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Review

Biomedical Compounds from Marine organisms

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Abstract: The Ocean, which is called the 'mother of origin of life', is also the source of structurally unique natural products that are mainly accumulated in living organisms. Several of these compounds show pharmacological activities and are helpful for the invention and discovery of bioactive compounds, primarily for deadly diseases like cancer, acquired immuno-deficiency syndrome (AIDS), arthritis, etc., while other compounds have been developed as analgesics or to treat inflammation, etc. The life-saving drugs are mainly found abundantly in microorganisms, algae and invertebrates, while they are scarce in vertebrates. Modern technologies have opened vast areas of research for the extraction of biomedical compounds from oceans and seas.

Key Words: Biomedical compounds, ocean, anti-cancer metabolite, anti-HIV metabolite

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Introduction

Marine biotechnology is the science in which marine organisms are used in full or partially to make or modify products, to improve plants or animals or to develop microorganisms for specific uses. With the help of different molecular and biotechnological techniques, humans have been able to elucidate many biological methods applicable to both aquatic and terrestrial organisms. According to [1], only 10% of over 25,000 plants have been investigated for biological activity. The marine environment may contain over 80% of world's plant and animal species [2]. In recent years, many bioactive compounds have been extracted from various marine animals like tunicates, sponges, soft corals, sea hares, nudibranchs, bryozoans, sea slugs and marine organisms [3,4]. The search for new metabolites from marine organisms has resulted in the isolation of more or less 10,000 metabolites [5], many of which are endowed with pharmacodynamic properties.

The deep knowledge about nerve transmission has been learnt using squid and its giant nerve axons and the mesenteries of vision have been unraveled using the eyes of horseshoe crabs, sharks and skates. The surf clam is proving an excellent model for the cell cycle and its regulation while the sea urchin is a model for understanding the molecular basis of cellular reproduction and development. The objective of this review is to highlight some of the recent developments and findings in the area of marine biotechnology with special reference to the biomedical potential of marine natural products.

Availability of Marine Natural Products

Natural products have long been used as foods, fragrances, pigments, insecticides, medicines, etc. Due to their easy accessibility, terrestrial plants have served as the major source of medicinally useful products, especially for traditional or folk medicine. According to [6], about 25% of all pharmaceutical sales are drugs derived from plant natural products and an additional 12% are based on microbially produced natural products. The marine environment covers a wide thermal range (from the below freezing temperatures in Antarctic waters to about 350°C in deep hydrothermal vents), pressure range (1-1000 atm), nutrient range (oligotrophic to eutrophic) and it has extensive photic and non-photic zones. This extensive variability has facilitated extensive speciation at all phylogenetic levels, from microorganisms to mammals. Despite the fact that the biodiversity in the marine environment far exceeds that of the terrestrial environment, research into the use of marine natural products as pharmaceutical agents is still in its infancy. This may be due to the lack of ethno-medical history and the difficulties involved in the collection of marine organisms [7]. But with the development of new diving techniques, remote operated machines, etc., it is possible to collect marine samples and during the past decade, over 5000 novel compounds have been isolated from shallow waters to 900-m depths of the sea [2].

Some Clues from the Physiological Study of Marine Organisms

Life originated in the sea and during evolution, marine organisms have developed into very sophisticated physiological and biochemical systems. During the adaptation to the terrestrial environment, a number of physiological changes have taken place, but in most cases, the basic functions were almost completely retained. The architecture of the shark liver is similar to that of the human liver and the biochemical transformations which take place in a shark's liver, appear to be similar to those that occur in a human liver [8], with slight modifications [9]. The eyes of man and octopus are very similar in structure and function irrespective of the fact that no evolutionary link exists between them [10]. Insulin from fish such as cod exerts the same hormonal activity in mammals as does homologous insulin and insulin from tuna (which has a 40% difference in amino acid residue [11]) that has been used to treat diabetic patients [9]. This suggests that the basic physiological functions of molecules may remain the same regardless of the structural changes, which may possibly occur during evolution [9]. Marine thermococcales have been an important source of high fidelity thermostable DNA polymerases (Pfu, Vent, Pab, etc.) [12] and in addition, the high structural conservation and complementation of DNA replication proteins between euryarchaeal *Pyrococcus* and humans make hyperthermophilic archaea a model of choice to study eukaryotic DNA replication [13].

The knowledge of the physiological and biochemical features of marine organisms might contribute to the identification of natural products of biomedical importance. According to [9], an extract of regenerating fish nerve may induce regeneration of an injured nerve in rabbit.

Marine Bacteria as a Source of Metabolites

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been isolated from microorganisms, many based on their use in traditional medicine. In the past century, however, an increasing role has been played by microorganisms in the production of antibiotics and other drugs for the treatment of some serious diseases. Since the discovery of penicillin in 1929 to the Taq DNA polymerase obtained from *Thermus aquaticus* (Yellowstone hot spring) in 1989, nearly 50,000 natural products have been discovered from microorganisms. Over 10,000 of these are reported to have biological activity and over 100 microbial products are in use today as antibiotics, antitumour agents, and agrochemicals [14].

In spite of such successes in drug discovery from microorganisms, marine microorganisms have received very little attention. The difficulty in the search of metabolites from marine bacteria is mainly due to the non-culturability of the majority (over 99%) [15]. The studies made by the scientists at the Scripps Institution of Oceanography show that marine bacteria are capable of producing unusual bioactive compounds that are not observed in terrestrial sources [16,17]. Thermo-stable proteases, lipases, esterases, and starch and xylan degrading enzymes have been actively sought and in many cases are found in bacterial and archaeal hyperthermophilic marine

microorganisms [18]. An unusual gram-positive bacterium from deep-sea sediment, which produced a series of new natural products, macrolactin A-F of an unprecedented C24 linear acetogen origin has been isolated [19]. The major metabolite, macrolactin A inhibits B16-F10 murine melanoma cells in *in vitro* assays, showing significant inhibition of mammalian herpes simplex virus (type I and II) and protecting T lymphocytes against human immuno-deficiency virus (HIV) replication [14]. On the other hand [20], a microbial metabolite (from *Alteromonas* spp.) has been developed with anti-HIV potential as reverse transcriptase inhibitor from marine microbes isolated from the tissues of Bermudian marine sponge. Some *Vibrio* species have been found to produce a variety of extra cellular proteases. *Vibrio alginolyticus* produces six proteases including an unusual detergent-resistant, alkaline serine exoprotease. This marine bacterium also produces collagenase, an enzyme with a variety of industrial and commercial applications, including the dispersion of cells in tissue culture studies [17].

Marine toxins such as tetrodotoxin, saxitoxin, ciguatoxins and brevetoxins are potent and specific sodium channel blockers, and pharmacological studies with these toxins have played a major role in developing the concept of sodium channels in general and membrane channels and voltage–gated sodium channel in particular [21-23]. Several studies show that these toxins may be produced by marine bacteria [24-26]. These toxins are useful in neurophysiological and neuropharmacological studies, and marine bacteria could be an important source of these valuable molecules.

Metabolites from Marine Cyanobacteria

The fact that cyanobacteria in general and marine forms in particular are one of the richest sources of known and novel bioactive compounds including toxins with wide pharmaceutical applications is unquestionable. Among the five divisions of microalgae, studies of biomedical natural products have been concentrated on only two divisions, i.e., Cyanophyta (blue-green algae) and Pyrrophyta (dinoflagellates). Although several metabolites have been isolated from cyanophytes [27,28], most of them are isolated from fresh water species, which are cultured easily in comparison to marine organisms. Lyngbyatoxin-A and debromoaplysiatoxin are two highly inflammatory but structurally different metabolites isolated from toxic strains of *Lyngbya mausculata* collected in Hawaii [29], and anatoxin-a from *Anabaena ciecinalis* [28]. Some of the marine cyanobacteria appear to be potential sources for large-scale production of vitamins of commercial interest such as vitamins of the B complex group and vitamin-E [30]. The carotenoids and phycobiliprotein pigments of cyanobacteria have commercial value as natural food colouring agents, as feed additives, as enhancers of the color of egg yolks, to improve the health and fertility of cattle, as drugs and in the cosmetic industries. Some anti-HIV activity has been observed with the compounds extracted from *Lyngbya lagerhaimanii* and *Phormidium tenue*. More than 50% of the 100 isolates from marine sources are potentially exploitable bioactive substances. The substances tested for were either the ones that killed cancer cells by inducing apoptotic death, or

those that affected cell signaling through activation of the members of protein kinase-C family of signaling enzymes [31,32,33]. Cultured *Fusarium chlamydosporum* isolated from the Japanese marine red alga *Carpopeltis affinis* is the source of fusaperazines A & B, two new sulphur-containing dioxopiperazine derivatives, and two known compounds which had been originally isolated from the fermentation by the fungus *Tolypocladium* spp. [34]. Chalcomycin-B exhibited activity against a variety of microorganisms and microalgae [35]. Four new epipolysulphanyldioxopiperazines were isolated from a culture of the fungus *Leptosphaeria* spp. originating from the Japanese brown alga *Sargassum tortile* [36]. Absolute stereochemistries were determined by chemical analyses and transformations. Each compound possessed significant cytotoxic activity against the P388 cell-line, while one of the leptosins also exhibited appreciable cytotoxicity against a disease-oriented panel of 39 human cancer cell-lines, and specifically inhibited two protein kinases and topoisomerase-II [37]. Cultures of the marine fungus *Hypoxylon oceanicum* [38] from mangrove wood at Shenzen, China, yielded the macrocyclic polyesters and the linear polyesters [39]. The absolute configurations of the polyesters were deduced from circular dichroism (CD) spectral studies. The compounds exhibited modest activity against the phytopathogenic fungus *Neurospora crassa*. The anti-inflammatory and anti-proliferative properties of scytonemin, an extracellular sheath pigment originally isolated from the cyanobacterium *Stigonema* spp. have been reported [40,41,42]. Goniodomin-A, an antifungal polyether macrolide from the dinoflagellate *Goniodoma pseudogoniaulax* [43] has been shown to inhibit angiogenesis by the inhibition of endothelial cell migration and basic fibroblast growth factor (bFGF)-induced tube formation and is active *in vivo* [44]. An immunosuppressive linear peptide microcolin-A, which at nanomolar concentrations suppresses the two way murine mixed lymphocyte reaction, has been isolated from *Lyngbya majusculata* [45]. A unique thiozoline-containing compound, curacin-A, has been purified from the organic extract of a Curacao collection of *L. majusculata* [46]. This compound has been found to be an exceptionally potent antiproliferative agent as it inhibits the polymerization of tubulin, which shows some selectivity for colon, renal and breast cancer-derived cell lines [14]. A series of noval antibiotics agents have been isolated from dianoflagellates, antifungal agents from *Gambierdiscus toxicus* [47] and brevitoxins from *Ptychodiscus brevis*. As they depolarize the excitable membranes and their binding sites on sodium channel the mechanism seems to be different from that of other activators [14, 48]. Okadaic acid, a polyether fatty acid produced by *Prorocentrum* spp., has been a key molecule in studying signal transduction pathways in eukaryotic cells since it is a selective protein phosphatase inhibitor [49].

Metabolites from seaweeds

Seaweeds are abundant in the intertidal zones and in clear tropical waters. Marine algae have received comparatively less bioassay attention. Presently the seaweed industry consists of two kelps, three *Gelidium* species one *Gracilaria-/Gracilariopsis* species, etc. [50]. In addition, there are a number of seaweeds with economic potential [51]. It will be of great significance if these species

could be the major role players in drug development. Alternatively, findings from academic laboratories could result in new cultivation initiatives. Nonetheless, the red alga *Sphaerococcus coronopifolius* was shown to have antibacterial activity [3]; the green alga *Ulva lactuca* was shown to posses an anti-inflammatory compound; and an anti-tumor compound was isolated from *Portieria hornemannii* [52]. *Ulva fasciata* produces a novel sphingosine derivative has been found to have antiviral activity *in vivo* [53]. A cytotoxic metabolite, stypoldione, which inhibits microtubule polymerization and thereby prevents mitotic spindle formation, has been isolated from tropical brown alga, *Stypodium zonale* [54,55]. *P. hornemannii* is found to be a novel source of cytotoxic penta halogenated monoterpene, halomon, which exhibited one of the most extreme examples of differential cytotoxicity in the screening conducted by the National Cancer Institute (NCI), USA. Halomon has been selected for preclinical drug development since this compound shows toxicity to brain, renal and colon tumor cell-lines and preliminary *in vivo* evaluations have been encouraging [14]. An iodinated novel nucleoside has been isolated from *Hypnea valitiae*, which is a potent and specific inhibitor of adenosine kinase. It can be used in the studies of adenosine receptors in a variety of systems, and in studies on nucleotide metabolism and regulation [56].

The green alga *Codium iyengarii* from the Karachi coast of the Arabian Sea has been found as the source of a steroid, iyengadione and two new steroidal glycosides, iyengarosides A and B. Iyengaroside-A displayed moderate activity against a range of bacteria [57]. *Sargassum carpophyllum* from the South China Sea is the source of two new bioactive sterols. These sterols induced morphological abnormality in the plant pathogenic fungus *Pyricularia oryzae*; also exhibited cytotoxic activity against several cultured cancer cell lines [58]. *Sargassum polycystum* collected in the North China Sea yielded a new sterol, stigmast [59]. The fact that there are many algae that can convert simple polyunsaturated fatty acids such as arachidonic acids into complex eicosanoids and related oxylipins has been an exiting development [60]. Derivatives of arachidonic acids are important in maintaining homeostasis in mammalian systems and aberrant production of metabolites of this class occurs in diseases such as psoriasis, asthma, arteriosclerosis, heart disease, ulcers and cancer [14].

Metabolites from Sponges

Approximately 10,000 sponges have been described in the world and most of them live in marine waters. A range of bioactive metabolites has been found in about 11 sponge genera. Three of these genera (*Haliclona*, *Petrosia* and *Discodemia*) produce powerful anti-cancer, anti-inflammatory agents, but their cultivation has not been studied [61]. The discovery of spongouridine, a potent tumor-inhibiting arabinosyl nucleoside in Caribbean sponge *Cryptotethia crypta*, focused attention on sponges as a source of biomedically important metabolites. The identification of the pharmacophore led to the synthesis of a new class of arabinosyl nucleoside analogues, one of which is arabinosyl cytosine, which is converted into arabinosyl cytosine

triphosphate and incorporated into cellular DNA where it inhibits DNA polymerase, is already in clinical use for the treatment of acute mylocytic leukemia and non-Hodgkin's lymphoma [56]. The compound manoalide from a Pacific sponge has spawned more than 300 chemical analogs, with a significant number of these going on to clinical trials as anti-inflammatory agents. An aminoacridine alkaloid, dercitin, has been isolated from the deep-water sponge, *Dercitus* spp. that possesses cytotoxic activities in the low nanomolar concentration range and in animal studies, prolongs the life of mice-bearing ascitic P388 tumours, and is also active against B16 melanoma cells and small cell Lewis lung carcinoma [62]. Halichondrin-B, a polyether macrolide from Japanese sponge *Theonella* spp., has generated much interest as a potential anticancer agent [14,63]. The theopederins are structurally related to mycalamide-A from marine sponge, *Mycale* spp. collected in New Zealand [64] and onnamide-A from marine sponge, *Theonella* spp. collected in Okinawa [65], which show *in vitro* cytotoxity and *in vivo* antitumour activity in many leukemia and solid tumour model systems [66]. Isoquinolinequinone metabolite cribostatin from the Indian Ocean sponge *Cribrochalina* spp. shows selective activity against all nine human melanoma cells in National Critical Technologies (NCT) panel [67]. Spongstatin, a macrocytic lactone from the Indian Ocean collection of *Spongia* spp., is the most potent substance known against a subset of highly chemoresistant tumour types in the NCT tumour panel [68]. Two new α-pyrones (herbarin) along with a new phthalide, herbaric acid, were isolated from two cultured strains of the fungus *Cladosporium herbarum* isolated from the sponges *Aplysina aerophoba* and *Callyspongia aerizusa* collected in the French Mediterranean and in Indonesian waters, respectively [69]. Herbarins displayed activity in the brine shrimp assay [69]. A culture of the fungus *Emericella variecolor* isolated from a sponge collected in the Caribbean Sea off Venezuela yielded varitriol, varioxirane, dihydroterreinand varixanthone, which were characterised by spectroscopic methods and chemical transformations [70]. Varitriol displayed increased potency toward some renal, central nervous system and breast cancer cell-lines in the NCI's 60-cell line panel, while varixanthone displayed antimicrobial activity against a range of bacteria. The antimicrobial glycolipid caminoside-A, isolated from Dominican specimens of *Caminus sphaeroconia*, was found to be a potent inhibitor of the bacterial type-III secretion system [71]. Lembehynes B and C, isolated from an Indonesian species of *Haliclona*, were found to possess neuritogenic activity against neuroblastoma cells [72].

Potent phosphate inhibitors have been isolated from sponges like, okadaic acid from *Halichondria okadai*, motuporin from *Theonella swinhoei* and calyculin-A from *Discodermia calyx* [73,74]. Inhibitors of phospholipase such as manoalide and scalaradial have proved to be useful tools to study the role of this enzyme in the release of arachidonic acid, which is a key molecule, involved in the biochemical processes leading to inflammation [75]. A number of receptor antagonists with potential as biochemical tools or structural leads to the development of therapeutics have been isolated from sponges. Examples include xestobergsterol (isolated from *Xestospongia berguista*), which inhibits immunoglobulin E mediated histamine release from mast cells and is 5000 times more potent than the antiallergic drug disodium cromoglycate [76]. Leucettamine A isolated from *Leucetta microraphis*, is a potent and selective antagonist for the

receptor for leukotrine, a non-peptide metabolite of arachidonic acid produced mainly in inflammatory cells [77]. Batzelladine A & B, novel polycyclic guanidine alkaloids from the Carribean sponge *Batzella* spp., exhibit potent inhibition to the binding of HIV glycoprotein, on CD4 receptors of T cells [14]. The series of polymethoxydienes, similar to the alkenes isolated from the cyanophyte *Tolypothrix conglutinata* [78], were isolated from a Philippine specimen of *Myriastra clavosa*, and found to be moderately cytotoxic. *Plakortis nigra*, collected from a depth of 115 m in Palau, was found to contain epiplakinic acid G and H, and the γ-lactones along with several β-carbolines (vide infra). All compounds have been found to inhibit the growth of HCT-116 cells [79]. A peroxylactone originally isolated from a *Plakinastrella* species [80] has been synthesized as a racemic mixture [81]. Two new 1,2-dioxolane peroxide acids have been isolated from *Porolithon onkodes* [82]. The moderately cytotoxic thioester irciniamine has been isolated from an *Ircinia* spp. collected in Japan [82]. The previously reported motuporins A–C [83] along with the new congeners, motuporins D–F have been found to inhibit the invasion of breast carcinoma cells into new tissues. These compounds have been isolated from *Xestospongia exigua* collected in Papua New Guinea along with an unresolved mixture of three isomers of motuporins [83]. *Hyrtios erecta* collected from the Egyptian Red Sea has been found to contain salmahyrtisol A and B and sesterstatins, all of which have shown significant cytotoxicity in human cancer cell-lines [84]. A peroxy steroid, from an Okinawan species of the genus *Axinyssa*, has been found to inhibit the growth of several human cancer cell-lines [85]. Three oxygenated sterols have been obtained from a collection of *Polymastia tenax*. The compounds have been found to have significant cytotoxicity to a range of human and murine cancer cell-lines [86].

Metabolites from Cnidarians

The discovery of prostaglandin in corals in the late 1960s contributed greatly to the rapid developments in the field of marine natural products [14]. Palytoxin, which is one of the most potent known toxins, is the product of *Palythoa* species of the family Zoanthidae. It is a useful tool for probing cellular recognition processes since it stimulates arachidonic acid metabolism and down-regulates the response to epidermal growth factor by activating a sodium pump in the signal transduction pathway using sodium as the second messenger [56]. Bioassay-guided fractionation of extracts obtained from soft coral, *Lobophytum crassum*, indicated ceramideas a moderately antibacterial component [87]. New examples of cadinene-skeleton sesquiterpenes, xenitorins A–F, have been isolated from *Xenia puerto-galerae* [88]. The relative stereochemistries of xenitorins A–F are secured by nuclear overhauser enhancement spectroscopy nuclear magnetic resonance (NOESY NMR) experiments. Xentorin A and E exhibited cytotoxicity towards the A and P388 tumour cell-lines. The structure and stereochemistry of alcyopterosin-E, a nitrate ester-containing sesquiterpene isolated from *Alcyonium paessleri* [89], was secured by total synthesis [90]. Lophotoxin from the genus *Lophogorgia* preferentially binds to the nicotinic subunit of acetylcholine receptors and blocks out cholinergic nicotinic pathway in a complex set of interacting

neurons [55]. Pseudopetrocin-E, a tricyclic diterpene pentoside from gorgonians of the genus *Pseudopterogorgia*, shows anti-inflammatory and analgesic activities equal in potency to industrial standard indomethicine [14]. A further study of *Subergorgia suberosa* yielded the sesquiterpene suberosols A–D [91]. Relative stereochemistries have been determined by NOESY NMR experiments and all the four metabolites exhibited cytotoxicity towards the P388 murine leukaemia cell-line, while suberosol C and D also exhibited cytotoxicity towards the A-549 and HT-29 tumour cell- lines.

The first chemical study of the soft coral *Lemnalia flava*, collected off Mombasa, Kenya, has yielded lemnaflavoside and three monoacetate derivatives [92]. Clavubicyclone from *Clavularia viridis* exhibited mild cytotoxicity towards MCF-7 and OVCAR-3 tumour cell-lines [93]. Bioassay-directed fractionation of the soft coral *Cespitularia hypotentaculata* yielded diterpene cespitularin A–D, a norditerpene cespitularin E and three further diterpenes, cespitularin F–H, with a novel skeleton [88]. Variable potency and selectivity was observed for the eight compounds towards tumour cell-lines A-549, HT-29 and P388. Two new dolabellane-type diterpenoids as well as the known diterpene clavenone [94] were isolated from *Clavularia* species [95]. An artificial culture of *Erythropodium caribaeorum* has been found to produce a range of diterpenes including the antimitotic agents eleutherobin and aquariolide-A [96]. Saponin was isolated from *Lobophytum* spp. collected from Hainan Island, China. Further [97] investigation of the stony coral *Montipora* spp. from Korea yielded three diacetylene, one of them were the most potent cytotoxin towards a range of tumour cell-lines [98]. *Radianthus macrodactylus*, collected in the Seychelles, yielded three high molecular weight (20 kDa) cytolysins, two low molecular weight cytolysins, RmI (5100 Da) and RmII (6100 Da), and InI, a 7100 Da trypsin inhibitor [99]. The sodium channel toxins Bg II and Bg III, isolated from the sea anemone *Bunodosoma granulifera* [100], have been found to be especially potent towards insect sodium channels [101]. The extracts from *Pseudopterogorgia elizabethae* (contains pseudopterosins) and *Eunicea fusca* (contains fucoside-A) can be used in cosmetic industries [16,102,103].

Metabolites from bryozoans

The bioactive compounds are comparatively less in quantity from bryozoans. Most of the extracted products are alkaloids [61]. A sample of *Flustra foliacea* collected in the southern North Sea yielded deformylflustrabromine, which displayed moderate cytotoxicity against the HCT-116 cell-line [104]. The marine bryozoan *Amathia convoluta* collected from the east coast of Tasmania was the source of the tribrominated alkaloids convolutamine-H and convolutindole-A. The compounds displayed potent and selective activity against *Haemonchus contortus*, a parasitic nematode of ruminants [105]. *Watersipora subtorquata* from Tsutsumi Island, Japan, was the source of bryoanthrathiophene. This compound exhibited potent anti-angiogenic activity on bovine aorta endothelial cell (BAEC) proliferation [106]. Asymmetric syntheses of amathamide A and B, alkaloids from the bryozoan *Amathia wilsoni* collected in Tasmania [107], have been accomplished

starting from 3-hydroxybenzaldehyde [108]. Bryostatin, a potent anti-cancer compound from *Bugula neritina* [103,109] shows remarkable selectivity against human leukemia, renal cancer, melanoma and non-small cell lung cancer cell-lines. This compound modulates the signal transduction enzyme protein kinase-C (PKC). The major metabolite convolutamide-A from *Anthia convoluta* exhibits *in vitro* cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells [110]. *Cribricellina cribreria* has yielded β-carboline alkaloid, which exhibited cytotoxic, antibacterial, antifungal and antiviral activities [111]. Indole alkaloids isolated from *Flustra foliacea* have shown strong antimicrobial activity [112].

Metabolites from molluscs

More than 2600 scientific studies over the last 20 years testify to the important contribution of toxins extracted from cone snails to medicine and cellular biology. To date, only 100 out of a potential 50,000 toxins have been extracted and analyzed [113]. The *Conus* species have evolved deadly nerve toxins and small, conformationally constrained peptides of 10-30 amino acids. Some of the conotoxins block channels regulating the flow of potassium or sodium across the membranes of nerve or muscle cells; others bind to N-methyl-D-aspartate receptors to allow calcium ions into nerve cells; and some are specific antagonists of acetylcholine receptors responsible for muscle contraction. Thus, conotoxin are valuable probes in physiological and pharmacological studies [114]. Neosurugatoxin isolated from *Babylonia japonica* is useful in characterizing two classes of acetylcholine receptors [56]. Dolastatin, a cytotoxic peptide from *Dolabella auricularia* is an antineoplastic substance [115]. Ulapualide-A, a sponge-derived macrolide isolated from the nudibranch *Hexabranchus sanguineus* exhibits cytotoxic activity against L 1210 murine leukemia cells and antifungal activity, which exceeds that of clinically useful amphotericin-B [116]. Chromodorolide-A isolated from *Chromocloris cavae* exhibits *in vitro* antimicrobial and cytotoxic activities [117]. Onchidal from *Onchidella bieyi* is a useful probe for identifying the active site residues that contribute to binding and hydrolysis of acetyl cholinesterase [56]. A team from the University of Melbourne extracted the conotoxin from a cone-shell snail. It not only inhibits pain as being 10,000 times more powerful than morphine, but also accelerates the recovery of injured nerves [118]. The absolute stereochemistries of membrenones A–C,ϒ-dihydropyrone-containing polypropionates isolated from the skin of the Mediterranean mollusc *Pleurobranchus membranaceus* [119], have been determined by stereocontrolled syntheses of the enantiomers [120]. The first synthesis of siphonarin-B has confirmed the absolute stereochemistry of the metabolite [121] isolated from the molluscs *Siphonaria zelandica* and *S. atra* [122]. Bursatellanin-P, a 60-kDa protein was purified from the purple ink of the sea hare *Bursatella leachii* [123]. The protein exhibited anti-HIV activity. The first total syntheses of aplyolides B–E, ichthyotoxic macrolides isolated from the skin of sea hare *Aplysia depilans* [124], have been reported confirming the absolute stereochemistry reported for the metabolites [125,126].

Metabolites for tunicates

Didemnin-B from the Caribbean tunicate *Tridemnum solidum* was the first marine compound to enter human cancer clinical trial as a purified natural product [14], but was unsuccessful in further trials [127]. Nevertheless, this class of cyclic peptides provides important structural lead for a variety of antiviral, anticancer and immunosuppressant activities [128]. The inhibitor of matrix metalloproteinase (MMP2) from an ascidian of the family Polyclinidae collected off Western Japan was identified as sodium1- (12-hydroxy) octadecanyl sulphate [129]. Two unusual trithiocane derivatives were isolated from the ascidian *Perophora viridis* collected off North Carolina [130]. Relative stereochemistries were deduced from NOESY NMR experiments, while methylthiopropionate (MTPA) derivation of the hydroxyl helped secure the absolute configuration. Both compounds exhibited mild antibacterial activity as well as toxicity towards brine shrimp. Halocidin was isolated as an antimicrobial peptide (3443 Da) from the hemocytes of the solitary ascidian *Halocynthia aurantium* [131]. Cloning of a peptide precursor from a cDNA library prepared from pharyngeal tissues of the tunicate *Styela clava* identified clavaspirin as an antibacterial peptide [132]. Lepadins D with an unidentified counterion, lepadins E and lepadins F were isolated as antiplasmodial and antitrypanosomal alkaloid constituents of a *Didemnum* spp. ascidian collected from Stanley Reef, the Great Barrier Reef [133]. Coproverdine is a cytotoxic alkaloid isolated by bioassay-directed fractionation of an unidentified ascidian collected at the Three Kings Islands, New Zealand [134]. Ecteinascidin isolated from *Ectenascidia turbinata* shows potent activity *in vivo* against a variety of mouse tumour cells [135]. Cytotoxicity towards a variety of murine and human tumour cell-lines was observed. Rubrolide-M, recently isolated from a Spanish collection of the ascidian *Synoicum blochmanni* [136], was synthesised using palladium-catalysed coupling methodology [137]. Eudistomins from *Eudistoma* species exhibit potent antiviral activity *in vitro* and have been synthesized in quantities sufficient for *in vivo* antiviral analysis [138]. Besides eudistomins, a number of potent PKC inhibitors have been isolated from *Eudistoma* spp., which includes staurosporine aglycone, 11-hydroxy staurosporine, trithianes and pentathiepins [139,140,141]. The compound bistratene isolated from *Lissoclinum bistratum* enhances the phosholipid-dependent activity of PKC and may be a useful probe for studying molecular mechanisms of cell growth and differentiation [142] as well as anticancerous drugs [56]. The compound and related congeners were found to exhibit cytotoxicity towards human tumour cell-lines. Sebastianines A and B isolated as biologically active pyridoacridine metabolites, which show cytotoxic activities towards colon cancer cells, have been extracted from a Brazilian collection of the ascidian *Cystodytes dellechiajei* [143]. A study of the Thai ascidian *Ecteinascidia thurstoni*, using a KCN-pretreatment isolation procedure, identified the known two alkaloids ecteinascidins and the two novel analogues ecteinascidins [144]. The identified ecteinascidins exhibited potent cytotoxicity towards tumour cell-lines and growth inhibition of *Mycobacterium tuberculosis* H37Ra. The sulphated steroid was found to be responsible for sperm activation and attraction in Japanese collections of the ascidians *Ciona intestinalis* and *C. savignyi* [145]. The *in vivo* antitumour activity

of the dimeric disulphide alkaloid polycarpine, isolated from the ascidians *Polycarpa clavata* [146] and *P. aurata* [147], and related synthetic analogues has been investigated [148].

Metabolites from echinoderms

Physiologically active saponins have been studied extensively from sea stars and sea cucumbers [149], but not so useful as drugs because of their tendency to cause cell lysis [14]. Even then, glycosylated ceramides and saponins continue to be the major classes of metabolites identified in echinoderms. A full account of the isolation and characterization of hedathiosulphonic acids A and B, isolated from a deep-sea urchin *Echinocardium cordatum* [150], has been reported [151]. Imbricatine from the sea star *Dermasterias imbricata* is the first benzyltetrahydroisoquinolone alkaloid from a non-plant source and shows in the NCI human cell-line screen [14]. A study of the starfish *Diplopteraster multipes* indicated a range of sterol sulphates [152,153]. Lysastroside-A a new steroidal glycoside was isolated from the starfish *Lysastrosoma anthosticta* collected in the Sea of Japan [152]. Ten new saponins, certonardosides A–J were isolated from the starfish *Certonardoa semiregularis* collected off the Coast of Komun Island, Korea [91]. The absolute configurations of the side chains were secured by the 1H NMR analysis of MTPA esters. All compounds were evaluated for a range of antiviral properties towards HIV, herpes simplex (HSV), Coxsachie (CoxB), encephalomyocarditis virus (EMCV) and vesicular stomatitis virus (VSV), but only mild potency was observed for certonardosides-I and certonardosides-J. Linckosides A and B, neuritogenic steroidal glycosides, were reported from an Okinawan collection of the starfish *Linckia laevigata* [154]. In the search for antagonists of the chemokine receptor subtype-5 (CCR5) as possible anti-HIV agents, bioassay-guided fractionation of an Andaman and Nicobar Island, India, collection of the sea cucumber *Telenata ananas* afforded two triterpene glycosides [155]. Both compounds exhibited inhibitory activity in a CCR5, while no activity was observed towards the related chemokine receptor CXCR2. A new route for the synthesis of a ceramide sex pheromone isolated from the female Hair Crab, *Erimacrus isenbeckii* [157,158], was reported [158], while squaric acid ester-based methodology was used in a new synthesis of echinochrome-A, a polyhydroxylated napthoquinone pigment commonly isolated from sea urchin spines [159].

Metabolites from Fish, Sea Snakes and Marine Mammals

Metabolites extracted from fish, sea snakes and aquatic mammals are scanty. Various fish species are used to extract fish oil, rich in omega-3 fatty acids, which are used in the preparation of various kinds of drugs for the remedies of human beings, such as arthritis and many others. Through out the world about 500 species of fish are considered toxic. The most spectacular substance of pharmacological importance extracted from fish is tetradotoxin (TTX), the puffer or fugu poison. Other toxins isolated include ciguatoxin from electric rays, which is served as a potent antidote for pesticide poisoning [160]. TTX isolated from puffer fish and many other marine

organisms has become a useful tool for researchers studying the voltage-gated sodium channel, and tetradotoxins also plays an important role in many biological experiments [23]. A new class of water-soluble broad-spectrum antibiotics, squalamines has been isolated from the stomach extracts of dogfish shark, *Squalus acanthias* [161].

The sea snakes belong to the family Hydrophiidae. An anticancerous drug, namely "Fu-anntai", which has antiblastic effects on cervical carcinoma, stomach cancer, rhinocarnoma and leukemia cells, has been extracted from them in China [162]. A group of scientists in Australia have extracted a novel drug from rat snake [163].

Conclusions

"Poison kills the poison," the famous proverb is the basis for researchers in finding the biomedical metabolites from living organisms. Sea has got plenty of metabolites and other resources in living or dead form. Sponges (37%), coelenterates (21%) and microorganisms (18%) are the major sources of biomedical compounds followed by algae (9%), echinoderms (6%), tunicates (6%), molluscs (2%) bryozoans (1%), etc. [61]. The main emphasis is given in the search of drugs for deadly human diseases as cancer and AIDS. The scientists at different parts of the world have extracted various drugs for such diseases in recent years.

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