It is a different-patterned derivative of ecteinascidin that was isolated from tunicate *E. turbinata* extracts. According to Calvo et al. (2017), lurbinectedin causes DNA alkylation, inhibits active transcription, causes DNA breakage, and ultimately induces apoptosis.

5.9. Evaluation of marine bio-drugs in clinical trials

In general, the procedures listed below are employed to separate MNP from a marine invertebrate: Target identification, supply assurance, potential derivatization and substance library production, biological and/or chemical and/or genetic screening, identification and selection of interesting extracts, isolation and structure elucidation of compounds with promising biological activity and/or novel structures, broad pharmacological and toxicological investigations of drug candidates for pharmacodynamics, pharmacokinetic, and safety parameters, and registration in accordance with the law (Martins et al., 2014); clinical trials. However, Fig. 2 shows these steps from one side.

In order to acquire bio-drugs from marine invertebrates, the marine environment must now be reevaluated and new methods must be developed (Carter, 2002). Presently, the preclinical drug pipeline continues to assist the clinical pipeline with potentially beneficial compounds while supplying hundreds of novel marine natural chemicals post-safety screening each year. It has taken more than 30 years for any other natural product of marine origin to get licensed for clinical use since 1974 (when the FDA approved three marine medications) (Malve, 2016).

Over the past 5 years, 262 marine chemicals have been the subject of preclinical pharmacology research in 35 nations, including the USA; they are currently a part of the preclinical pharmaceutical pipeline. 102 natural marine chemicals have been shown to exhibit promising antibacterial, antifungal, antiprotozoal, antitubercular, and antiviral properties. Around 60 marine chemicals have been identified to be potent for the immunological and neural systems, and some anti-diabetic and anti-inflammatory actions have also been noted, according to Mayer et al. (2013) analysis. Finally, it was discovered that 68 promising molecules obtained from marine sources interacted with a variety of

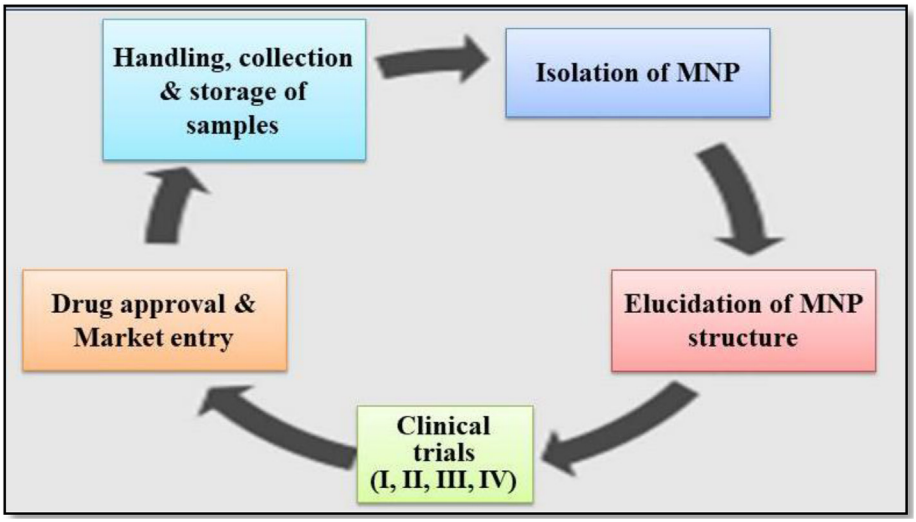

Fig. 2. Main stages of discovery, processing, approval, and marketing of marine bio-drugs (modified from Sruthi et al., 2020).

molecular targets and receptors. These findings suggest that these molecules may help to develop a variety of pharmacologically active classes of drugs when more in-depth research is done to confirm their mechanism of action (Mayer et al., 2013).

It is ensured through the clinical trial procedure that novel treatments are superior than current ones. Clinical studies are fundamentally divided into three phases. Phase I studies (15–50 participants) determine the safest manner to administer a novel medicine as well as its efficacy. The disease's response to the new medication is another thing that doctors watch for. Phase II trials examine whether a particular type of disease reacts to the new medication in fewer than 100 individuals. Hundreds of people are tested in phase III trials to determine whether a novel treatment is superior than accepted practices. Before a bio-drug is officially licensed, phase IV studies require administering it to thousands of people (Malve, 2016). However, Table 1 mentions just some famous compounds obtained from marine invertebrates and shows their biological effects.

5.10. Marine bio-drugs in clinical phase III trial

5.10.1. Eribulin

It is a polyether macrolide natural chemical that was originally taken from sea sponges, and preclinical animal models have shown it to have strong anticancer potential. According to Mayer et al. (2010), eribulin is a powerful chemical that induces irreversible antimitotic activity that results in cell death by the apoptotic pathway. Eribulin's clinical effectiveness is being compared with that of

Table 1. Some compounds extracted from marine invertebrates with clinical effect (modified from Malve, 2016).

Clinical trail	Compound name	Marine source	Disease
	Hemiasterlin	Sponges	Bacterial infection
	Enfortumab vedotin	Mollusk	Tumors
	Leconotide	Marine snails	Cancer (anti-pain)
	GTS-21 (aka DMBX)	Marine worm	Alzheimer's
	CGX-1160	*Conus geographus*	Pain
Phase I	ACV1	*Conus victoriae*	Pain
	Didemin B	Sea squirts	Inflammation
	Discodermolide	Sponge *Discodermia dissolute*	Cancer
	Zalypsis	Sponges and tunicates	Cancer
	Aplidine	Ascidian *Aplidium albicans*	Cancer
	IPL-576,092 (aka HMR-4011A)	Sponge *Petrosia contignata*	Anti-asthmatic
Phase II	Bryostatin 1	Bryozoan *Bugula neritina*	Cancer
	Elisidepsin	Mollusk	Cancer
	Ecteinascidin 743	Ascidian *Ecteinascidia turbinate*	Cancer
Phase III	Tetrodotoxin	Octopus and shellfish species	Pain
	Eribulin	Sponges	Cancer

capecitabine and other preferred treatment options in ongoing Phase III studies (Malve, 2016).

5.10.2. Tetrodotoxin

A well-known 'marine toxin' and guanidine derivative with plenty of substitutions. It is currently undergoing Phase III trials as an analgesic for poorly managed cancer-related pain; it is not an antitumor agent. To evaluate the effectiveness of tetrodotoxin against the neuropathic pain associated with chemotherapy-induced peripheral neuropathy, a Phase II trial is now being conducted (Malve, 2016).

5.10.3. Soblidotin

Is a synthetic derivative of dolastatin 10, which has the dolastatin backbone. In addition to its tubulin inhibitory effect, it also has vascular disruptive properties that result in the collapse of the vasculature within the tumor. This medication is undergoing Phase I, II, and III clinical studies with several firms in an effort to deploy it as a weapon against certain monoclonal antibodies connected by personalized peptides (Mayer et al., 2010).

5.11. Marine-derived compounds in clinical phase II trial

5.11.1. 3-(2,4-dimethoxybenzylidene)-anabaseine; GTS-21

It is a man-made version of the alkaloid anabaseine, which is present in a variety of aquatic worm species belonging to the phylum Nemertea. According to reports, DMXBA is good for the central nervous system and helps many lab animals with sensory gating deficiencies and poor cognition. In a recent Phase II clinical trial, patients with schizophrenia shown a notable improvement in cognitive skills (Mayer et al., 2010).

5.11.2. Plitidepsin

It is a marine depsipeptide that is currently produced using complete synthesis. *Aplidium albicans*, a tunicate that was discovered in the Mediterranean Sea, was the main source of its isolation. Plitidepsin has an extremely low nanomolar (nM) range of IC50 values and is a highly effective apoptosis inducer. According to Mayer et al. (2010), the most common side effects of plitidepsin were muscle toxicity, an increase in transaminases, overall weariness, diarrhea, and cutaneous rash.

5.11.3. Elisidepsin

It is a brand-new cyclic peptide that comes from marine sources and is a member of the Kahalalide chemical family. It is now in Phase II of development and has preliminary data supporting its anticancer effectiveness and promising therapeutic index. It has demonstrated strong in vitro cytotoxic activity against a variety of human tumour cell lines, which might be due to the production of oncolytic cell death as opposed to apoptotic cell death (Mayer et al., 2010).

5.11.4. Zalypsis

It is a brand-new alkaloid with the ability to bind DNA. It is connected to jorumycin, which is derived from the skin and mucus of the Pacific nudibranch (*Jorunna funebris*), as well as to renieramiycins, which are extracted from several sponge and tunicate species. These compounds were the subject of prior preclinical in vivo research, which revealed significantly high anticancer activity in cells of breast, prostate, and kidney malignancies and limited antitumor activity in colon cancer cells. The primary toxicities linked to Zalypsis therapy throughout the Phase I trials were reversible haematological problems or abnormalities in liver enzymes (Mayer et al., 2010).

5.11.5. Pseudopterosins

Pseudopterosin A is a potent phorbol myristate acetate inhibitor that has been shown to promote topical inflammation in a mouse model and impede the formation of phagosomes in tetrahymena cells. Pseudopterosins were discovered to enhance the re-epithelialization process with qualitative enhancement in the early wound repair process in a double-blind, Phase II clinical trial (Mayer et al., 2010).

5.12. Marine bio-drugs in clinical phase I trials

5.12.1. Bryostatin 1

It contains bryostatin 3, one of the 20 known variants, which was isolated from the bryozoan *B. neritina*. Since 2007, bryostatin trials against different carcinomas have been reported in at least four Phase I and eight Phase II studies, all of which combined the use of biologicals or cytotoxins. As a potential treatment for Alzheimer's disease, bryostatin is presently being evaluated in two Phase I trials (Mayer et al., 2010).

5.12.2. Leconotide

It is a 27-residue peptide with three CYS-CYS linkages. It is undergoing Phase I trials for the treatment of cancer and is comparable with ziconotide. Although it was initially administered intravenously (as ziconotide) in studies (Jayamanne et al., 2013), systemic administration is now employed (Yanagita and Takenaka, 2012).

5.12.3. Hemiasterlin

It is a tripeptide that was initially isolated from marine sponges and is cytotoxic. The Phase I studies revealed dose-limiting toxicities such neutropenia/ febrile neutropenia as well as several other side effects include general fatigue, nausea, vomiting sensation, and constipation (Mayer et al., 2010).

5.12.4. Enfortumab vedotin

It combines monomethyl auristatin E and a completely human IgG1k antibody for use in immunotherapy. It is reportedly being tested in a Phase I study to treat solid tumours; it was isolated from a marine mollusk (Miyaoka et al., 1998).

6. Investment in marine bio-drug production

As the United Nations Decade of Ocean Science for Sustainable Development 2021–2030 begins, it is now time to take purposeful and systematic steps to support the whole marine biodiscovery pipeline and eliminate its bottlenecks (Sigwart et al., 2020). Besides, the lengthy and expensive nature of the marine drug development process necessitates long-term strategic investments (Sigwart et al., 2020).

The development of bio-drug compounds from marine resources also requires a substantial and effective contribution from the industrial business community and private finance sector. At every stage, there must be intimate partnerships between academia and industry. Essentially, if that specific lead molecule is successful, the pharmaceutical business must invest in clinical trials. Marine medications won't have a chance on the market unless supply can be managed in a way that is both commercially and environmentally viable. In terms of resources, security, etc., the government should also take the necessary actions in the development of marine pharmaceuticals (Sruthi et al., 2020).

The fact that scientific and technological knowledge is frequently dispersed across numerous academic institutions and businesses is a significant obstacle to varied types of academia-industry collaboration, even though NP-based drug development offers a special niche for these partnerships. Supporting translational NP research in academia requires concentrated efforts, but has grown increasingly challenging in recent years due to a drop in the number of major corporations actively engaging in NP research. For instance, the Austrian Drug Screening Institute (ADSI), the Michael Popp Research Institute for New Phyto-Entities, Bionorica Research, and Biocrates Life Sciences AG are just a few of the organisations that are part of the Phytovalley Tirol, Austria initiative to speed up NP-based drug discovery. Virtual consortia, like the recently formed International Natural Product Sciences Taskforce (INPST), which offer a platform for the fusion of know-how, technology, and materials from the participating academic and industrial entities, could be another option (Atanasov et al., 2021).

It's interesting to note that Alejandro M.S. Mayer of Midwestern University in Illinois, USA, maintains a website called 'The Global Marine Pharmaceuticals Pipeline' that records MNPs and medications and provides summaries of both licensed medications and those that are now undergoing clinical trials. Currently, twenty medications with marine origins are undergoing clinical trials (Malve, 2016). The National Cancer Institute (NCI) and the U.S. Department of Agriculture (USDA) successfully introduced Taxol into modern medicine more than 50 years ago. It took a group of chemists, pharmacologists, and oncologists a long time to get taxol from that point to its current position as one of the most effective new cancer treatments. Eleutherobins, sarcodictyins, and discodermolide are just a few of the MNPs that have attracted significant industry attention as a result of the drive to create better compounds (Jordan, 2001).

In addition, Additionally, governmental funding agencies should stop making long-term, high-priority expenditures in marine bio-discovery, particularly the early-stage compound discovery phase. There should be more chances for early-career researchers everywhere to participate in high-risk research without endangering their careers. Additionally, it is important to share data and chemical libraries via international networks (Sigwart et al., 2020).

On the other hand, a number of businesses have found success in this way in the marine biotechnology sector. The marine biotechnology industry is dominated by businesses like Abbott Laboratories, Nofima, Lonza Group Ltd., Aker Biomarine, New England Biolabs Inc., Cyanotech Corporation, GlycoMar, Prolume Ltd., Marinova, and Qingdao Codo International Ltd. Additionally, significant players engage in strategic alliances with businesses that complement their product line through actions including product approvals, acquisitions, and partnerships (Marine Biotechnology Market MBM, 2022).

Further, the PharmaSea project also concentrated on discovery research as well as the creation and marketing of bio-drugs derived from marine creatures. Under the FP7 programme, the European Union provided funding for it. The highly interdisciplinary collaboration of 24 partners from 13 countries representing business, academia, and

nonprofit organisations forms the foundation of the collaborative effort. Researchers from the fields of marine genetics, biosynthesis, and chemical structure analysis are joined by legal specialists at PharmaSea. Successfully, the PharamaSea project has completed two tales. The first is Prialt, which was isolated from cone snails and demonstrated very potent analgesic properties in people. In hospitals, it was given as a drip to people who were near death, such as cancer patients. The second is Ara-C, which was extracted from a marine sponge and described as an adjuvant to radiation and chemotherapy for leukaemia (PSC, 2023).

Statistically, the marine biotechnology industry is anticipated to experience erratic growth trends over the long term, but supply chain and inflationary problems are anticipated to persist in 2023 (MBMOR, 2022). The size of the worldwide marine biotechnology market was 5.9 billion dollars in 2022, and according to projections, it will rise at a compound annual growth rate (CAGR) of 7.09 % from 2023 to 2032, reaching 11.7 billion dollars (Marine Biotechnology Market MBM, 2022) (Fig. 3).

The market for marine pharmaceuticals was valued at US$26.500 billion in 2020, while by the end of 2027, it is anticipated to have grown to US$48.1 billion, with a CAGR of 8.5 % over the 5-year period. In 2018, the market for drugs produced from marine sources was estimated at USD 10.5 billion, and by 2025, it is anticipated to grow to USD 21.9 billion. The market for pharmaceuticals made from marine sources is anticipated to expand at a CAGR of 11.20 % from 2019 to 2025.

The market for drugs produced from marine sources was worth US$ 2.1 billion in 2020; it is anticipated to grow to US$ 38.9 billion by the end of 2027, at a CAGR of 8.8 % from 2021 to 2027 (Marine Biotechnology Market MBM, 2022). The medical sector's revenue share will be close to 33 % in 2022. GlaxoSmithKline and LifeMine Therapeutics agreed to a USD 70 million deal in March 2022 to use LifeMine's fungi-based drug development engine to produce three candidates. The marine-based drug tisotumab vedotin-tftv (brand name Tivdak) was approved by the FDA in September 2021 for adult patients with recurrent or metastatic cervical cancer and disease progression during or after therapy (Marine Biotechnology Market MBM, 2022).

7. Challenges facing marine bio-drugs and future prospective

A few significant obstacles must be overcome in order to obtain bio-drugs from marine sources. The varying environmental conditions could cause the same organism to consistently produce distinct metabolites (Sruthi et al., 2020). The fact that the marine animals' own microbes, rather than their invertebrate hosts, are often responsible for producing the bioactive compounds, poses a significant problem (Martins et al., 2014). Recently, for example, homogenous microbial communities separate from marine plankton or sediments were discovered by molecular phylogenetic investigations of the microflora of marine sponges from various oceans (Hentschel et al., 2002).

Generally, material supply is the key issue in marine drug discovery research. The removal of marine invertebrates from the environment could have detrimental effects due to their rarity, difficulty in collecting, and slow growth (Wu et al., 2022). For instance, 1 metric ton of *B. neritina* would need to be harvested in order to produce 1.4 g of Bryostatin-1, an anticancer therapeutic candidate that is now

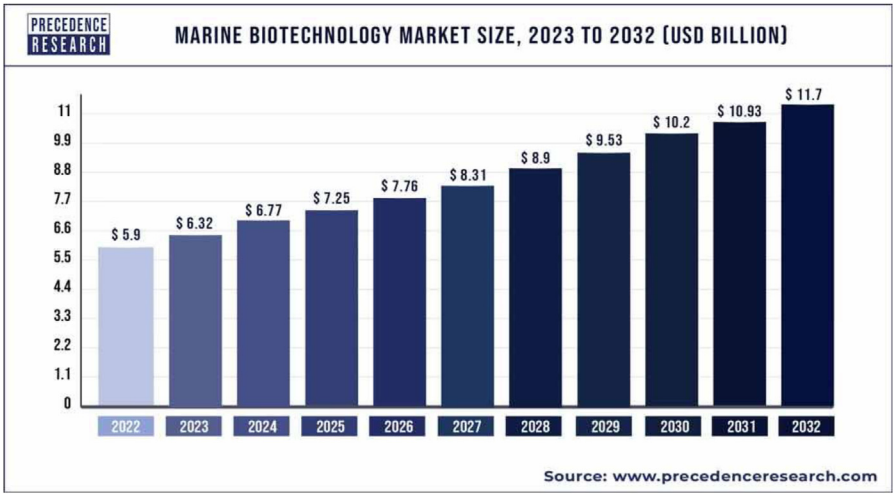

Fig. 3. Size of global marine biotechnology market from 2023 to 2032 (Marine Biotechnology Market MBM, 2022).

undergoing phase II clinical trials (Ancheeva et al., 2018). Chemical synthesis methods and 'Pharmaceutical aquaculture' of physiologically active marine biota have previously been used as solutions to the issue. When dealing with less complicated compound structures, the chemical synthesis method is a workable choice. Aquaculture, however, can be a solution when working with structurally complicated substances where total or even semi-total synthesis is exceedingly difficult to offer (Fajarningsih, 2012).

Alternative approaches to this issue have been developed, including: i) aquaculture for sustainable supplies of marine-derived drug material, particularly marine invertebrates (such as sponges, bryozoans, tunicates, etc.); ii) chemical synthesis of marine-derived drugs (such as ziconotide isolated from *C. magus*); and iii) another newly emerging approach in marine drug discovery to improve MNP drug discovery outcomes. These results provide credence to the theory put up by Ancheeva et al. (2018) that the bioactive substances identified from marine invertebrates, such as sponges, were produced by endosymbiotic microbes. The genetic data can be used to produce compounds once a gene has been discovered (Fajarningsih, 2012).

Additionally, reducing the environmental impact is a key concern in bioprospecting (Hunt and Vincent, 2006). Additionally, the extremely high cost of discovery and the lengthy period it takes for the majority of problems affecting marine bio-drugs to enter the global drug market drive up the overall cost, which has an impact on the medicine's final cost. The primary drawbacks of finding bioactive substances from marine resources are illustrated in Fig. 4 below.

Martins et al. (2014) did a fantastic job of illuminating the business and market factors that are important but frequently disregarded in the creation of new NPs. The following are some of the issues that must be resolved during the very early stages of development: (i) What are the product's possible industrial applications and the market demand for that specific compound activity? (ii) How much would a kilograms of the finished bioactive material cost in total? (iii) The compound's ideal formulation and optimum delivery method; (iv) What manufacturing method is being used, and is the supply sustainable? Lastly, (v): How will the product enter the supply chain? The responses to these queries will be used to evaluate the progression of marine bio-drug discoveries up until they became actual drugs available on the market.

To improve the outcome of MNP drug discovery, the application of microbiology, biochemistry, genetics, bioinformatics, genomics, and meta-genomics has increased recently (Fajarningsih, 2012). The biological assay methods for extracts, fractions, and pure chemicals are another area where marine drug development programs might be improved. Automation of assay-based separation design for MNPs has the potential to significantly enhance the

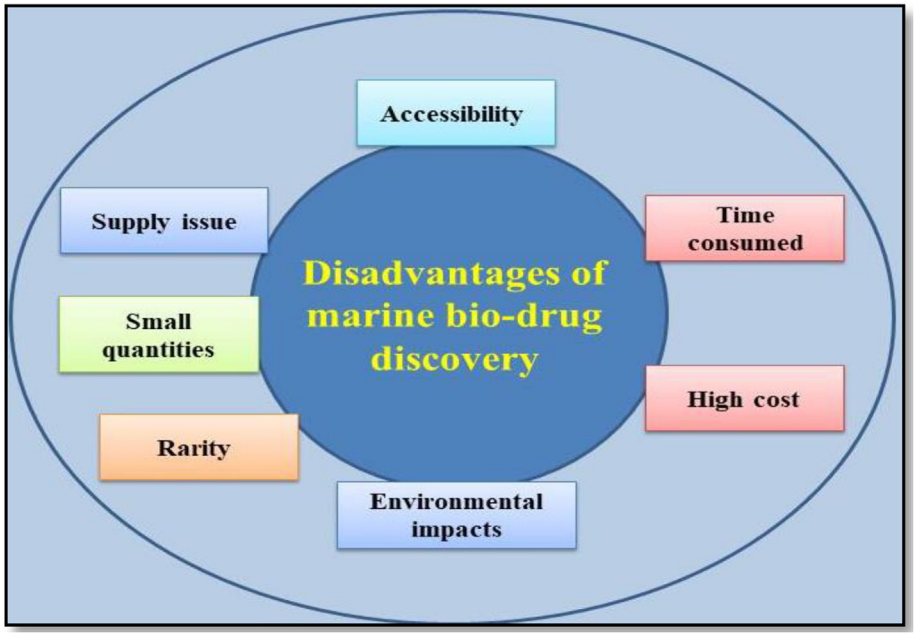

Fig. 4. Diagram displaying disadvantages of bio-drug discovery from marine resources (modified from Sruthi et al., 2020).

discovery of many kinds of NPs in nature (Sruthi et al., 2020). In order to introduce NPs to the world of high-throughput screening, libraries of crude extracts were initially developed. Purified compound libraries, also known as peak libraries, were later introduced as a way to reduce cycle time, and these represent important advancements over the conventional procedure. Pre-purification of extracts is one way to increase efficiency, but it also requires a significant investment of resources before screening can begin. new technologies that can be applied to swiftly connect a chemical species with a target activity (Siegel et al., 1998).

8. Conclusion

Effective treatment is usually required for severe human illnesses such virus infection, tumor development, cancer, inflammation, angiogenesis, blood pressure, thrombosis, etc. So, the demand for new pharmaceuticals depends heavily on ongoing research and discoveries. On the other hand, marine settings are found all over the world and have a variety of distinctive ecosystems that serve as homes for lower and higher order plants and animals. As a result, finding bioactive NPs that show significant potential for the treatment of human and fish diseases is extremely easy. The diversity of marine invertebrates (sea stars, sea sponges, sea cucumbers, sea urchins, sea worms, soft corals, sea hares, etc.) isolated from Egyptian waters of the Mediterranean and Red Seas was the subject of promising findings from considerable research. These species could potentially be used in the bio-drug sector. Despite the fact that research on marine organisms is still in its infancy in comparison to terrestrial ones, powerful medications like cytarabine (Cytosar-UW, DepocytW), vidarabine (Vira-AW), and ziconotide (PrialtW) have been licensed and are in use today. The most potent bioactive substance(s) must first be identified, and then their structures must be clarified.

It should be thought about if public funding agencies should make long-term, high priority investments in marine bio-discovery. Abbott Laboratories, Nofima, Lonza Group Ltd., Aker Biomarine, New England Biolabs Inc., Cyanotech Corporation, GlycoMar, Prolume Ltd., Marinova, and Qingdao Codo International Ltd. are just a few of the businesses that have participated in the marine biotechnology market. According to statistics, the medical sector had a revenue share of around 33 % in 2022, and the size of the global marine biotechnology market is expected to double by 2032 and grow throughout the projection period of 2023–2032.

Conflicts of interest

No conflicts of interest.

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