Review Article

Biomaterials from Sponges, Ascidians and Other Marine Organisms

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ABSTRACT

Biomaterial, one of the most interesting fields of modern science deals with the biologically derived materials or substances that are used within a biological system. Although according to the sources two types are there yet in terms of several advantageous properties natural biomaterials are far more important than synthetic biomaterials. Among the natural sources the newest one and also the most potent one identified to be is the marine environment. The most undiscovered part of the earth, this marine environment is the powerhouse of millions of undiscovered species generating the greatest biodiversity zone. Here in these article biomaterials from various marine organisms like sponges, ascidians, crustaceans, sessile organisms, corals, actinobacteria, seaweeds, fungi have been reported. The uses of some of the important biomaterials are also discussed. For future work first an appropriate characterisation method should be developed for isolating the sample organisms from marine environments. Extreme environments underwater like hydrothermal vent, hyper saline region etc and also various thermocline and halocline environment provide unusual microorganisms producing uncommon bioactive compounds. Development of new strategies coupled with chemical synthesis method could pave the way for future discovery in this actively growing field.

Keywords: Ascidians, Biomaterials, seaweeds, sponges.

INTRODUCTION

Biomedical engineering is an area that deals with traditional engineering approaches to improve the fundamental quality of life by solving various problems in the fields of life science and medicine. Interestingly the subject of biomaterial science tends to be the answer for the majority of problems associated with biomedical engineering. Biomaterial may be defined as 'a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body'.[1] Although there exists a debate within the scientific community regarding the exact definition of biomaterials, whether it is materials those interact with the biological systems or these are the materials which have been derived from biological organism, yet it's of no confusion that biomaterial science is concerned about the interaction between the biological metabolism and these substances. An ideal biomaterial should exhibit some properties like non toxicity, it should produce appropriate host response, should avoid adverse tissue reactions and rejections, biological or corrosion resistance to degradation, should possess sufficient amount of mechanical and rheological strength etc. Biomaterial industry is the emerging industry of 21st century. It has been observed that this domain accounts for 2-3% of the overall health expenses in developed countries.[2] Significant industrial growth is expected within the next 20 years ultimately generating a multi-billion dollar industry.

Types of Biomaterials

Biomaterials can be derived either from nature or synthesised artificially in the laboratory using metallic components, polymers, ceramics or composite materials. These materials are used for various biomedical applications. Some of their uses have been listed in table 1.

Table 1: Medical applications of synthetic biomaterials

Category	Material	Application
Metallic components	Stainless steel Nickel-Titanium Gold alloy Co-Cr-Mo-Ni alloy Hg-Ag amalgum	Fracture fixation[3] Bone plates[4] Dental restoration[5] Bone and joint replacement[6] Dental restoration[7]
Polymers	Polyethylene Polyethylene terephthalates Polypropylene Polyesters Poly tetra fluoro ethylene Silicones Hydrogel	Joint replacement[8] Vascular prosthesis[9] Sutures[10] Drug delivery system[11] Soft-tissue augmentation[12] Soft tissue replacement[13] Opthalmology[14]
Ceramics	Zirconia Alumina Calcium phosphate	Joint replacement[15] Dental implant[16] Bone repair[17]
Composites	Bisphenol A-glycidyl-quartz/ silica filler	Dental restorations[18]

Natural

When the biomaterial comes from the natural sources, then it is termed as natural biomaterial. Throughout the human civilization biological structures and natural substances have always been a model system for solving critical challenges in engineering, building and material science. Nature has always provided a wide array of substances with significant diversity in structure and functions.[19] The bio mimetic potentiality of these substances can also be applied to the biomaterial research arena. Although synthetic biomaterials have been commercialised for various biomedical application they have certain disadvantages including toxicity and reduced ability of tissue remodelling. The major advantage of nature derived biomaterials is the increased chances of biocompatibility, biodegradability, tissue remodelling, cell adhesion, proliferation, differentiation and less toxicity. Furthermore wide variety of organisms of earth provides a great opportunity to discover their biomaterial potentiality. Among the natural sources the most predominant one is marine environment. From the very first day of its existence, the earth contains marine environment. The age of terrestrial organism is much younger in comparison to marine organisms. Which is why there exists much higher biochemical diversity in the marine realm and this diversity is directly proportional to the probability of getting novel biomaterials.

Diversity of Marine Organisms

Aquatic environment is the main component of natural sources. Aquatic organisms can be divided into two types fresh water organisms and marine organisms. 72% of earth has been covered by aquatic systems. Among these 97% of earth's water content is within the oceans. Life begun at sea and afterwards many of the species of marine system were unable to make the transition to the terrestrial life. Consequently marine organisms have higher genetic diversity than freshwater and terrestrial species.[20] As an example, all except one of the 35 animal phyla are found in the sea and surprisingly half of these are primarily marine.[21] A comparative study showed that average heterozygosity was considerably less in freshwater fish subspecies with respect to marine population.[22] Elliott et al.,[23] showed that genetic diversity of the Orange Roughly needs only 200 migrants per year to be maintained which infers that marine organisms probably exchange up to 100 times more migrants than freshwater species in every generation. Several theories suggest that there may be 5 million[24] to 10 million[25] under scribed deep sea species. Various groups of the sea include Echinodermata (starfish and sea urchins), Brachiopoda (lamp shells), Bryozoa (moss animals), Sipunculida (Peanut worms), Polychaeta (bristle worms), Pycnogonida (Sea spiders), Tunicuta (sea squirts) and Ctenophora (comb jellies) and the three large groups that are confined to the marine environment only are Cnidaria (anaemon, corals), Crustaceae (crabs, bernacles etc.) and the Mollusca (snails, slugs etc.).

Marine Organisms: A Source of Different Biomaterials

The incredible diversity of the marine organisms has become the reason of attraction for the entire scientific community in the field of biomaterial research. Starting from the marine sponges and ascidians up to the mussels, barnacles, crustaceans etc. have been already reported as potential sources of commercially important novel biomaterials. According to size they can be broadly classified into two categories macro-organisms and micro-organisms.

a) Macro-organisms

Sponges

Sponges are the most primitive of all the multi cellular organisms that have been existing 700-800 million years and approximately among 15000 sponge species, only 1% lives in the freshwater, remaining in the marine habitat.[26] Sponges are excellent research subjects due to their fibrous skeletons[27] and mineralized spicules, containing amorphous silica[28] or calcium carbonate. The skeletal formation of *demospongiae*, *hexactinellida*, *calcarea* etc. can be attributed as natural bio composite material based on rigid glass or calcium carbonate consequently increasing the possibility of developing a novel bone replacement biomaterial. Recently production of active metabolites by various species of sponges has gained attention. Sponges produce various toxins to compete for space with other species, to repel and escape the predators and for intra community communication. Discovery of various bioactive compounds[29,30] including anticancer, antichemotactic[31] and antifouling agents[32] suggests production of potential pharmaceutical agents.

Ascidians

These are the marine invertebrate organisms which are filter feeders. Their habitat includes all over the world generally in shallow water having salinity more than 2.5%. Thousands of natural marine products have been found in ascidians. In a similar manner as that of sponge they also require synthesis of chemical substances for survival in highly dangerous predation environments. Identification of these compounds has led to the discovery of many potent drugs. Bioactive compounds of different types of polyketides, hydrocarbons, enediynes, peptides, alkaloids, terpenes, tubericidins etc. have been isolated from ascidians.[33] A composite skeletal tissue has been reported from ascidian which consists of amorphous and crystalline calcium carbonate in two separated domains having an organic sheath in between. The calcitic layer consists of characteristic magnesium.[34] Moreover the therapeutic potential of glycol amino glycans has been proved. One of the current materials of importance chondroitin sulphate has been isolated from marine ascidians.[35] Ascidians also provide the source for important bioactive compounds like depsipeptide with anti tumorigenic property,[36] lamellarian[37] and imidazoles alkaloids[38] and cyclic peptides.[39]

Table 2: Biomaterials from marine sponges and ascidians

Sponges	Ascidians
Silica[40]	Cellulose[34]
Aragonite[40]	Calcite[34]
Chitin[40]	Calcium Carbonate[34]
Collagen[41]	Chondroitin Sulfate[35]
Stevensin[42]	Antitumor depsipeptide[36]
3-Akylpyridinium[29]	Lamellarian alkaloids[37]
3-Alkylpyridine[29]	Cyclic peptides[39]
Terpenes[43]	Imidazole alkaloids[38]
Sterols[43]	Polyketides[33]
Cyclic/ linear peptides[43]	Odd chain hydrocarbons[33]
Alkaloids[43]	Enediynes[33]
Fatty acids[43]	Peptides[33]
Peroxides[43]	Alkaloids[33]
Amino acid derivatives[43]	Terpenes[33]
Antibiotics[43]	Tubericidins[33]

Crustaceans

Marine crustaceans such as crabs, shrimps, krill's, lobsters, prawns etc. provide a great source of two important polysaccharides chitin and chitosan. Chitin is the second most naturally abundant polymer after cellulose.[44] Chitin forms the crystalline micro fibrilar structure of the exoskeleton of arthropods and fungi and some yeast.[45] Although fungal chitin is more uniform than animal one yet isolation of fungal chitin is difficult due to its association with various other polysaccharides e.g, mannan, poly galactosamine etc.[46] Structurally a linear chain of (1-2) linked 2-acetamide-2-deoxy-β-D-glucopyranose units.[47] The chain arrangement of crude extracted chitin produces two forms α and β.[48] Chitosan is none other than another form of chitin which is produced by achieving a certain a degree of deacetylation. It is the only cationic pseudo natural polymer as a result of which it is widely used in many applications due to its unique characteristics.[49] In aquaculture sector mainly shrimp and prawn are predominant. Shrimp chitin antibacterial activity has also been reported.[50]

Sessile Organisms

These are the incredible class of marine organisms including mussels, barnacles, sea anemones, urchins, starfishes, tube worms, limpets etc. They have the unique ability for the production of adhesive substances for attachment to the substratum of the rocks or clinging to the coastlines against the turbulent flow of water of the sea or oceanic environment.[51] This attachment is particularly important for the purpose of reproduction, signal for food supply, escape from the predators etc. Mussels generate a byssal thread and an adhesion plaque thereby attaching via specialised adhesive proteins consist of hydroxyproline and dihydroxy phenylalanine.[52] On specialised high energy surfaces mussels sticks with a strength of almost 300 Kilopascals.[53] The threads are composed of collagen resembling proteins whereas the plaques are of cross linked protein matrix. One major constituent of these adhesives is that 3,4-dihydroxyphenylalanine (DOPA) an uncommon amino acid produced by the post translational modification of tyrosine.[54] Absence of this amino acid causes the loss of adhesion ability of the proteins.[55] The property of adhesion ability along with special characteristics of biocompatibility and biodegradability makes it suitable candidate for industrial and medical adhesives.[56]

Corals

The oceanic environment provides a wonderful combination of calcified sessile and free living organisms containing a wide array of micro scale organised skeletal materials. These structural materials are usually made of calcite and aragonite which are nothing but the crystalline form of $CaCO_3$ and silicate materials. In biomedical applications coralline calcite or aragonite has been successfully applied for replacement of fractured bone due to their ability of forming strong chemical bond with in vivo soft tissue and bones.[57] The specialised advantage of using coralline apatite is increased chances of resorption by the attack of enzymes like carboanhydrase.[58] Secondly its porous crystalline structure permits the blood supply for the newly formed bones by allowing in growth of blood vessels ultimately infiltrating the implant.[59] Use of porus coral apatite has also been established for the *in vitro* culture of prokaryotic and eukaryotic cells. Interestingly coralline (*Goniopora, Millepora*) calcium carbonate converted hydroxy apatite constructs also show the ability of bone differentiation.[59,60]

Seaweeds

Loosely the term seaweed indicates the class of marine algae comprising red, brown and green algae. From the biomaterial science perspective marine algae is an excellent source of commercially important biomaterials. Polysaccharides like agar, alginate, fucoidan and carrageenan are obtained from algae. Agar is a typical linear copolymer of hydrophobic basic alternating repeating units of 1,3-linked β-D-galactopyranose and 1,4-linked 3,6-anhydro-α-L-galactopyranose.[61] This structural polysaccharide is found to be present in the cell wall of red algae especially within the genera Gelidium[62] and Gracilaria.[63] Along with these two Ceramium, Acanthopeltis and Pterocladia are the main sources of commercial agar.[64] Alginate is another kind of commercially important biopolymer having its predominant existence in the cell wall of brown algae *Laminariapallida*, *Laminaria japonica*, *laminariadigitata*, *Ascophyllum* and *Macrocystis*.[65] The component of polysaccharide in the sea weed has been used for the production of bioplastics.[66] For various biomedical applications and enzyme immobilization purposes alginate has been proved to be worthwhile. Carrageenans are high molecular weight polysaccharides composed of

D-galactose backbone. Among the 15 different structures, the major sources of industrially relevant κ-carrageenan, ι-carrageenan and λ-carrageenan are red seaweed *Kappaphycusalvarezii*, *Eucheumaspinosum* and *Gigartina species*.[67] Another specialised sulphated polysaccharide fucoidans can be extracted from brown algae. Several adventitious properties of algal fucoidans over the marine invertebrates like higher anticoagulant activity[68] resulted in the use of marine brown algae such as Komby, hijiki, derwrack, mozuku as its major source. Moreover marine algae of Rodophycophyta division has been successfully implemented as a starting material for the extraction of calcium carbonate to produce hydroxyapatite.[69]

Micro-organisms

Actinobacteria

Actinobacteria, is one of the largest bacterial phyla consisting of mainly organisms with high G+C content.[70] Although primarily thought of as a soil bacteria, there presence in more numbers has been established in freshwater[71] and marine sediments.[72] This class of bacteria consists of most economically significant prokaryotic organisms which produce almost half of the bioactive compounds in the Antibiotic Literature Database.[73] The members of this group show excellent physiological, morphological and metabolic diversity as evident by the production of various secondary metabolites and extracellular enzymes.[74] Extreme environment of the marine actinobacteria habitat starting from temperature below 0°C, extreme pressure (up to 1100 atm approximately) at the deep sea floor to highly acidic conditions with extremely hot temperature (100°C) near the hydrothermal vents may be the possible reason for the production of wide classes of bioactive materials.[75]

Fungi

Meristematic black yeast, these are the fungi that resides in hyper saline waters, represented by halophilic *Hortaeawerneckii*, *Phaeothecatriangularis*, *Trimmatostroma*, halotolerant *Aureobasidiumpullulans*,[76] and different species of the genus Cladosporium, taxonomically and phylogenetically closely related to black yeasts.[77] Cellular dehydration due to extracellular freezing and hyper saline stress can accumulate many solutes, which can be a good cryoprotectants and osmolytes. Glycerol and mycosporine like amino acids (MAAs) are the potent substances which functions as water soluble UV-absorbing (310-320nm) compound.[78] The pure compound from *Collemacristatum* prevented pyrimidine dimer formation and cell destruction by absorption of UV-B radiation.

Uses of marine biomaterials

In recent years biomolecules from marine sources have gained wide attention due to their bio mimetic potentiality. With their incredible structural similarity as well as biocompatibility, they have found significant usage in various biomedical applications.

Table 3: Biomaterials obtained from other marine organisms

Organisms name	Biomaterial obtained	References
Crustaceans		
Crab	Chitin $CaCO_3$	79 80
Shrimp	Chitin Chitosan	81 82
Oyster	Proteolytic enzyme Chitin	83 84
Squid pen	Chitin Hydroxyapatite Chitosan	85 86 87
	Chitin Chitosan	88 89
Sessile organisms		
Mussels	Adhesive protein	90
Bernacles	Bernacle cement	91
Sea anemones	Silk like protein Adhesion protein	92 93
Sea urchins	Adhesive protein Calcite Calcium Carbonate	94 95 96
Starfishes	Adhesion protein Collagen Calcium Phosphate	97 98 99
Tube worms	Chitin cement protein	100 101
Corals		
Bamboocoral	Calcium carbonate	102
Octocoral	Calcite	103
Actinobacteria		
Streptomyces sp.	Polyketide Pyrroloiminoquinone Pyrrolizidine	104 105 106
Actinomycete sp.	Indolocarbazole Isoprenoid	107 108
Actinomadura sp.	Indolocarbazole Phenazine	109 110
Seaweed		
Red algae	Agar Carrageenan Calcium Carbonate	62 67 69
Brown algae	Alginate Fucoidans	111 68
Green algae	Bioplastics	66
Marine fungi		
Black yeast	Glycerol	112

a) Calcium carbonate and hydroxyapatite

Calcium and phosphate composite material such as hydroxyapatite has some special importance in the biomaterial science because of their analogy with the mineral components of the bone. Although calcium carbonate is the more abundant form of calcium in the marine environment yet calcium phosphate composites like hydroxy apatite is of more importance from the application point of view. Calcium carbonate can be found in the crystalline form of calcite or aragonite in octocorals, bamboocorals etc. Though there is variety of sources yet the unique properties of coral calcium carbonate like porosity, architecture, pore interconnectivity etc. made them the primary candidate for orthopaedics and dentist applications.[113]These criteria are important for bone regeneration purpose. Several different study indicated one major limitation of calcium carbonate for using it as a possible bone substituent because of its faster resorption.[114] For this purpose now the focus has been shifted to the production of calcium phosphate compounds such as hydroxy apatite which has all the properties of calcium carbonate but with increased efficiency in terms of resorption. Several synthetic methods such as hydrothermal,[115] sol-gel,[116] chemical precipitation,[117] reverse microemulsion[118] and polymer assisted method[119] etc. have been reported already. Coral is now also widely used for the hydroxy apatite production. Porous hydroxy apatite microstructure produced from coralline carbonate showed the advantage of circulation of body fluids and the capability of farm attachment with the tissue substratum.[120] Hydroxyapatite ceramic carrier has been successfully applied in repairing tibial gaps in sheep model by autologous transplantation of bone marrow osteoprogenitor cells.[121] For dentist application biomimetic nanohydroxyapatite toothpastes have been found to be useful for the remineralisation of enamel surface.[122] Coralline hydroxyapatite implant also has the ability of cosmetic reconstruction without any risk of infection.[123]

b) Biosilica

Bio derived silica, commonly termed as biosilica, is made up of amorphous silica and is produced in many marine organisms such as sponges, diatoms, choanoflagellates and radiolarians. Among all these bio silicifying organisms' sponges and diatoms are the two most important sources. The process of biosilica formation is mediated by the enzyme silicatein through the formation of various concentric layers.[124] The naturally occurring silica has been identified as a bio composite with high flexibility and toughness which could be credited to their layer based structural organisation and hydrated nature.[125] Silica based biomaterials have additional properties of biocompatibility and adventitious reaction product formation after implantation.[126] The bioactive glasses based on silica has a wide range of applications involving bone tissue replacement, soft tissue augmentation, maxillofacial reconstruction, urological tissue augmentation, ossicle replacement etc. Biosilica can offer the properties of nanotoxicity, high stability and a hydrophilic and porous nanoscale structure useful for applying in the encapsulation of drugs.[127] Biosilica induces the expression of the important mediator BMP 2 which is responsible for inducing the differentiation of bone forming progenitor cells and also inhibits the function of osteoclasts, thereby acting as a promising candidate for treatment of the disease of osteoporosis.[128] Recently silicon substituted hydroxyapatites are being developed which increases the bioactivity and mechanical properties of bone substituted material. The increased bioactivity leads to excellent osteo integration by promoting the reaction between bone and implant owing to increase in solubility of the material.[129]

c) Alginate

One of the most important biomaterials which has found number of applications in biomedical engineering due to its unique properties of gelation and biocompatibility. The alginate hydrogels are especially the subject of interest. The extraordinary property of structural mimicking of extracellular matrices of the tissues has led to an extensive use of alginate hydrogels for the purpose of wound healing, drug delivery and tissue engineering. Hydrogels are basically hydrophilic polymeric networks which have the capacity to accept water thousands of times of their dry weight. This hydrogel can play a significant role for devising a controlled drug delivery strategy.[130] Polycaprolactone,[131] chitosan[132] and carbon nanotube[133] have been successfully applied for drug delivery with alginate hydrogels. Specific tissue engineering systems have been produced based on the alginates such as artificial pancreas where alginate is used for islet cell encapsulation, alginate delivery vehicle mediated bone regeneration system, bio artificial liver etc.[134] Moreover the alginate has been found to be a good candidate for skeletal mussel regeneration. The hydrophilic property of alginate allows it to retain a moist environment by adsorption and desorption process and subsequently alginate hydrogel can be used efficiently for the purpose of wound dressing.[135] Cell immobilization is another promising application of alginate gel systems. Entrapment of the cells within the gel allow them to be cultivated within different types of bioreactors to obtain high cell densities.[136]

d) Chitosan

Chitosan, a linear polysaccharide comprise of randomly distributed glucosamine residues, can be obtained from chitin by enzymatic or chemical method. Chitosan is one of the major sources of surface pollution in coastal areas. Recently it has been established that due to its excellent coagulating properties it can be used for the purpose of wastewater treatment.[137] Important properties of biocompatibility, non-toxicity with the specialised advantage of antimicrobial activity has lead to the implementation of chitosan based films for food packaging which can be an appropriate alternative of commercially available packaging materials which hampers the environment.[138] Repeated reuse of these biomaterials provide an attractive route for waste management. These chitosan films have also been established as a potential local drug delivery system.[139] Uses of chitosan include preparation of an immobilizing and permeabilizing matrix for microorganisms, delivery system for nucleic acids,[140] hollow fiber membranes for removal of ions,[141] matrix for artificial skin, tablet binder, plant cell culture and surgical sutures.[142] Chitosan is also used as a composite material by blending with hydroxyapatite or producing hybrid with alginate for bone tissue engineering.[143]

e) Fucoidan

One of the most important biomaterials found mainly in the marine brown algae is the sulphated polysaccharide fucoidan. It has a significant role in controlling the acute and chronic inflammatory response by the mechanism of enzyme and complement cascade inhibition. Fucoidan has been found to contain several interesting properties that may lead to prevention of the disease of cancer. Evidence has been discovered that this sulphated polysaccharide can inhibit proliferation and induce apoptotic cell death of human lung carcinoma cells,[144] human breast cancer cells by the activation of caspase 8.[145] Enzyme digested fucoidan extracts suppress the expression and secretion of various angiogenesis factors thereby produce inhibitory effect on angiogenesis of tumor cells.[146] Furthermore immunomodulating activity of fucoidan empowers it to act as a potential mitogen for lymphocyte and macrophage activation.[147] Fucoidan can be used for the treatment of osteoarthritis. Oral administration of seaweed extract containing fucoidan inhibited the symptoms of osteoarthritis.[148] For biomedical applications fucoidan – chitosan micro complex has been produced as a carrier for controlled release of specialised growth factor and the findings suggested growth factor containing fucoidan-chitosan hydrogel can be used for the treatment of ischemic disease.[149] Another blended hydrogel consisting of chitosan, alginate and fucoidan has found successful application in healing-impaired wound dressing.[150] Low molecular weight fucoidan is in use for bone extracellular matrix formation in 3D culture.[151]

CONCLUSION

All the aforementioned evidences suggest that marine organisms have the capacity to generate a wide range of useful biomaterials. The major area of concern for the scientific community is the enormous diversity of marine ecosystems and exploitation of this feature for the generation of novel biomaterials. Already nature derived biomaterials have taken a giant leap beating the synthetic biomaterials in terms of its several beneficial properties. With the advent of marine derived biomaterials there will be a new horizon in the field of biomedical science. The first and foremost step should be proper isolation method. Marine environment is entirely different from the terrestrial one having great differences in pressure, temperature etc. So, application of suitable isolation technique along with laboratory based chemical approach should be developed for research, development and commercialisation of the biomaterials. At the time of birth the earth had extreme environment which are still present in large amount in marine environment in the form of hydrothermal vent, hot springs etc. Also thermocline and halocline environment demand special mention in this context. These are all sources of unique microorganisms which can be investigated for novel bioactive compounds. Therefore in conclusion we can say that by the help of intense research and discovery, strategic approach should be taken for the exploration of one of the finest attractions of modern science.

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