BIODIVERSITY OF MARINE PHARMA

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ABSTRACT

The biodiversity of ocean living resources provide an ample scope for the extraction of drugs and chemicals for therapeutic purposes. The oceans are the source of a large group of structurally unique natural products that are mainly accumulated in invertebrates such as sponges, corals, bryozoans, molluscs, tunicate, shark, sea hare etc. Nature has gifted mankind continuously with a broad and structurally diverse arsenal of pharmacologically active compounds that continue to be utilized as highly effective drugs to combat a multitude of deadly diseases or as lead structures for the development of novel synthetically derived drugs that mirror their models from nature. There are a growing number of marine-derived chemicals in the late stages of development particularly in the anti-cancer, anti-viral and anti-inflammatory domains. The sea's potential as a medicine cabinet remains largely in the realm of exploration and experimentation. But science is moving quickly, and the world's waterways may soon yield some effective medical treatments, if not some miracle cures. The world's oceans and waterways may harbor the next generation - drugs, biologics, and even a few medical devices. India has enormous assets—human, infrastructural, natural, and financial which should be used to the best of our welfare. Marine products, many of which have yet to be discovered are the key to the development of new types of drugs and products, which will allow us to address public health and environmental issues in the next century. Humankind must adhere to boundaries for harvesting the living resources from the sea in order to ensure disease free endeavour. The following table cables man with medicine of marine resources.

MARINE BIODIVERSITY

The deep sea harbors some of the most diverse ecosystems on earth. This diversity holds tremendous potential for human benefit. More than 15,000 natural products have been discovered from marine microbes, algae and invertebrates, and this number continues to grow. The uses of marine-derived compounds are varied, but the most exciting potential uses lie in the medical realm. More than 28 marine natural products are currently being tested in human clinical trials, with many more in various stages of preclinical development (Salomon *et al.,* 2004 and Newman and Cragg, 2004). To date, most marketed marine products have come from shallow and often tropical marine organisms, due mainly to the ease of collecting them. Advances in submersible technology have permitted scientists to explore the cold depths below, where they have discovered an extraordinary cornucopia of life previously unknown to science such as cold-water corals as colorful and exotic as their warm-water counterparts, giant sponge reefs up to a mile long and 50 feet high, and a host of exotic creatures adapted to life in the cold, dark depths. For example, deep-water "glass sponges" form silica-based structures that may improve the function of fiber-optic cables, and similar sponges are beginning to provide insights into bone regeneration. Marine-derived compounds are used in a variety of consumer products, including skin creams, hair treatments, and cosmetics (Sundar *et al.,* 2003 and Morse, 1999). But increasing scientific interest is now being focussed on the potential medical uses of organisms found in the deep sea. These organisms have developed unique adaptations that enable them to survive in dark, cold, and highly pressurized environments. Their novel biology offers a wealth of opportunities for pharmaceutical and medical research.

Marine microorganisms are a source of new genes, the exploitation of which is likely to lead to the discovery of new drugs and targets. Secondary metabolites produced by marine bacteria and invertebrates have yielded pharmaceutical products such as novel anti-inflammatory agents (eg. pseudopterosins, topsentins, scytonemin, manoalide), anti-cancer agents (eg. bryostatins, discodermolide, eleutherobin and sarcodictyin) and antibiotics (eg. marinone). Melanins have a range of chromophoric properties that can be exploited for sunscreens, dyes and colouring. They also sequester different kinds of organic compounds, inducing fungicides and antibiotics, which may allow them to act as slow-release agents.

Actinomycete bacteria, among the most common microbes on the planet, are the source of almost 70 percent of the world's naturally occurring antibiotics. Even more remarkably, they have characterized 10 new genera of microbes, including the genus *Salinospora*, from which they have isolated more than 2,500 new strains. *Salinospora* microbes have been isolated in large numbers from diverse ecosystems, including tropical and subtropical marine locations such as the Caribbean Sea, the Red Sea, the ocean waters around Hawaii, and the Sea of Cortez (Mincer *et al.*, 2002 and Feling *et al.*, 2003).

SPONGES

- Sea sponges are used in drugs for treating asthma and cancer.

- Certain sponges yield anti-inflammatory and antibiotic substances.

- A substance obtained from sponges – manoalide - is being tested as an anti-inflammatory drug.

- Sea anemones provide a heart stimulant.

CORAL REEF

The wealth of new medicines, which can be obtained from the ocean, has only just been acknowledged over the past 10 years. On coral reefs there is an estimated biodiversity of 9,00,000 species and already the few corals, sponges, algae that have been studied for medical properties have provided new anti-cancer agents, anti-inflammatory agents and advanced UVC sun screens. The potential for finding new anti-biotics is huge as marine animals are exposed to over 3,000 more bacterial species than terrestrial animals.

DEEP SEA CORALS IN BONE GRAFTING AND COLLAGEN SUBSTITUTION

Bone grafts to repair fractures are the second most common medical transplants, after blood transfusions, in the United States. The procedure can be expensive and painful, and it sometimes leads to complications such as infection and tissue rejection. As a result, bone substitutes have long been explored as replacements for donor grafts. Natural coral has been used as a bone substitute for more than 10 years in orthopedic, trauma, craniofacial, dental, and neurosurgeries. Corals have a structure similar to that of human bone, with a hard outer sheath and a spongy inner core. Even if coral is not used at the site of the original injury, it can be used to replace bone harvested from the patient at the donor site, making it possible to reharvest bone later at the same site if necessary. Coral bone substitutes have enormous potential, both in their natural and hybrid, synthetic forms. At present, the tropical coral genera *Porites*, *Alveopora*, *Acropora* and *Goniopora* are being used as bone substitutes; these are the

only families known to have the correct pore diameter and the ability to connect properly with bone (Chiroff *et al.,* 1975; Vuola *et al.,* 2000 and Parikh, 2002).

Bamboo corals like *Keratoisis* and *Isidella* (family Isididae) are often found at depths of more than 1,000 meters. These corals have jointed axes made of bony calcareous structures alternating with nodes made of a protein-based material called gorgonin, giving the skeletal structure of the coral - an appearance that resembles fingers. The skeletal structure and dimensions of bamboo coral are almost identical to those of bone (Ehrlich *et al.,* 2003; Etnoyer and Morgan, 2003).

The establishment of biotechnological approaches for the cultivation of bamboo corals will open a new and unique path for the development of natural bone implants. Gorgonin is of interest to scientists for two reasons. First, it possesses chemical groups that are responsible for cross linking and hardening structural proteins in nature. Second, it closely resembles both keratin, which forms the basic structure of hair and nails, and collagen, which is an important component of bone.

The antiviral drugs Ara-A and AZT and the anticancer agent Ara-C, developed from extracts of sponges found on a Caribbean reef, were among the earliest modern medicines obtained from coral reefs. Other products, such as Dolostatin 10, isolated from a sea hare found in the Indian Ocean, are under clinical trials for use in the treatment of breast and liver cancers, tumors and leukemia. Working with extracts from a sponge *Plakinistrella,* found in the Indian Ocean, Harbor Branch researchers have discovered unique chemical compounds that could lead to new treatment for

fungal infections that threaten the lives of AIDS and cancer patients. The compounds are members of a completely different class of antifungal agents called cyclic peroxide-acids, and in laboratory tests have been shown to kill two human pathogens; *Candida albicans,* which causes skin infections and thrush, and can endanger the lives of AIDS patients, and *Aspergillus fumigatus,* which causes dangerous lung infections in people with weakened immune systems, such as cancer patients who are undergoing chemotherapy.

LOBSTER

British scientists have cracked the puzzle of why lobsters turn pink in the pot. Their shell loses its natural blue-black colour due to changes in a key protein and now researchers understand precisely how. The colour-change molecule is a powerful antioxidant and of great interest to the medical world. The discovery could lead to new treatments for a number of human diseases including cancer. It also raises the possibility of novel "lobster-colour" food dyes that could provide a more natural alternative to existing colourants. A live lobster is normally blue-black. It is camouflaging for hiding among rocks on the ocean floor to avoid predators. Its shell changes colour due to the structure of a protein called beta-crustacyanin. Part of this molecule is able to change shape, bending the shape of another molecule attached to it, called astaxanthin. Astaxanthin on its own is orange, if it binds to beta-crustacyanin, its light-absorption properties are altered and it turns blue. On cooking, the crustacyanin unit is broken down, and astaxanthin becomes stuck in the orange form. This carotenoid astaxanthin is a powerful antioxidant, which protects against damage from cell membranes and tissues (Shirley Pomponi and Alan Duckworth, 2003).

MOLLUSCANS

Molluscs are another prime species that have a wide range of uses in pharmacology. Seahare, which is a shelled organism, produces a substance that has undergone clinical trials for the treatment of cancerous tumors. It produces a compound that shows good potential for bladder cancer. Ziconotide is a 25 amino-acid linear peptide exhibiting three disulfide bonds; it occurs along with other peptides in the venom of the predatory Indo-Pacific marine mollusc, *Conus magus* (Olivera, 2000), *C. magus* and other *Conus* species are fish-hunting molluscs that use their venom to paralyse their prey (Kohn, 1956). The remarkable analgesic activity of ziconotide (the compound proved to be 1,000 times more active than morphine in animal models of nociceptic pain) is due to the blockage of calcium channels (McCleskey *et al.,* 1987 and Olivera, 2000).

The alpha-toxins from different species of *Conus* show selectivity towards either muscle or brain receptors. These toxins are useful tools for examining the molecular nature of diseases in which the function of nicotinic receptors in the brain is impaired, such as Alzheimer's disease, Parkinsons's disease and Epilepsy.

BRYOZOANS

Bryostatin - a promising new chemotherapy for leukemia and melanoma: Bryostatin, a natural product produced by a bryozoan - *Bugula neritina* (a sessile filter-feeding invertebrate), is an exceedingly exciting new form in chemotherapy.

SEA-WHIPS

Pseudopterosins - Extracted from the octocoral (sea whip) *Pseudopterogorgia elisabethae*; anti-inflammatory and analgesic agents, that reduce swelling and skin irritation, accelerate wound healing; acts as an inhibitor of phospholipase - A, which is a key enzyme in inflammatory reactions.

TUNICATES

Sack-like sea squirts living on the sea floor make a complex anti-tumor drug, hundreds to thousands of times more powerful than any cancer potion now in use. Ecteinascidin and Phthalascidian (two drugs), work by interacting with DNA and an unknown protein in cancer cells. The drugs do not kill tumor cells; rather, they prevent them from reproducing and growing. Endostatin, another potent drug works by blocking the development of blood vessels that bring oxygen and sustaining nutrients to tumors (William Cromie, 2000).

FISH SPECIES

Salmon, which, like humans, produces a hormone called calcitonin that helps to regulate calcium and decreases bone loss. For osteoporosis (a crippling disease marked by a wasting away of bone mass) patients, taking salmon calcitonin, which is 30 times more potent than that secreted by the human thyroid gland, inhibits the activity of specialized bone destroying cells called osteoclasts that absorb bone tissue. This enables bone to retain more bone mass. Salmon calcitonin is approved only for postmenopausal women who cannot tolerate estrogen, or for whom estrogen is not an option (John Henkel, 1998).

- Cod and shark liver oils are great sources of vitamins A and D.

- The Romans were said to employ the barbs of sting rays in the treatment of toothaches.

- Tetrodotoxin from pufferfish, sunfish, porcupine fish and salamanders is used in the treatment of cancer.

- Various compounds from stonefish (the world's most venomous fish) are used for lowering blood pressure.

- A group of enzymes, known as omega 3 fatty acids, which come from certain fish and marine mammals, reduces the build-up of cholesterol in the blood.

SEAWEEDS

680 species of marine algae belonging to Rhodophyta, Phaeophyta, Chlorophyta commonly known as red, brown and green seaweeds respectively, have also been identified in both inter-tidal and deep water zones. Among these seaweeds green algae are rare while red algae are small and delicate, with a feathery appearance. It is considered as the medicinal food for the 21st century. The bioactive compounds found in seaweed await a major breakthrough for a variety of applications in medical field. Many types of seaweed are rich in vitamins and minerals.

Brown algae yield a gummy substance called algin and red algae produce jellylike substances called agar and carrageenan. These substances are used as additives in food products and drugs to give them a smooth texture and help them to retain moisture. The brown algae contain plenty of iodine and are used for curing goiter. Some of them are also

used as vermifuges, soothing lotions, cosmetics and drugs. Alginic acid, which comes from a certain species of seaweed, is being used to treat diabetics.

MARINE PHARMACEUTICAL RESOURCES

Over 800 different species of marine flora and fauna collected from Indian coasts including island groups were subjected to investigations to identify bioactive compounds. During the last few years, about 4,000 samples were extracted/fractionated and subjected to a wide spectrum of screening for biological activities such as antidiabetic, anti-hyperlipidaemic, antidiarrhoeal, antimicrobial/antiviral, antimalarial and so on. 597 samples exhibited various types of biological activities and out of these 16 samples were identified for follow up studies in different areas. Over the years, 319 pure compounds have also been isolated. Some of these possess interesting biological activities while some others, though inactive, had novel chemical structures, like alkaloids, glycosides, aminoacids; fatty alcohol esters. Ocean organisms have been widely used in the Ayurvedic system of medicine as well.

CANCER COMPOUNDS OF THE DEEP

The majority of marine-derived compounds are obtained from either microorganisms or stationary bottom dwelling organisms such as corals, sponges, and tunicates. Because stationary organisms cannot evade predators through movement, they rely heavily on chemical defense mechanisms to protect themselves. These mechanisms generate compounds that frequently show significant bioactivity, or effects on living cells or organisms, such as those, which cause human ailments. Two compounds originally isolated from deep-sea organisms are now in

human clinical trials as anticancer compounds. Several others are in preclinical stages and show considerable promise.

E7389

This compound is a cell-killing derivative of halichondrin B, one of a number of compounds originally isolated in 1985 from the Japanese sponge *Halicondria okadai*. The deep-sea sponge *Lissodendoryx* sp., which occurs at depths near 330 feet (100 meters) in waters surrounding New Zealand, was later discovered to contain halichondrins in greater concentrations than shallow-water species. Working with halichondrins from these deep sea sponges, researchers from Massachusetts-based Eisai Pharmaceutical, in conjunction with the National Cancer Institute, developed E7389, a synthetic compound that is currently in its first phase of human trials (Phase I) for the treatment of non-small cell lung cancer and other cancers (Newman and Cragg, 2004).

Discodermolide

Isolated from the sponge *Discodermia dissolute*, found near depths of 140 meters, discodermolide is one of the most promising natural products discovered to date and it was originally found in the Bahamas in 1990 by scientists from Harbor Branch Oceanographic Institution. Discodermolide has been shown to be more potent for use against solid tumors (Newman and Cragg, 2004).

Dictyostatin-1

Dictyostatin-1 is an anticancer compound in preclinical development. The compound was originally isolated in 1993 from a shallow-water sponge, *Spongia* genus, which lives off the coast of the Republic of Maldives (Isbrucher *et al.,* 2003).

Sarcodictyin/Eleutherobin

Sarcodictyin was first reported in the late 1980 s from the Mediterranean coral *Sarcodictyon roseum*, found at depths of upto 100 meters. Several years later, a similar compound called eleutherobin, was isolated from a shallow-water *Eleutherobia* species in western Australia; these two compounds had a similar mode of action and are in preclinical development stages (Hamel *et al.,* 1999).

Salinosporamide A

Salinosporamide A, isolated from the microbe, *Salinospora,* collected at depths of more than 1,000 meters, exhibits strong cytotoxicity against melanoma, colon cancer, breast cancer, and non-small cell lung cancer. It also shows great potency as a powerful anticancer agent with a new way of controlling cancer cell growth (Feling *et al.,* 2003).

CONCLUSION AND SCOPE

The success rate of finding a new active chemical is 500 times higher in marine organisms than from terrestrial sources. The world's oceans and waterways may harbor the next generation of drugs, biologics, and even a few medical devices. Many platform-dwelling species have compounds that could be used in medicine, industry and food, by applying biotechnology. Conserving our marine environment is a matter of enormous importance for a number of reasons. Perhaps one of the more significant resources held within the genetic composition of the ocean inhabitants will lead to the development of pharmaceuticals for the next millennium. A large percentage of the nation depends on the sea’s living resources for its economic viability. Therefore, we must actively and aggressively seek alternate and additional value from the nation’s living marine resources in the form of new products, discovered in the sea and then

produced through biotechnology or generated through aquaculture. The deep sea is a potentially huge source of medically important compounds, a source that science has only begun to explore.

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Table 1: Selected marine natural products currently in clinical trials (Fusetani, 2000)

Source	Compounds	*Disease area*	Phase of clinical trials	References
Salinospora (microbe)	Salinosporamide A	**Cancer**	Preclinical development	Feling, *et al.* (2003)
Blue green algae	Cryptophycins	**Prostrate and Breast cancer**	Preclinical development	**John Henkel, 1998**
Genus Caulerpa, Cladophora, Bryopsis, Boodlea, Chaetomorpha, Ulva, Enteromorpha and Valoniopsis (Indian marine green algae)	Extracted Compound comparable to heparin	**Blood anticoagulant activity**	Preclinical development	Shanmugam, *et al.* (2001)
Agelas mauritianus (sponge)	KRN7000b	Cancer	I	Kikuchi, *et al.* (2001)
Luffariella variabilis (sponge)	Manoalide	Inflammation/ psoriasis	I	De Rosa, *et al.* (1998)
Petrosia contignata (sponge)	IPL 576,092c	Inflammation/ asthma	I	Coulson and O'Donnell (2000)
Pseudopterogorgia elisabethae (soft coral)	Methopterosind	Inflammation/ wound	I	Mayer, *et al.* (1998)
Lissodendoryx sp. (sponge)	**E7389**	Cancer	**I**	Newman and Cragg, (2004)
Discodermia dissolute (sponge)	Discodermolide	Cancer	I	Newman and Cragg, (2004)
Order Lithistida, Family Corallistadae (sponge)	Dictyostatin-1	Cancer	Preclinical development	Isbrucher, *et al.* (2003)

Source	Compounds	*Disease area*	Phase of clinical trials	References
Sarcodictyon roseum (coral)	Sarcodictyin/ Eleutherobin (related compounds)	Cancer	Preclinical development	Hamel, *et al.* (1999)
Spongosporites ruetzleri (sponge)	Topsentin	Anti-inflammatory: Arthritis, skin irritations Cancer: colon (preventive) Alzheimer's	Preclinical development	National Research Council (2002)
Family Isididae (coral)	Orthopeadic implants	Bone grafting	Preclinical development	Ehrlich, *et al.* (2003)
Amphiporus lactifloreus (marine worm)	GTS-21e	Alzheimer/ Schizophrenia	I	Kem, (2000)
Conus magnus (cone snail)	Ziconotide	Pain	III	Osenbach and Harvey (2001)
***Perna viridis* (Green mussel)** *Crassostrea madrasensis* (Estuarine oyster) *Crassostrea gryphoides* (Giant oyster) *Meretrix casta* (Estuarine clam) *Villorita cyprinoides* (Black clam) *Polymesoda erosa* (Mud clam)	**Antiviral drugs**	Possess high antiviral activity	Preclinical development	Chatterji *et al.* (2002)
Dolabella auricularia (sea hare)	Dolastatin 10	Cancer	II	Vaishampayan, *et al.* (2000)
Dolabella auricularia (sea hare)	LU103793a		II	Smyth, *et al*. (2001)

Source	Compounds	*Disease area*	Phase of clinical trials	References
Bugula neritina (bryozoan)	Bryostatin 1	Cancer	II	Varterasian, *et al.* (2001) and Blackhall, *et al.* (2001)
Aplidium albicans (tunicate)	Aplidine	Cancer	I/II	Gomez, *et al.* (2001)
Ecteinascidia turbinata (tunicate)	Ecteinascidin 743	Cancer	II/III	Delaloge, *et al.* (2001) and Villalona-Calero, *et al.*(2002)
Tridemnum solidum (tunicate)	Didemnin B	Cancer	II	Mittelman, *et al.* (1999)
Squalus acanthias (shark)	Squalamine lactate	Cancer	II	Bhargava, *et al.* (2001)

a Synthetic analogue of dolastatin 15

b Agelasphin analogue (α-galactosylceramide derivative)

c Synthetic analogue of contignasterol (IZP-94,005)

d Semisynthetic pseudopterosin derivative

e Also known as DMXBA, 3-(2, 4-dimethoxybenzylidene)-anabaseine

DRUGS FROM THE DEEP

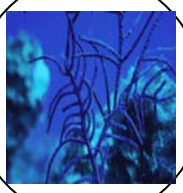
Conus

Alzheimer's disease, Parkinsons's disease and epilepsy

Bugula neritina

Bryostatin - *leukemia and melanoma*

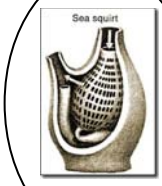
Sea Whip



Pseudopterosins – anti-inflammatory and analgesic agents

The mangrove

Anticancer ecteinascidins



Phthalascidian, Endostatin - anti-tumor drugs