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BIOACTIVE COMPOUNDS FROM MARINE INVERTEBRATES AND THEIR PHARMACEUTICAL POTENTIAL

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ABSTRACT: Marine environment is an exceptional storehouse of novel bioactive natural products that are mainly found in invertebrates such as sponges, arthropods, annelids, molluscs, *etc*. This diversity has been the source of unique chemical compounds. A large portion of these natural compounds has been extracted from marine invertebrates. Marine invertebrates are rich sources of bioactive compounds and their biotechnological potential attracts scientific and economic interest worldwide. Marine invertebrates are extremely diverse, largely productive, untapped oceanic resources with chemically unique bioactive compounds. Marine natural products are generally secondary metabolites. The number of natural products isolated from marine organisms increases rapidly. Isolated compounds from marine invertebrates have been shown pharmacological activities. They are helpful for the invention and discovery of bioactive compounds, primarily for deadly diseases like cancer, an Acquired immunodeficiency syndrome (AIDS), osteoporosis and so forth. So marine life is fascinating and has great potential for the development of drugs. The present review aims to know about the bioactive compounds produced by marine invertebrates and their use and application in the pharmaceutical field.

INTRODUCTION: Marine environment is the largest aquatic ecosystem on the planet with high salt content and the most important source of biodiversity in the world [1]. Marine habitats offer diverse ecosystems and serve as an excellent source of natural bioactive molecules, novel compounds, secondary metabolites and enzymes. Marine natural products have attracted attention to biologists and chemists all over the world for the last five decades [2].

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Marine organisms, especially those that are sedentary in nature, have evolved biochemical and physiological mechanisms that include producing bioactive compounds for communication, protection against predation, infection and competition. Environmental pressure like competition for space, nutrition and self-defense for marine organisms produces a diverse array of compounds called secondary metabolites.

These secondary metabolites are adaptive and play a key role in the host's defense against the pathogen, parasites, predators, competition and epibiota [3]. From small to medium molecular weight, marine bioactive compounds are produced for greater survivability or fecundity. Many marine organic compounds have been shown to be also useful for humans: as drugs, agricultural medicine,

cosmetics and health foods. By the end of the year 2020, nine marine-derived anticancer drugs are available on the market and the field is currently growing exponentially [4]. Marine invertebrates are extremely diverse, largely productive, untapped oceanic resources with chemically unique bioactive lead compounds contributing a wide range of screening for the discovery of lead compounds with an extensive array of pharmacological properties owing to the presence of polyphenols, alkaloids, terpenoids and other secondary metabolites. Despite the enriched bioactive compounds, the marine invertebrates are largely unexplored for identification, screening, pre-clinical and clinical assessment of lead compounds and their synthetic analogs remain a major task to be solved. This marine environment harbors a wealth of organisms that produce a wide variety of primary and secondary metabolites with demonstrated significant biological activities [5].

Marine invertebrates-derived compounds may be useful as an alternative medicine for various diseases. A large number of biologically active compounds are isolated from marine invertebrates. The best-known examples include eleutherobia from eleutherobia family of corals, sarcodictyin from Mediterranean stolonigeran coral, the bryostatin from Bryozoan *Bugulla neritina* and the dolastatin from the seahare *Dollabella auriculata* [6]. The present review focuses on the potential use of bioactive compounds from marine invertebrates and its pharmaceutical importance.

Bioactive Compounds from Poriferans: Sponges (porifera) are sessile aquatic organisms, filter feeders and the oldest multi-cellular animals. There are more than 8700 species, including marine and non-marine species, according to the worldwide Porifera Database [7]. Most bioactive compounds from sponges have anti-inflammatory, antitumor, antibiotic or antifouling, antiviral, antimalarial and immune or neurosuppressive effects. Marine sponges have the potential to provide future drugs against important diseases such as malaria, cancer and a range of viral diseases. Of 10000 marine sponges, 11 genera are known to produce bioactive compounds and only three genera Haliclona, Petrosia and Discodemia are anticancer, antimalarial compounds [8]. Marine sponges are a rich source of bioactive compounds with anticancer activity. One natural compound from marine sponges with promising anticancer activity is Renieramycin M. They were isolated from marine sponges belonging to genera Reniera. The preclinical results reveal that Renieramycin M induces apoptosis in lung cancer cells through the p53-dependent pathway. The compound may inhibit progression and metastasis of lung cancer cells [9]. (+)-Discodermolide is a natural polyketide that was isolated in 1990 from the Bahamian deep-sea sponge, *Discodermia dissoluta*. Preclinical studies showed that (+) – discodermolide potently inhibited the proliferation of several cultured (multidrug-resistant) cancer cell lines by stabilizing their microtubules, leading to the arrest of cell division in the M phase of the cell cycle. The drug showed promising activity against pancreatic cancer and various other drug-resistant malignancies [10].

A synthetic analog of Halichondrin B which was originally isolated from a Japanese sponge *Halichondria okadai*. The mechanism of cell toxicity was studied that the halichondrins are potent tubulin inhibitors and causing a characteristic G2-M cell cycle arrest with disruption of the mitotic spindle11. Girolline is a 2-aminoimidazole derivative isolated from the New Calidonian Sponge *Pseudaxinyssa cantharella*. It is a potent anticancer agent, as it inhibited protein synthesis in eukaryotic cells at the termination step rather than at the initiation [12].

Immunosuppressive compounds were isolated from a deepwater marine sponge at the end of 1980s. A total of 10 marine bacterial strains were isolated from the marine sponge *Callyspongia difusa*, which showed remarkable antagonistic activity against clinical bacterial pathogen. The findings, according to researchers, suggest that *Bacillussp*. contribute novel antibiotics to overcome infection and also for the production of potential immunomodulator [13]. Biologically active two compounds, namely sesquiterpenoids and avarol, which was exhibited antimicrobial activity and also found active against 'AIDS' virus and it was first isolated from a Mediterranean sponge *Dysidea avara* and later on from an Australian sponge Dysidea sp [14]. Antifungal and antimicrobial activities have been reported in the tetracyclic furanoditerpenes isolated from sponge *S. officinalis*. Bisindole alkaloids cis-

3, 4-dihydrohamacanthin B and bromide-oxytopsentin have been isolated from the South African spong *Topsentia pachastrelloides* and shown to have antimicrobial activity [15]. Sponges can produce bioactive compounds which has antiviral activity. The important antiviral lead of marine origin is a nucleoside Ara-A (vidarabin) isolated from sponge *Tethyacrypta*. It inhibits viral DNA polymerase and DNA synthesis of herpes, vaccinica and *Varicella zoster* virus [16]. Norbatzelladine L isolated from a marine sponge of genus Monanchora has an antiviral activity against Herpes Simplex virus type (HSV-1) [17]. Several sponges-derived anti-malarial compounds have been discovered in the last few decades. It has been reported that Manzamine A has potent antimalarial activity against rodent malarial parasite *Plasmodium berghei in-vitro* [18].

Bioactive Compounds from Coelenterates: The phylum cnidaria includes more than 10,000 species that are widespread throughout the ocean, with only a few species have been found in freshwater. This phylum has been divided into five classes: Anthozoa (including corals), Cubozoa (cube jellyfish), Hydrozoa (the most variable class), Scyphozoa (true jellyfish) and Staurozoa (the most recently characterized class) [19].

There has been much interest in the metabolites of jellyfish, sea nettle, the Portuguese man of war and the sea wasp release nematocyst venom from the tentacles produce painful injuries that contain complex mixtures of enzymes and pain-producing factors. The nematocyst venom of *P. physali* is a mixture of toxic protein and enzymes which showed multi-action, including dermonecrosis, neurotoxicity, hemolysis and cardiotoxicity [20].

Soft coral is a rich source of secondary metabolites such as diterpens, sesquiterpenes, furanoditerpenes, terpenoids, capnellenes and steroids from Lobophytum, Sinularia, Sarcophyton, Capnella, Dendronephthya. They have HIV inhibitory, cytotoxicity, anti-inflammatory, anticancer and antimicrobial activity [21, 22]. The glycosides, cervicosides and prostanoids claviridenones, from the soft corals *Sinularia cervicornis* and *Clavularia viridis* were shown to have antitumour activity against human cancer cells lines. The polyoxygenated steroids from *Alcyonumpata-gonicum* and another coral species *Nephteaerecta* were represented the most numerous group of coral diterpenoids which have mild to strong cytotoxicity to human cancer cell lines. Other cytotoxic and cytostatic compounds from soft corals were eleutherobin and sarcodictyin [23].

Several macrolides like bryostatin-1andbryostatin-2 were isolated from *Bugulaneritina*. Some of these metabolites were showed a high order of antineoplastic activity [24]. In Sinularia sp., a tetra prenylatedspermine derivative has been isolated, sinulamide, which revealed an ATPase inhibitory activity. Sinulide is a potential antiulcer drug, as it inhibits the production of gastric acid [25]. Prostanoids isolated from *Clavulariaviridis* exhibited potent inhibitory effects on phytohemagglutinin-induced proliferation of peripheral blood mononuclear cells. A less active diterpene, Asteroid A from Asterospicularialaurae exhibited cytotoxicity against human hepatocellular carcinoma [26]. *Pseudopterosin* is tricyclic diterpenepentose glycoside isolated from the sea whip *Pseudopterogorgia elisabethaea* Caribbean soft coral species. These compounds have anti-inflammatory and analgesic properties that exceed the potencies of existing cyclooxygenase inhibiting non-steroidal anti-inflammatory drugs [27].

Among Anthozoa, soft corals, especially those belonging to the Alcyonlidae family, are recognized as a rich source of a large variety of bioactive molecule ranging from sesquiterpenes to diterpenes, polyhydroxysteroids and polyamine metabolites [28]. They have cytotoxic, anti-inflammatory and antimicrobial activities. *Sinularia gyrosa* lead to the discovery of interesting antiviral compounds, such as an unusual norcembrane type diterpenoid and three new gyrosanols [29].

Sesquiterpenoid metabolites isolated from Eunicea sp. display antiplasmodial activity against the malarial parasite *P. falciparam* [30]. *Simularia* and *Sarcophytons* pecies produced an interesting bioactive compound with antiviral properties against various influenza strains. A polyhydroxylated sterol together with three new ceramide derivatives was isolated from *Sinularia candidula*, a soft coral living in the Egyptain Red sea. These compounds exhibited selective antiviral

activity against the orthomyxovirus of the avian influenza H5NI, revealed by plaque reduction assay in MDCK cells [31].

Bioactive Compounds from Marine Annelida: The Annelida phylum is made up of a bilaterally symmetrical animal with bodies that consist of three regions. The diversity of annelids comprises ringed or segmented worms, including ragworms, earthworms and leeches. Annelids have been divided into three taxonomic classes Polychaeta, Oligochaeta and Hirudinea [32]. Marine polychaete has been used to treat several pathophysiological conditions such as arthritis, osteoporosis, bone cancer, *etc*. The bioactive compound has been isolated from a marine annelid Arenicolamarina. The compound arenicins are 21 residue peptides, which are completely killed *E. coli* [33]. The coelomic fluid of the annelid has antibacterial activity. Water, methanol and acetone extract from the whole body tissue of Polychaeta Perinereis cultrifera have potent antibacterial and antifungal activity [34].

Numerous studies on the effectors of the innate immune system have demonstrated the contribution of antimicrobial peptides (AMPs). The most important AMP isolated from marine annelids is histidine. It is purified from the ragworms *Neris diversicolor* [35]. Hedistin was identified from the coelomocytes of the sandworm *N. diversicolor*. The principal source of AMPs in annelids had been found in three species of marine Polychaetes Arenicola marina, *Nereis diversicolor* and *Perinereisai buhitensis*. Perinerin is the bioactive compound isolated from the clam worm *Perinereisai buhitensis*. The coelomic fluid of *Perinereis cultrifera* presents potent antibacterial and antifungal activity [36]. Lumbricin^{-1} is a proline-rich antimicrobial peptide of 62 amino acids showing antimicrobial activity *in-vitro* against fungi, gram +ve and gram -ve bacteria. AMPs have been studied in two species of leeches *Theromyzontessulatum, H. medicinalis*. Three AMPs were isolated and fully characterized from the body fluid of *T. tessulatum*. These are theromacin, a cysteine-rich AMP exhibiting bactericidal activities, theromyzin an anionic peptide with bacteriostatic properties, Neuromacin, like theromacin displayed bactericidal activity against gram-positive and gram-negative bacteria [37, 38].

Bioactive Compounds from Marine Arthropoda: Arthropod is an invertebrate animal having an exoskeleton, a segmented body and paired jointed appendages. Arthropods form the phylum euarthropoda, which includes insects, arachnids, myriapods and crustaceans [39]. Antimicrobial activity has been found in the hemolymph and hemocytes of the Northern shrimp *Pandalus borealis*, the hermit crab *Paguru-sbernhardus*, the spider crab *Hyasaraneus* and the king crab Paralithodes camtschatica. Callinectin is a cationic antimicrobial peptide of 3.7kDa that represents the major antibiotic activity from blue crab *Callinectes sapidus* [40]. The extracts from crustaceans is another source of antimicrobial peptides. Hemolymph extracted from the male and female branchyuran crabs, *Liagorerubromaculate*, possessed strong antibacterial activity [41].

The hemocyte protein (Sp-ACFs) from mud crab Scylla paramamosainis a potent anti WSSV (white spot syndrome virus) compound when tested in hematopoietic tissue cell culture from the freshwater crayfish *Cherax quandricarinatus* [42]. An agglutinin named limulin was discovered in *Limulus polyphemus*, a sialic acid-binding lectin, playing a role in the host defense mechanism. Indian variety horseshoe crab, *Carcinoscorpius rotundacauda* contains sialic acid-binding lectin carcinoscorpin, which acts as an opsonizing agent [43]. Venomous arthropods are a rich source of bioactive compounds. The antibacterial peptide scygonadin from the crab *S. paramamosai* probably plays a physiological role in reproductive immunity. Scygonadin could interfere with the replication of the white spot syndrome virus in cultured crayfish haematopoietic cells [44].

Bioactive Compounds from Molluscs: The phylum mollusca is one of the most attractive invertebrate phyla and they are widely distributed worldwide, having many representatives in the marine and estuarine ecosystem, including whelks, clams, mussels, oysters, scallops, squids octopods [45]. *Marine mollusc* area source of secondary metabolites with wide range of pharmaceutical applications.

That is, they are isolated and tested for anticancer, anti-inflammatory, antimicrobial properties [46]. Two species of marine mollusc namely *Thais tissoti* and *Babylonia spirata* contain bioactive compounds possessing strong antimicrobial properties against human pathogens *Klebsiella pneumonia*, *Proteous mirabilis* [47]. The four novel antimicrobial peptides from *Rapanavenosa* gastropod of Asiatic origin, which represents a serious threat to the malacological resources of marine water, is an interesting source of antimicrobial peptides. Proline-rich peptides isolated from hemolymph sample show strong antimicrobial activity against *S. avereus* and K. pneumoniae [48].

Marine mollusc have anticancer activity. There are many biologically active compounds that were isolated from mollusc species.Dolastatin-10 the linear peptide and dolastatin-15 desipeptide were isolated from seahare *Dollabella auricularia* of the Indian Ocean. They have promising anticancer properties [49]. Dolastatin-10 is a pentapeptide having four unique structural residues, Dolavalin, Dolaisoleucine, Dolaproline and Dolaphenine, along with valine. It interferes and disrupts cell division by mitosis. It acts as an antimitotic agent. Their significant inhibition property of mitotic cell division suggested that they can effectively target cancer cells [50]. Kahalalides are a group of cyclic peptides isolated from the Indo-Pacific mollusc *Elysia rufescens*. Kahalalides are probably secondary metabolites synthesized by the mollusc from peptides produced from its diet of green algae notably *Bryopsis pennate* [51].

There are 7 Kahalalide peptides. Kahalalide F, a depsipeptide, is the largest and most active. Kahalalide F exhibits potent *in-vitro* antitumour activity against a host of solid tumour, including human prostrate, breast cancer cell lines and hepatocellular liver carcinoma. It also exhibited significant non activity on non-tumour human cells [52]. Glycosaminoglycan like polysaccharides isolated from the marine mollusc *Cerasto dermaedula*. This compound has exhibited antiproliferative activity in chronic myeloid leukemia as well as in relapsed acute lymphoblastic leukemia models. Turbostatin, 1-4 a depsipeptide derived from the Asian marine *mollusc Turbo stenogyrus* found to have potent anticancer property [53]. Haemocyanins and hemocyanin-derived peptides from marine and terrestrial gastropods have potent antiherpes virus [54]. A series of bioactive compounds with promising anti-inflammatory and analgesic properties have been identified and isolated from seaweeds, marine bacteria, invertebrates, tunicates and include fishes. Cone toxins of cone species have potential anti-inflammatory natural ingredients that synthesize several structurally and functionally diverse compounds, which provide a wide range of therapeutic applications [55].

Bioactive Compounds from Echinoderms: Echinoderms are deuterostome invertebrates with a phylogenetic position closely related to chordates and hemichordates. The phylum contains about 7000 extinct species, including sea lilies, feather stars, brittle stars, starfish, sea urchin, and dollars and sea cucumber and about 13,000 extinct species with a fossil registry from the early Cambrian period. Marine organisms belonging to echinoderms are rich in bioactive compounds, although a low chemical diversity has been recorded compared to other phyla [56, 57].

Bioactive compound astero saponins were reported as hemolytic, antineoplastic, cytotoxic, antitumour, antibacterial, antiviral, antifungal and anti-inflammatory activities [58]. Many cerebrosides, pyrimidine nucleosides, thymine deoxyriboside and uracil deoxyribose have been isolated from the star fish *Acanthester planei* [59]. Echinoderms are a potential source of novel antibiotics. Antibacterial activity in different body parts of the sea urchin *Strongylocentrotus droebachiensis*, the starfish *Asterias rubens* and the sea cucumber *Cucumariafrondosa*. Antibacterial and antifungal activity has been found in the alcoholic extract of holothurian species. The antibacterial activity has been found in the extract of the body wall, coelomocytes and eggs in a variety of species [60].

The sea urchin gonads contain polyhydroxylated napthoquinone, echinochrome A which is potent in antioxidant activity. And also, it contains other valuable bioactive compounds such as polyunsaturated fatty acid and beta carotene have preventive effects on cardiovascular disease and cancer. The phospholipase A2 from the sea star *Acanthes terplanci* has anti-HIV1 activity [61]. Seven known naphthopyrones and a novel

pyranolchromene were recently isolated from the water or ethanol extract of the Australian crinoid Capillaste rmulti radiatus and tested for HIV-1 potential [62]. Echinoside A and dis- echinoside A, which are glycosylated triterpenes isolated from the sea cucumber Pearsonothuriagraeffei, showed cytotoxic activity and had both potent compounds activity in blocking cell cycle progression and induce apoptosis [63]. Three fungal triterpene glycosides, including scabraside A, echinoidea A and holothurin A, were isolated from *Holothurin scabra* [64].

Frondoside A is a mono sulphated pentaoside isolated from *Cucumaria frondosapossess* immuno modulatory properties. Frondoside A increased cell-based immunity is a preventive agent to improve the innate immune response. A hot water extract of sea cucumber *Stichopus variegatus* inhibit proliferation and produces concentration-dependent cytotoxicity in human colon cancer. The antitumour and antimetastatic effect of two sulfated triterpene glycosides Holothurin A and 24-dehydroechinoside A (DHEA), isolated from sea cucumber species. Frondoside A has also inhibited lung cancer and has a good potential for breast cancer treatment. Asteroids (seastar) produce steroid derivatives, fatty acids, ceramides and few alkaloids; some of them possess pharmacological activities [65].

Brittle stars or Ophivroids are the largest group of echinoderms. Several classes of secondary metabolites such as Carotenoids, gangliosides, brominated indoles, phenylpropanoids, several groups of terpenes and steroids are isolated from brittle stars [66]. Echinoids are the living representative of echinodermata [67]. The main MNPs of sea urchins are proteins, polysaccharides and pigments located in spine gonads, etc. Studies on their MNPs have mainly focused on protein derived from naphthoquinone pigments that shows antibacterial, antioxidant, anti-inflammatory activity [68, 69].

CONCLUSION: Marine natural products with their unique structural features and pronounced biological activities continue to provide lead structure in the search for new drugs from nature. Invertebrates such as sponges, coelenterates, annelids, arthropods, mollusc and echinoderms are either sessile or slow-moving and mostly lack morphological defense structures have so far provided the largest number of marine-derived secondary constituents, including some of the most interesting drug candidates. The curiosity of science and industry has established the oceans as a prospective source for new potential drug leads. Scientists have come up with drugs of various categories, out of which anticancer, anti-inflammatory, analgesics and antiviral are the most important to mention. These lead molecules are in different stages of preclinical and clinical testing stages around the world. Novel products from marine invertebrates exhibit potent activity in various in-vitro and *in-vivo* assays geared towards discovering pharmaceutical leads in this area. All the biologically active compounds from the marine invertebrates can cure non-curable disease and have antitumor, antimalarial, anti-inflammatory, antifungal, antiviral, antibacterial activities. The evolution of marine pharmacology as a specialty will help us optimize the use of marine resources around the marine environment.

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