MARINE ZOOCEUTICALS– SYNERGY OF ZOOLOGY & PHARMACEUTICALS

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ABSTRACT

In the medicine world now a new term zooceuticals is often heard. It is a term, which deals with the influence of drugs of zoological origin on pharmaceutical science. There are several medicines, which are used, now-a-days and their origin is from animals. Most of these drugs are proteins / peptides in nature. With the coming of sophisticated technologies to separate, characterize and mass produce proteins and peptides, the research on potent drugs of zoological origin is fast catching up and may be in the future provide with much needed breakthrough in several deadly diseases. The purpose of this review is to shed some light on some of the most prominent molecules of potential to be established as drugs of future. Most of these promising candidates have come from such uncommon organisms such as snake, bats, lizards, etc, and often very potent and toxic in higher doses. Some other rare species like desert pupfish, which can be used for human kidney disease, different species of snake whose venom contains derived toxins, are used in treatment of cancer.[1] The foregoing facts are only a glimpse at the huge resources with which nature is waiting for us to explore her, particularly the animal kingdom. An attempt has been made to point out the importance of zoology in the field of pharmaceuticals, with focus on pharmaceuticals obtained from marine source.

Keywords: Zooceuticals, marine pharmaceuticals, Toxins,

INTRODUCTION

Zooceutical sciences deals with the influence and contribution of zoology on pharmaceutical sciences. The zoological world around us is abundant with many substances that hold promise for the treatment of numerous diseases and medical conditions. A huge potential zoological repository of drugs remains untapped since most research is being channelized, at least in India, only to exploitation of herbal medicines. Today 56% of top selling prescription drugs contain natural compounds found in the wild and derived from endangered animals. Zooceuticals are available which already shown silver lining in fighting cancer, heart diseases, AIDS and other dreaded illness. Common belief is that only few of useful pharmaceuticals come from animal kingdom, viz; snake-anti venom, vit. A/D (shark/cod liver oil) or excipients such as beeswax, spermaceti, lecithin or cochineal. However, in many laboratories worldwide, a plethora of diverse animals are being systematically investigated to extract useful drug candidates for multitude of therapeutic indications.

Many of these drugs are proteins/ peptides in nature. With the coming of sophisticated technologies to separates, purify, characterize and the mass production of proteins and peptides, the research on drugs of zoological origin is fast catching up and may be in future provide the much-needed breakthroughs in several deadly diseases. The purpose of this paper will be to shed some light on some of the most prominent molecules of animal origin, which have been shown exceptional potential to be established as drugs of the future. Most of these candidate drugs have come from such

uncommon organisms as snake, bats, lizards, etc. and are often very potent and toxic in higher doses. So their use warrants extreme caution, though their discovery is often very fascinating and proves man's wonderful faculty of adventure and intellect. The following table (Table 1) gives a representative list of such zooceutical sources [1,2,3].

Table 1. Animals and major pharmaceutical components*

Sl. No.	Animals	Scientific name	Major Active component	Use
1.	Crocodile	Various species	Antibodies	Kills the virus that causes HIV/AIDS.
2.	Gila monster	*Heloderma suspectum*	Exendin-4	Antidiabetic
3.	Houston toad	*Bufo houstonensis*	Serotonin and alkaloid	Nervous disorders in humans
4.	Ecuador frog	*Eleuthenodac lylusiberia*	ABT-594	Painkiller
5.	Horseshoe crab	*Limulus polyphemus*	Limulus Amboecyte Lysate	In vitro Pyrogen testing reagent
6.	Salomon fish	*Oncorhynchus kisutch*	Calcitonin	Osteoporesis, paget's disease
7.	Yellow Israeli scorpion	*Leiurus quinquestriatus*	Neurotoxin	Haematological cancers, glioma, diabetes
8.	Bryazoan	*Bugula neritina*	Bryostatin-1 (macrocylic lactone)	Anticancer
9.	Leech	*Hirudo medicinalis*	Hirudin	Anticoagulant
10.	Malasian pit viper	*Calloselama rhodostoma*	35 kD defirogenating enzyme	Anticoagulant
11.	Cone snail	*Conus geographus*	Gx 1160 (hexa decapeptide)	Very Potent Analgesic
12.	Sharks	*Various species*	AE-941, Benefin	Anticancer, advanced nonresponsive prostate cancer, advanced nonresponding Kaposi's sarcoma.
13.	African clawed frog	*Xenopus laevis*	Maginin	Broad spectrum antimicrobials

*Some other rare species like desert pupfish, which show potential amelioration of kidney diseases, different species of snakes whose venom contains derived toxins with potential use in cancer.

The above facts are only a glimpse at the huge resources with which the nature is waiting for us to explore and exploit her treasure-trove, particularly the animal kingdom. We should channelize a part of our drug discovery effort to systemic and exhaustive exploration of land and marine animals for potent life saving drugs. Our indigenous natural diversity includes wonderful animals which when used judicially/judiciously and intelligently might result in wonder-drugs. Thus, we need to recognize the impact of zoological sciences in pharmacy, particularly as a source of valuable pharmaceuticals. A very rich, but hitherto largely unexplored source of zooceuticals is the ocean, which is a treasure-trove of wonder molecules yet to be fully explored and exploited. The remainder of the review deals with these marine zooceuticals.

Bioactive Marine Natural Products from Marine Invertebrates of Potential Therapeutic Agents

Till date, the best known marine natural products mostly are of protein/peptide in origin, but several other class of compounds have already been examined, explored and structurally elucidated to cater the ever-increasing human demands.

Steroids

Recently, a new insect-moulting hormone 2-deoxy-20-hydroxy-ecdysone has been isolated in 0.016% from *Zoanthus* sp showing promising oxytocic effect in guinea-pig uterus assay [4].

Sterols

Generally different zoosterols have shown varying degrees of unsaturation in the ring β and the side chain. Some of them are positional isomers and some of the sterols such as fucosterol [4a] isolated from marine sources have been reported to be non-toxic and have the ability to reduce blood cholesterol levels and exhibit anti-diabetic activity [4b]. The sterol also appears to reduce the tendency to from a fatty liver and excessive fate deposition in the heart [4c].

Saponins

Habermehl *et al.,* [5] have reported a number of Mediterranean echinoderms for their holothurin content, which were found to be toxic to may animal species including mammals [6,7]. The saponin fraction from *Stichopus japonicus* showed antifungal activity against *Trichophyton asteroids*, *Candida albicans* and other fungal species *in vitro* at concentrations of 2.78-16.7 mg/ml [8]. It was found to be also toxic to kerbs-2-ascites tumor cells *in vitro* [8] and inhibited fruitfully the growth of saroma-180 and adenocarcinoma in mice models [9]. Both the crude holothurin and hlothurin A were found to be cytotoxic to human epidermal oral carcinoma (KB) cell lines [10]. Holothurins from sea cucumbers have been found to have good pharmacological potential as neuromuscular and anticancer agents owing to the steroid moiety of the molecule. Hence, it is naturally targeted hoping that some more useful chemotherapeutic agents from various species of sea cucumbers can be exploited in near future.

Terpenoids

The extracts of gorgonians, which exhibited antibiotic activity have furnished a number of bioactive terpenoids [11]. A diterpene "eunicin" (m.p. 155°C $[\alpha]_D$-89°) exhibiting anti-microbial activity (inhibiting the growth of *Costridium feseri* and *Stabphyloccus sp.*) has been isolated from *Eunicea mimosa* Lomouroux [12].

Crassin acetate, reported to be toxic to *Entamoeba histolytica* at 20 µg/ml in *vitro*, has also been isolated from horny corals, *Pseudoplexaura porosa* and *P. wagenari* **[**13]**.**

Prostaglandins

These are a group of naturally occurring hydroxyl fatty acids exhibiting a broad spectrum of pharmacological activity. Their hormone like activity in fertility control, labor induction and renal physiology had attracted considerable attention of the scientific community. Two prostaglandins, e.g. 15-epi-PGA_2, its diester and $PGA_2\alpha$ have been purified from air dried cortex of the gorgonian *Plexaura homomalla* (Esper) in high yield 0.2-1.3% respectively [14].

Brominated Compounds

Many species of sponges are long-lived and are resistant to bacterial decomposition. They are found to produce antimicrobial substances. Indeed, this assumption was found to be true, as the extracts of large no of sponges have demonstrated a broad spectrum antibiotic activity. Some of these extracts have especially been active against *Staphylococcus*, *Pseudomonas*, acid fast bacteria and pathogenic yeasts such as *Monilia* sp. The sponge *Dysidea herbacea* from the Western Caroline Islands have produced antibacterial compounds showing activity against both gram (+ve and –ve) microorganisms. However, all these compounds are brominated products of 2-phenoxyphenol [15]. The sponge *Aplysia aerophoba* and *Verongia thiona* have yielded the antibiotic substance aerothionin having a spiro-cyclohexadienylizoxaozole skeleton [16-17]. The sponge *Phakellia flagellate* found in the

Great Barrier Reef has been found to contain an interesting bromine containing alkaloid dibromophalellin melting point at 237°C (at -45°C decomposed) $[\alpha]_D$-203° and 4-bromophakellin [72-74, 18-20]. These compounds have been reported to be responsible for the iodofrom-like smell of the particular animals. The brominated compounds isolated from marine animals generally show a broad-spectrum antibiotic activity, but most of them are toxic to other animals. Aplysin-21 given to mice via stomach tube produced immediate hyperventilation, hyper-salivation, ataxia, loss of motor coordination, respiratory paralysis and death.

Marine Toxins

Till date most of the reported marine toxins of prominent pharmacological activity have found to be composed of peptide origin from different zoological species. Some are reported below. These compounds are found to be moderate-to-severely toxic to different animal models.

Tetrodotoxin

This toxin is famous for many years, has been isolated from a variety of marine organisms, including pufferfish, newts and blue-ringed octopus [21-23]. It is believed to be a product of bacterial metabolism [24]. Tetrodotoxin is readily absorbed from the gastrointestinal tract. It usually alters the initial increase in the sodium permeability of the membranes, resulting nerve blockage. Tetrodotoxin has also been considered as a good hypotensive agent and respiratory inhibitor. It has also been used clinically as one of the pain-relieving agent in cases of patients suffering from the neurogenetic form of Hansen's disease (Leprosy). Tetrodotoxin and a number of its derivatives have been examined extensively for local anesthetic action. However, it is under the trial to provide useful information in understanding the mechanisms of selective membrane permeability [25].

Saxitoxin

This famous toxin [26] has been isolated from several marine organisms such as the Californian mussels *Mytilus californianus,* Alaskan butter calms *Saxidomus giganteus,* marine dinoflagellate *Gonyaulax catenella,* exoskeleton and muscle of the appendages of the toxic crabs *Zosimus aeneus* and *Platypodia granularia* [27]. Saxitoxin blocks nerve conduction by specifically interfering with the intital increase in sodium permeability of the membrane. The symptoms caused by the toxin include peripheral paralysis. In extreme cases, complete loss of strength in the muscles and finally death occurred which is caused due to respiratory failure [28]. Saxitoxin is absorbed from the gastro-intestinal tract. Saxitoxin produces effects on the cardiovascular system and a marked hypotensive effect even at a low concentration of 2 µg/kg. The oral LD_{50} for toxin in various species of animals is reported. In man, death had occurred following ingestion of as little as 1 mg of toxin [29]. The toxic compounds from marine algae appear to have biomedical potential. The compounds with neurotropic effects may yield important drugs.

Pahutoxin

Pahutoxin [30a,b,c] has been isolated from the skin secretion of the Hawaiian boxfish, *Ostracion lentiginosus*. It contained a quaternary nitrogen, an ester function and choline moiety. Acid hydrolysis with 2N-methanolic H_2SO_4 produces methyl-3-hydroxy hexadecanoate. Pahutoxin is a choline chloride ester of β- acetoxy `palmitic acid. It is found to be highly toxic to different cancer cell lines.

Sesquiterpenes

This class of compounds has phenolic and/or quinoid moiety isolated in the different species of sponges. The antimicrobial agent siphonodictyal-A and Siphonodactyl-B have been isolated by Sullivan *et al* [31,32]. Biologically, an active sesquiterpenoid "avarol" reported to be of antimicrobial activity and also active against

"AIDS" virus. This was first isolated from a Mediterranean sponge *Disidea avara* [33] and later on from an Australian sponge *Disdea* sp [31, 34]. Antifungal and antimicrobial activities have also been reported from the tetracyclic furanoditerpenes isolated from the sponge *Spongia officinalis* by Capelle *et al*, [35] *Agelas* species from the Pacific and Caribbean have produced diterpenoids containing a pruine or a 9-methyladenine unit [36]. These compounds exhibit antimicrobial and also significant Na^{+}-K^{+}-ATPase inhibitory activities. Agelasine A, Agelasine B from a species of *Agelas* [37] were found to be active against *Bacilus subtilis, Staphyloccus aureus, Candida albicans* and the marine bacterium B-392. Novel bicyclic and monocyclic diterpenoids with a 9-methyladenine unit possessing inhibitory effect on Na^{+}-K^{+}-ATPase have been isolated from the sea sponge *Agelas nakamurai* [38]. A class of tricyclic diterpenes having isocyano, hydroxyl, tetrahydropyranyl and chlorine functions and exhibiting antibiotic activity have been purified from *Acanthella sp* [39, 40]. Kalihimol A is found to be active *in vitro* against *Bacillus subtilis*, *Staphyllococcus aureus* and *Candida albicans*. Two new diterpenoids e. g. agelasidine B and agelasidine C exhibiting antimicrobial activity have been reported from the okinawan sponge *Agelas nakamurai* [39-41]. These compounds exhibited significant inhibitory activity on the contractile response of smooth muscles and enzymatic inhibitory action on Na^{+}-K^{+}-ATPase in pig brain. Manoalide which contains an α-β-unsaturated γ-lactone, functions as anti-inflammatory agent and has been found to be an inhibitor [42a, b,43,44] of phspholipase A_2. 20-24-Bishomoscalarane sesterterpenes, such as phyllofolactore A and phyllofolactore B have been isolated from Pacific sponge *Phyllospongia foliascens* and exhibited pronounced cytotoxicity against P-388 cell lines (IC_{50}=5 ug/ml) [45-49a]. This compound from this sponge also exhibits antifungal and anti-inflammatory activities [49b]. Several peptide alkaloids and proteins have been isolated and purified from the marine sponges. Matsunaga *et al*, [50-52] have isolated bioactive polypetides from *Discodermina kiiensis.* A glycoprotein (Geodiatoxin) of 27,000 dalton from *Geodia mesotrianea* [53], has had LD_{100} at 6 mg/kg in mice, also found to be active *in vitro* in 9KB tests, *in vitro* in murine P-368 cell line and lymphocyclic leukemia.

Marine Nucleotides

Marine sponges have been found to be good source of bioactive unusual nucleotides. 1-Methylisoguaniosine isolated from the sponge *Tedania digitata* [54-55] exhibiting direct interactions with adenosine receptors in guinea-pig brain tissues has been found to stimulate adenylate cyclase [56]. Furthermore, in contrast to asenosine it was resistant to demaination. Additionally, this compound was effective in displacing diazepam bout to rat brain membrane. The Xestospongin A, B, C and D from Australian species *Xestospongia exigua* [57-61a] have represented a new class of macrocyclic alkaloid incorporating two 1-oxaquinolizidine rings and are vasodialatory compounds, which induce relaxation of blood vessels *in vivo* [61b].

Other Promising Bioactive Metabolites from Different Divisions of Marine Invertebrates.

Corals

Guaiazulene from the gorgonian *Euplexaura erecta* [62] exhibits strong antimicrobial activity against *Pseudomonas auriginosa*. Subergorgic acid, proposed to be a cardiotoxin has been obtained from the Pacific gorgonian coral *Subergorgia suberosa* [63]. This has been found to inhibit neuromuscular transmission at a dose of 0.16µg/ml in silated guinea-pig heart assay. Two sesqiiterpenes active against phytopathogenic fungus *Cladosporium cucumerinum* has been isolated from the marine soft coral of the genus

Heteroxenia [64]. In addition, synthesis of the antitumor agent (-)-laulimalide has been already achieved. Several polyacetylenes exhibiting prominent selective cytotoxicity against different human tumor cell lines have been isolated from the marine sponge *Petrosia* sp [65]. Plakevulin A, a new oxylipid, inhibiting DNA polymerase X and Y has been isolated from the sponge *Plakorits* sp [66]. Two new tryptase inhibitors, cyclotheonamide E4 and E5 have been isolated from the marine sponge of the genus *Ircinia*. Cyclotheonamide E4 has exhibited potent inhibitory activity against human typtase (IC_{50}= 5.1 nM) showing the future potential of a therapeutic drug in the treatment of allergic diseases, including asthma [67]. Two new cytotoxic compounds viz, nakiterpiosin and nakiterpiosinone were isolated from the Okinawan sponge *Terpios hoshinota* [68]. The sponges of *Acanthella* genus are found to be the chief source of highly functionalized diterpene antibiotics. Eight Kalihinol-type diterpenes have been isolated from *A. cavernosa* [69]. *Haliclona sp*, a marine sponge, yields kendarimide A, a novel peptide which has been reported to reverse the glycoprotein mediated multidrug resistance in tumor cells [70]. Xestospongin C and D, have been isolated from marine sponge *Halicolna exigua* inhibits rat brain nitric oxide systhase activity [71]. Lamellarin α-20 sulfate, an ascidian alkaloid inhibited HIV-I integrase of virus in cell culture [72].

Coelenterates

The nematocyst venom of *P. physalis* is a mixture of toxic proteins and enzymes showing multiple actions e.g., dermonecrosis, neurotoxcity, hemolysis and cardiotoxicity. The cadiotoxin from this species was purified by immunochromatography. Several other classes under this division have been reported to be good storehouse of a diverse array of bioactive compounds which have been subjected to a battery of pharmacological investigations for putative future drugs [73].

Sea Anemones

Several species of sea anemones occur in the sea coasts throughout the world. The toxins produced by these organisms are polypeptides or proteins. The toxins are found very useful tools for studying the voltage dependent Na^+ channels in nerve and cardiac muscle cells. It has been suggested that coelenterate toxins would be suitable for studies of tumor cell cytolysis *in vitro* and *in vivo* [74].

Bryozoans

The bryozoan *Phidolopora pacifica* has yielded Phidolopin, a purine derivative largely responsible for high order microbial and antifungal activity [75-76a, b]. Several macrolides like bryostatin-1 and bryostatin-2 were isolated from *Bugula neritina* [77-79] showing high order of antineoplastic activity.

Molluscs

Striatoxin, a cardiotonic glycoprotein obtained from *C. striatus* [80] was found to have long lasting inotropic action on guinea-pig left atria. Its minimum lethal dose in the fish *Rhodeus ocellatus* was 1 μg/g body weight. Kelletinin-I and II isolated from marine molusc *Kelletia Kelletii* [81] inhibit the growth of *Bacillus subtilis* and L-1210 leukemia cells *in vitro*. Surugatoxin and Neosurugatoxin have been isolated from *Babylonia japonica* [82-83]. The antinicotine activity of the later molecule has been found to be 100 times that of the former. *Siphonaria dimensis* has furnished the antibiotic dimensin A and dimensin B [84]. The former inhibits the growth of *Staphylococcus aureu*s and *Bacillus subtilis* at dose of 1μg/disc and 5μg/disc respectively. The venom of *Conus geographus* is most dangerous to man.

Echinoderms

The metabolites of Echinoderms mainly responsible for the biological activity are saponins. Asterosaponins are hemolytic, antineoplastic, cytotoxic, antitumor, antibacterial, antiviral, antifungal and anti-inflammatory activities [85-86]. To date, the saponins of over 50 sea cucumbers have been studied [87]. Linckosides A and B, the new neuritogenic steroid glycosides were isolated from the Okinawan starfish *Linckia laevigata* [88]. These alkaloids are having an unusual decahydroquinoline skeleton and showing significant and selective anti-plasmodial and anti-trypansomal activities were obtained from the new tunicate species of the genus *Dedemnum* [89]. These bioactive alkaloids may serve as lead structure fro the development of new antimalarial drugs. Vitilevuamide, a bicyclic peptide was isolated from the marine ascidians *Didemnum cuculiferum* and *Polysyncranton lithostrotum*, showing cytotoxicity in several human tumor cell lines with IC50 values ranging from 6-311 nM [90].

Sea Hares

A bioactive nuclesoside, characterized as 1-methyl-isoguanosine has been found in the sponge *Tedania digitata*, [91-92] as well as, in the nudibranch *Anisodoris nobilis* [93-95]. The isoguanoside isolated from the marine nudibranch *Diaulula sandiegensis* [96] produces hypotension and relaxation of smooth muscles in mammals. Aplysiatoxin, a toxic metabolite has been isolated from the Hawaiian sea hare *Stylocheilus longicauda* [97]. Aplysistatin is a well-known antileukemic metabolite from the sea hare *Aplysia angasi* [98]. *Dolabella auricularia* has yielded several antineoplastic compounds named dolastatins [99-103]. Dolastatin 10, a novel pentapeptide isolated from the sea hare *Dolabella auriculata* is undergoing I Phase II clinical trials. Further studies revealed that it has been found to have substantial activity in the treatment of melanoma [104] Dolastatin 15, a potent antineoplastic peptide from *Dolabella auriculata,* is undergoing clinical trials in Europe and North America [105]. Dolabellanin β, a novel peptide containing 33 amino acid residues was isolated from the body wall of the sea hare *Dolabella auricularia* [106]. It was effective against some pathogenic microorganisms at a dose of 2.5-100 µg/ml [106]. Phase I clinical A phase II clinical trial of bryostatin I in patients with advanced lung cancer has been carried out [107]. Clinical trials were carried out on Dolastatin 10, in patients with advanced solid tumor [108] and the results are found to be encouraging.

Sea Urchins

Pedicellaria sp and some other species of sea urchins containd toxic substances. *Lytechinus variegatus* [109] and *Strongylocentrotus droebachiensis* [110] have yielded antineoplastic glycoproteins.

Tunicates

The most interesting compounds isolated from tunicates are the cyclic oligopeptides. *Lissoclinum patella* has been a good source of several cycle peptides [111-112]. Of these, ulicyclamide, ulithiacyclamide, and patellamide A, B and C exhibit antitumor activity against L1210 murine leukemia culture *in vitro*. A new class of depsipeptides of which some exhibit high order of antiviral (against RNA and DNA viruses) and antitumor (against L1210; P388 leukemia and B-16 melanoma cell lines) activities are obtained from *Trididemnum* species [113-114]. Other eudistomins having substituted β-carboline system and displaying modest activity against HSV-1 and *Bacillus subtilis* have been isolated from the same species [115]. Aplidin (APL) a novel depsipeptide from the tunicate *Aplidium albicans* exhibiting high order of cytotoxic activity has been under clinical studies. Sulfated polymannuroguluronate (SPMG), a marine sulfated polysaccharide, has entered in Phase II clinical trial in China as the first AIDS drug [116]. The mechanism of action of Alpidine is

still not clear, but cell cycle phase perturbations and the rapid induction of apoptosis appear to be a mechanism different from that of known anticancer drugs [117].

Clinical Trials of Some Novel Marine Drugs

Ascidians remain unique among the marine invertebrates as they overwhelmingly produce nitrogen containing metabolites. Although investigations on ascidians as potential source of drugs were initiated more recently than on some other marine invertebrates, it is significant that the first marine natural product to enter human clinical trials, is Didemnin-B, an ascidian secondary metabolite. A survey of the biological activities of the secondary asidian metabolites reveals that cytotoxicity is the most frequently observed activity against a variety of tumor cell lines [118].

Alpidin (Alp)

Aplidin (R) (APL) a novel depsipeptide from the tunicate *Aplidium albicans* exhibiting high order of cytotoxic activity was under clinical studies. Sulfated polymannuroguluronate (SPMG), a marine sulfatedpolysaccharide has entered in phase II clinical trial in China as the first AIDS drug [119]. A novel depsipeptide from the tunicate *Aplidium albicans* exhibiting high order of cytotoxic activity is undergoing clinical studies. A sensitive and highly specific liquid chromatographic method with electrospray ionization tandem mass spectrophotometric detection (LC-ESI-MS/MS) was described for its estimation in human blood plasma and urine.

Dolastatin-10

The tubulin interactive agent dolastatins-10 entered into Phase I clinical trials in early 1990s [120-123]. Owing to its rare and limited occurrence in natural sources, scientists made an attempt to synthesize the chemical analogs of this compound and synthesis of this compound was accomplished. Later this was used for prostate cancer and metastatic melanoma in man [124-125] in the Phase II clinical trial. LU103793 (dolastatin analogue) in patients with metastatic breast cancer has been carried out. LU103793 is a synthetic analogue of dolastatin 15 and inhibits tubulin polymerization. The patients were given a dose of 2.5 mg/kg/day and the test compound over 5 consecutive days every 3 weeks [126].

Soblidotin (Tzt-1027, Auristatin Pe)

Owing to its potent anticancer activity one of the compound TZT-1027 (Auristatin PE or Soblidotin, is currently undergoing Phase I clinical trials in Europe, Japan, and the United States [127-128]. Recent studies indicate that the transfected vascular endothelial growth factor (VEGF)-secreting human lung cell line (SBC-3/VEGF) and the mock transfected cell lines in nude mice were totally inhibited at early or advanced stage xenografts at the concentration of 1-2 mg/kg by Soblidotin. Interestingly, these findings established that TZT-1027 also exhibited a potent antivascular effect at these concentrations [129]. Phase II trial for this particular compound is underway.

Cematodin (Lu-103793)

Cematodin another derivative of dolastatin 15 is undergoing Phase I clinical trials for the treatment of breast and other cancers. The Phase I level data were found to be highly encouraging and this compound has been subjected to Phase II studies against malignant melanoma, metastatic breast cancer and non-small-cell lung cancer [130-137]. Phase II trials are still ongoing for breast, ovarian, lung, prostate, and colon carcinomas [138].

Synthadotin

Synthadotin [ILEX 651, is an active synthetic pentapeptide analog of the natural dolastatin 15 and has been found to have its action by targeting tubulin depolarization. [139-142]. A Phase II clinical study has been on to explore what effect ILX-651 has on metastatic melanoma. ILEX-651 has been chemically modified to enhance its

improved pharmacologic properties and is orally bioavailable with a potentially enhanced therapeutic window. The Phase II studies are ongoing to examine the efficacy and tolerability of ILEX-651 in patients with recurrent or metastatic melanoma. Preliminary results from an earlier study depicts that this compound is very well active against a range of solid tumours.

Applidine

Dehydrodidemnin-B (aplidine) was first reported in 1990 [143] and its antitumor property was first reported in 1996 [144-145]. In the year 2000 the total chemical synthesis of this compound was achieved, [146] which comes out with the generic name "aplidine or dehydrodidemnin-B" and trade name of Aplidin. It was placed into Phase I clinical trials in 1999 for the treatment of solid tumors and non-Hodgkin's lymphoma. Recently this compound has entered into Phase II clinical trials in Europe and Canada covering renal, head and neck, and medullary thyroid. The mode of action of this novel molecule is yet to be deciphered properly, but it appears to block VEGF secretion and blocks the corresponding VEGF-VEGF Receptor-1 autocrine loop in leukemic cells [147].

Kahalalide F

The cyclic depsipeptide kahalalide-F was isolated from the Sacoglossan mollusk *Elysia rufescens* [148-150a, b] and later it entered into preclinical trials. Actual mode of action of this compound had not yet been fully determined, but it was known to target lysosomes. [151a, b] Thus it is suggested that it may have selectivity for tumour cells such as prostate tumours, which have high lysosomal activity. The compound was synthesized by solid phasepeptide techniques [152] and found to be active for the treatment of androgen- independent prostate cancer. Currently this compound is under the Phase II clinical trials for the treatment of prostate cancers [153] Recent reports point out that kahalalide-F induces cell death via "oncosis" possibly initiated by lysosomal membrane depolarization in both prostate and breast cancer cell lines [154].

Hemiasterlin (Hti-286)

Hemiasterlin was originally isolated from the South African sponge *Hemiasterella minor* [155a, b]. This sponge also the chief source of a large number of peptides, including geodiamolides A-F, hemiasterlins-A and B, and other criamides and geodiamolides [156]. Hemiasterlin and the A and B derivatives were found to interact with tubulin and gives microtubule depolymerisation in an identical manner to that reported for vinblastine and nocodazole. Recently, hemiasterlin, and its derivatives have been synthesized [157-159]. This compound is currently in Phase I clinical trials and scheduled to enter Phase II shortly. The *in vitro* and *in vivo* animal data were recently published [160]. Very recently interesting data on HTI286-dolastatin-10 hybrids [161-162] have been published and the hybrids were found to be much more active than dolastatin-10 in cells that express the P-glycoprotein efflux pump.

Human immunodeficiency virus (HIV) replication requires integration of viral c-DNA into the host genome, a process mediated by the viral enzyme integrase. A new series of HIV integrase inhibitors e.g. thalassiolins A, B and C have been isolated from *Thalassia testidium*. Thalassiolins the most active of these molecules displayed *in vitro* inhibition of the integrase catalyzed strand transfer reaction (IC_{50}=0.4μM) and an antiviral IC_{50} of 30 μM [163].

CONCLUDING REMARKS

Till now only a fraction of the total marine population has been brought under judicious evaluation for the production of future drugs. The major problem previously was the lack of proper extraction devices from deep sea and it is in the

recent times that a great no of marine biota has been subjected to a battery of investigations leading to clinical trials. The quality of the screening methodology employed is the most important factor in drug discovery for any type of biological activity. The predictability of the screens for clinical activity remains absolutely critical, since if the screens identify compounds which are clinically inactive, all the efforts which help the development of such compounds gets wasted. The correlation of screening bio-actives with clinical activity is an extremely cumbersome process to establish sometimes since it takes a good many no of years from pre-screening of the active compounds to the final results of clinical trials are available. The data base sometimes gets encircled within a few compounds which could ultimately reach clinical trials. There are special problems encountered in screening extracts from marine origin. Generally, the active principle present in the crude extracts are present in very low concentration, therefore, the screen for their detection often becomes very sensitive, in general, *in vitro* test methods are more sensitive than *in vivo* method. Besides, screening protocols demand to be more selective and specific. The second problem in screening crude extracts is that the pre-screen, screen or bioassay used must be insensitive to the other associated ingredients /compounds present in the extract which sometimes comes out as potential interfering substances. The assay must also be insensitive to ubiquitous compounds which will give false actives. The assays also must be highly selective. So, the assay chosen ought to meet the other requirements of good, including validity, predictability, correlation, reproducibility, and the cost should be reasonable. Which is why though a good lot of marine compounds have been investigated for different pharmacological activities but only a fraction of these compounds till date have reached the final clinical trials and at last to the perfect dosage forms to be marketed.

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