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RESEARCH

Marine-derived bioceramics for orthopedic, reconstructive and dental surgery applications

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Abstract

Bioceramics are a fast-growing materials group, which are widely used in orthopedics, maxillofacial, dental, and reconstructive surgeries. They are produced using raw materials either from synthetic or natural sources. As naturally originated resources, the bones of sheep and cows are used after converting to calcium phosphates. Human-originated sources in the past were obtained from human cadaver bones, however now-a-days this has been discontinued. On the other hand, the "golden standard" in the reconstruction surgery has been using patients own bones, -i.e., autogenous bones, which heal better than other alternatives. Besides natural products, synthetic materials are produced from a range of inorganic raw and natural materials based on marine sources, such as corals, and other marine-derived materials (i.e., seashells, nacre). These are used to produce bioceramics and hence implants, devices, and bone grafts. Although during the last four decades a number of excellent books and book chapters have been published, no comprehensive review has been yet reported to cover the available marine materials and to indicate the related work and corresponding references to allow for both medical and ceramic scientists to access directly and open new avenues for further research on marine structures and their applications in orthopedic, maxillofacial, and reconstructive surgery areas. Hence, this review covers the general marine structures, their locations and availability in different countries and, current research on production methods of these unique structures that are difficult to fabricate synthetically. The authors are confident that this comprehensive review will be an excellent source not only for the ceramists, but also for the medical scientists.

Keywords Bioceramics · Hydroxyapatite · Marine-materials · Orthopedic and maxillofacial surgery · Bone grafts

Introduction

When the holiday is over and it is time to go home will always remind us of the beauty to take things with us as souvenirs. Like jewels from the sea scattered on the shores are seashells, snails, mussels, scallops, clams and other marine molluscs that tempt us to collect and carry home.

One of the most commonly collected shells are molluscs. Whatever their taxonomic origin is, usually they are made of the superimposition of a few calcified layers and binding organic layers in between each layer that give their unique mechanical properties [1, 2].

Molluscans are represented as the second-most species-rich phylum with an estimated 150,000–200,000 extant species on Earth, which are classified in eight classes. *Molluscs* transformed over the time going back to the geological period to inhabit nearly every ecosystem on Earth, from arid hot deserts up to cold mountain areas. So far, their great majority occurs in the sea, where they account for around a quarter of all known species. It is generally known that shells and pearls are used to treat asthma, cough, mucus, and sore throat problems as well. Moreover, the utilization of molluscan composites to treat and prevent respiratory and infection-associated diseases is well documented [2, 3].

Seashells represent the exoskeletons of molluscs such as clams, sea snails, oysters, and others. These shells present three distinct layers in their structures, which generally comprise a high amount of calcium carbonate ($CaCO_3$) and a small quantity of proteins ($< 2\%$). $CaCO_3$ is not dissolved in water and is made of calcium ions that are secreted from the cells of these animals, on one hand, and the carbonate ions that are present in the water, on the

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other hand [4, 5]. But it must be not forgotten that, they are in the mineral form of calcite or aragonite [6]. This type of shells, unlike typical animal structures, do not contain in their composition only cells. For example, mantle tissue, which is situated under and in contact with the shell, stashes proteins and/or minerals extracellularly forming the shell's structure. The growing mechanism of the seashells is either from the bottom to the top, or by the addition of shell material at the margins [4]. Seashells appear after the bio-mineralization process, in which inorganic solids are produced by the living organisms. Consequently, shells represent protective barriers for many marine animals, i.e., molluscs and/or other sea-creatures. Most of these animals do not have a backbone and for this reason they are called invertebrates [5, 6].

$CaCO_3$ is an inorganic calcium salt which originates from either shelled-molluscs, limestones, *coccolithophores*, plant ashes, chalk, or marbles. It was recently reported in the nanotechnological domain as a viable porous biocompatible and pH-sensitive material [7].

Since very ancient times, the marine-derived biomaterials, i.e., molluscan shells, corals, bath sponge skeletons, and byssus threads, were used for various applications. Nowadays, the reach to an industrial level has become a necessity and somehow achievable due to the fast development of different new processing technologies and research into various marine-culture systems [8].

The marine environment can offer endless potential solutions for various engineering, bioengineering, tissue engineering, and other medical applications [9]**.**

The use of bioceramics in orthopedics, aesthetics, and dentistry has been reported more than three decades ago in some comprehensive reviews [9, 10]. Applications like dental and percutaneous implants, periodontal treatments, alveolar augmentation, orthopedic, maxillofacial, aesthetic, and spine surgeries, are therefore targeted.

Regina Rosa and her collaborators reported on very high $CaCO_3$ content in the case of mussels (at earlier ages, the sea creatures with a shell, i.e., mussels, used to be called "shellfishes") and oysters. Thus, the inferred CaO content of mussels was 95.7%, oysters 98.2%, and commercial $CaCO_3$ powder, 99.1% [11]**.**

After harvesting the obtained market product (i.e., the meat), the rest of the mussels could follow a process for improving their appearance and added value. In this process step, these kinds of mussels are often cooked by steaming until the shell's complete removal. Ninety-five percent of $CaCO_3$ can be found in the composition of these shells, and the rest consists of organic matter and/or other related composites. One should note that the remains of mussels and oyster shells are always disposed in the environment as trash. Thus, their improper discard decreases the oxygen and microalgae which exist in the water, and are responsible for the nutrition of oysters and mussels. As a consequence, the growth of these sea creatures is hindered [11].

Important public health concerns regarding the final destination of the wastes derived from oysters and mussels, are met both in Brazil and Korea, where almost 300,000 tons of oyster shells are generated each year. Therefore, the Korean authorities funded a project that aimed to increase recycling of this waste, because if left untreated for longer periods of time, it can generate nasty smells because of the decay of the flesh remnants attached to the oyster or the microbial disintegration of various salts into gases (i.e., NH_3, H_2S). The possible reuse of these oyster-shell wastes as construction materials for modern buildings [12] and supplements for animal feeds [11] was reported.

Koteswarao et al. reported on the fabrication of seashell ash as building cement replacement, with particle sizes similar or finer than the ones corresponding to the cements used nowadays in technology. These seashells may produce improved concrete material in terms of chemical composition and specific gravity, on one hand, and compressive, flexural and/or tensile strengths, on the other hand. One should note from various sea mussel ashes that, the investigation of this new type of materials will reduce environmental issues and provide better solutions for today's concrete technology [5].

A great number of books, book chapters, and articles summarized traditional, new, and innovative methods for hydroxyapatite (HA) extraction using biological sources (i.e., mammalian, poultries, aquatic or marine, shells, plants and algae, or various minerals) [13]**.** Moreover, the effect of the extraction process and natural waste source on the characteristics of the HA such as Ca/P molar ratio, crystallinity and phase assemblage, particle sizes, and morphology was also debated [14]. In another study, Vijay et al. reported on the successful fabrication of HA nanoparticles derived from eggshell wastes, using very inexpensive approaches [15]. The process of HA isolation from the nonmarine sources is much easier than in the case of marine ones. In this respect, thermal calcination is a simple, very efficient, and inexpensive method that can be applied for the fabrication of HA in great amounts [16].

Biomaterials are generally used as joint and cochlear substitutes, bone plates, orthopedic hip implants, bone cements, artificial ligaments and tendons, dental implants for teeth fixation, vascular grafts, heart valves, skin repair devices, and/or contact lenses. Nowadays, extracting HA and other biomaterials from marine resources is getting more popular. Marine animals are structured and constituted of materials with a vast range of properties and characteristics, that justify their potential applications in the biomedical domain [22, 23]. Marine-derived structures, biogenic materials, and biomimetic approaches used for the fabrication of these advanced biomaterials generally address the shortcomings of the current scaffold designs, which are unresponsive from the biological point of view, throughout the renewal process and lack of required versatility [18]. Natural structures like corals, shells, and sea urchins can be converted to bioactive ceramic materials such as HA to actively support the osseointegration process in the human body [19]. In literature, there are also some well-written reports on the production of HA from nacreous aragonite materials [25, 26]. Using hotplate and ultrasonic methods, Tuyel et al. conducted studies of HA production using various natural-derived resources, such as cuttlefish (i.e., *Sepia officinalis*), Chinese sweet water pearl powder, the Pacific Kumamoto oyster (i.e., *Crassostrea sikamea*), the bivalve mollusc (i.e., *Venus verrucosa*), and the common European oyster (i.e., *Ostrea edulis*) [22].

Mainly for a much clearer explanation from the materials point of view, it can be said that biomaterials can be classified as ceramics, polymers, metals and composites [1]. The main ceramics are HA, tricalcium phosphate (TCP), bioglass®, and alumina. As main usable polymeric biomaterials, it can be spoken about polymethylmethacrylate (PMMA), dacron, cellulose, silicone, hydrogels, sodium alginate, chitosan, polyurethanes and many different others. Composite biomaterials are a mixture of polymeric and a range of oxide ceramic materials. The main metallic biomaterials include titanium, cobalt chromium alloys, tantalum stainless steel, and amalgam (for dental applications) [23].

Replacements of damaged or diseased body parts are normal practice in today's modern medicine. These replacements are usually made of a wide variety of solid materials such as polymers, ceramics, composites, metals, or combinations of these materials. Historically, natural by-products date from 3000 B.C., when the Egyptians had used sutures, which were made from animal sinew (tendon), coconut shells, wood and ivory for repairing wounded skulls and replacing the extracted or broken teeth [29, 30]. The last decades have witnessed a clear evolution of the biomimetic marine-derived materials towards a wide use in tissue regeneration applications. Novel tissue engineering scaffolds, characterized by improved properties (i.e., bio-responsivity), are always needed to guide the natural processes of tissue regeneration [26].

When speaking about CaP-based bioceramics (i.e., crystalline materials), simple phases like HA and β−TCP, or a mixture (in various proportions) of these two (called biphasic CaP) are reported [27].

It is known that HA is a widely used material for various biomedical applications including the reconstruction of the most parts of the human skeleton. Bioceramics like HA were widely tested and used as bone graft materials since the 1960s. Autogenous bone grafts are generally preferred as bone grafts. Because these grafts can necessitate a supplementary surgery for the patients, they are not used anymore. As a consequence, allografts were chosen as viable alternatives to autogenous bone grafts [28]. For the fabrication of these grafts, tissues from humans or animals are used.

The importance of using waste materials from environmentally sustainable processes was very well pointed out in a recent study [29]. Thus, aquatic resources like bones and scales of various fishes (the Northern Atlantic sword, *Xiphias gladius*, and tuna, *Thunnus*), and even seashells were indicated as environmentally sustainable choices for future biomedical applications [36, 37]. It should be stressed that, their purity and not to introduce toxic materials should be the priority in both research and clinical environments.

Basic marine-derived biomaterials

Corals

Corals are marine invertebrates, and their skeleton was firstly applied for human bone grafts in 1970s, and they are still used nowadays [31]. These structures consist of calcium carbonate in the form of tree-like branches that alternate with joint-like axes. Corals are generally used as sources to fabricate commercial products such as bone graft materials, with excellent biocompatible characteristics [31]. In general, corals can be found near clean ocean parts and seas (i.e., Pacific Ocean, Red Sea, Persian Sea, Gulf of Mexico, the Indian Ocean, and various tropical and subtropical areas of the Australasia). Australia has very rich varieties of corals mainly all around the continent [32]. Great Barrier Reef is one of the world's most beautiful natural places which contains abundant coral reef populations although unfortunately it has been under stress due to the global climate change and resultant bleaching. Artificially grown coral is a better alternative. Corals can be transformed into various CaP biomaterials using different techniques, among which, the most successful one is the hydrothermal processing [33]. The following equation summarizes the process to produce relatively pure and homogeneous coralline HA.

$$10CaCO_3 + 6(NH_4)_2HPO_4 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 6(NH_4)_2CO_3 + 4H_2CO_3 \tag{1}$$

In smaller nontropical parts of the Earth, such as the Marmara Sea (Turkey), there are approximately 300 alive coral colonies that have been discovered in the reef off the Princes' Islands (near the Port of Istanbul), in the areas around Neandros (also known as the Rabbit Island) [34].

Porous materials, ranging from submicron to mm, are naturally collected in the marine environments [31]. The natural corals can be seen as future, sustainable materials thanks to their porous structure (with dimensions in the range of 100 to 500 µm), having similar morphology with the one corresponding to the cancellous bone. It was reported that, a favorable pore size and microstructural composition are key factors, which facilitate the ingrowth of fibro-vascular tissues or bones [35].

In Fig. 1a–d, a hump coral (*Porites cydrindrica*) and a Mediterranean red coral (*Corallium rubrum*) are illustrated. Amongst the naturally produced meso-crystals, the complex structure of the axial Mg-calcite skeleton belonging to the red coral is captivating. At macroscale, the inorganic skeleton consists of radially organized units (~ 200–300 µm wide), named "herrington units." This coral was used in form of jewelries since ancient times and is one of the most valued living marine resources on our Planet. One should note that corals play a key-role in numerous ecosystems: they provide three dimensional (3D) complexities to our environments, by organizing and stabilizing the ecosystem [36].

Another important coral is hydrozoan (*Millepora dichotoma,* MD). It is a typical species from the Red Sea that contains a porous skeleton in form of aragonite crystalline calcium carbonate. The artificially grown MD was indicated as a raw material for the production of CaP, primarily HA bioceramics [37]. It can be applied either as a carrier—in drug delivery systems, or as a bone graft—in tissue engineering field. Applying the hydrothermal process, Karakan et al. [37] promoted in their study the artificial cloning of various coral species for both ecological reasons and production of controlled high-purity raw materials for biomedicine [37]. Bisphosphonates, simbavastin bisphosphonates, and antibiotics such as gentomycin have been used within coral and coralline apatites as new local drug delivery devices.

It should be emphasized that the Red Sea (*Mare Rubrum*) represents a very interesting place for corals, being a warm and highly saline marine environment. It is an extension of the Indian Ocean, being situated between the Arabian Peninsula and Africa. The whole coastal reef complex spreads over 2000 km shoreline and is characterized by a high degree of chemo diversity, that comprises over 200 soft and 300 hard coral species [38].

Another successful technique indicates that, due to the use of corals, the resultant HA is demonstrated to possess a much greater strength and bioactivity than prior to its conversion [39].

Macha et al. [40] demonstrated in their work the conversion of coralline materials to CaP compounds (i.e., HA, monetite and whitlockite), using moderate temperatures. Thus, two conversion methods were indicated: (i) the first one, a solid-state topotactic ion-exchange reaction route, using solutions of ammonium phosphate, which mainly produces HA, and (ii) the second one, a dissolution–recrystallization mechanism, using solutions of orthophosphoric acid phosphate, which produces both dibasic CaP anhydrite-DCPA (monetite) and HA, and whitlockite phases.

Coralline apatites and corals have been and are still used as bone grafts in both orthopedics and maxillofacial surgery and compete with other bone graft materials. Bone grafting in dentistry and periodontology is compulsory to restore mandibular or maxillary bone volume before the implantation of prosthetic tooth root. In vivo properties of new bone graft products intended for human use [41] are generally studied using various animal models. One should note that, despite the fact that these animal studies generally provide relevant information concerning the bio performance, the implanted biomaterials do not automatically behave similar inside the human body.

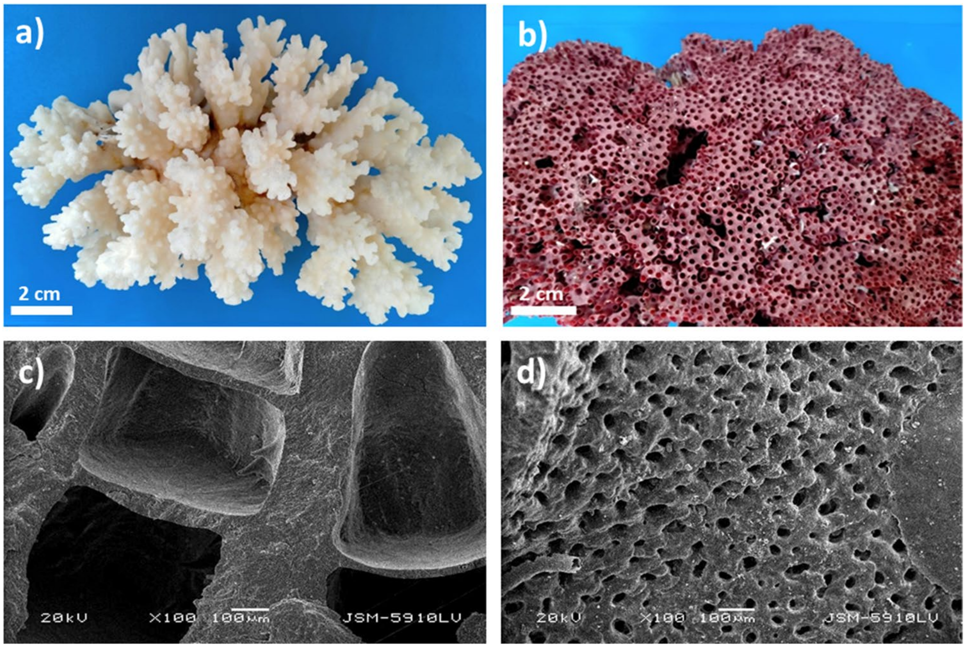


Fig. 1 **a P**hotograph of a hump coral *(Porites cylindrica)*, × 100. **b** Photograph of a red coral (*Corallium rubrum*), × 100. **c** SEM image of a hump coral from upper surface. **d** SEM image of a red coral from upper surface

Bovine HA (BHA), frequently applied both as a bone graft material and a porous apatite granule, and dicalcium phosphate anhydrous (monetite) granules were implanted bilaterally inside human patients. After six months implantation period, histomorphometrical investigations of the biopsies indicated that, in the case of monetite, the amount of bone regenerated with ~ (60 ± 13%) which was a value significantly higher than the one obtained in the case of BHA, ~ (33 ± 5%). Moreover, the volume of unresorbed graft was superior in the case of the teeth sockets functionalized with BHA, ~ (38 ± 6%) in comparison to those functionalized with monetite, ~ (26 ± 14%) [42]. It was therefore demonstrated that, both the osteoinductive and osteoconductive performances of synthetic bone graft substitutes are connected with their microstructural and physiochemical characteristics. Thus, comprehensive conclusions on the “optimal” properties of synthetic CaP bone graft substitutes are still hard to be drawn.

Along with the progress of 3D technology in medicine, the use of corals attracted an enhanced interest. Thus, coral skeletons are either used to create artificial 3D constructs for the field of tissue engineering, or as convenient drug carriers. Nowadays the extensive production of coral-derived materials is still limited because of the protection of coral reefs. However, additional research on the usage of corals as 3D porous models in materials science is under continuous consideration [8].

Despite the fact that coral reefs occupy just 0.1% of the oceans’ area, they can sustain instead 25% of all marine species living on our Planet. It is interesting to note that, an important percentage of population depends on coral reefs, either for their day-by-day sustenance, or protection from life-threatening storms. Unfortunately, the coral reefs from almost half of the world’s shallow waters were destroyed, and in the absence of immediate actions to approach the climate changes, pollution, sedimentation, overfishing, and unsustainable coastal development, these life-sustaining natural wonders will surely disappear in the near future [43].

It should be stressed that, the number of corals needed for biomedical applications is not large and a range of research and commercial production in Israel, Ireland and Australia to grow corals for this purpose in artificially controlled tanks is progressing well and it is expected that the future use of these artificially grown corals will be the common source of these unique materials.

There are also some important studies in which corals were used in conjunction to polymeric materials like chitosan to obtain a complex material with an ability to resist to high loads. As known, one common approach in the field of bone tissue engineering is to use a biomaterial obtained from a mixture of culture-expanded osteogenic cells grown onto a suitable temporary scaffold able to mimic the natural extracellular matrix. This scaffold then progressively degrades and is ultimately substituted by the freshly developed bone tissue [44].

Various seashells

Mussels and sea snails

Mussel represents the name commonly used for the members belonging to numerous families of bivalve molluscs, originating both from saltwater and freshwater environments. All these families have in common a shell, that has an elongated and asymmetrical outline in comparison to other edible clams, either with a round or oval shape. Similar to other bivalves, mussels present a large organ, which is named “foot.” In the case of freshwater mussels, the foot is larger, muscular, and generally hatchet-shaped, while for marine mussels, it is much smaller and presents a tongue-like outline. In addition to humans, marine mussels are generally eaten by starfishes, seabirds, and by many species of predatory marine gastropods [45].

Figure 2a represents an illustration of razor shells (*Ensis magnus*). *Cerastoderma* are seen on the whole western European coasts and very dense located around England (see Fig. 2b). These are bivalves which belong to the *Pharidae* family. They originate from the sandy beaches in northern Europe (from south up to Biscay Bay). They have a special clam which, in case of need, can dig with its powerful foot towards safe places. Being very tasty mussels (which can reach up to 23 cm in length); they can be found in many

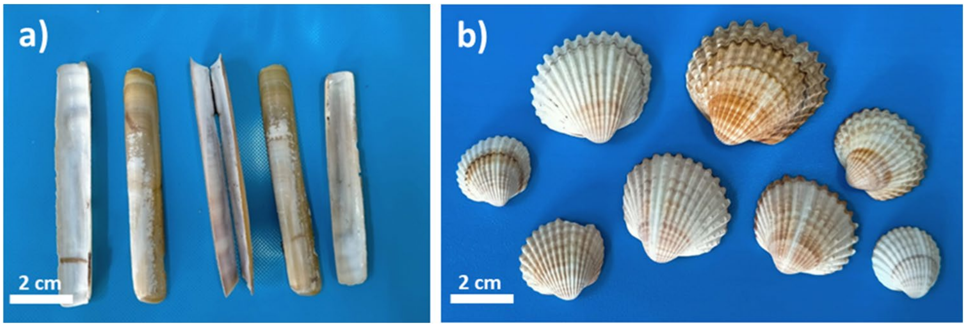


Fig. 2 **a** Photograph of a razor shell (*Ensis magnus*). **b** Photograph of a common European cockle, *Cerastoderma edule*

European restaurants [46]. Unfortunately, their number is drastically declining because of overfishing [47].

Conus Virgo represents a sea-snail species, a marine gastropod mollusc, which belongs to the cone snails family (i.e., *Conidae*). Because these sea snails are predatory and very venomous, they should be handled with care [47]. These marine species live in the Red Sea and in the tropical Indo-West Pacific of Tanzania, Madagascar, Aldabra, Chagos, the Mascarene Islands, India, the Philippines, and Australia (Fig. 3a and b). Their solid shells are rounded below the shoulder-angle, have sizes in the range of (50–151) mm, and a pale yellowish-brown, tinged with violet color (as seen in Fig. 2b) at the base [48]. The spire is flatly convex, slightly striate throughout and more distinctly at the base. They have sexual reproduction, and they are the native creature up to Mascarene Islands, Mozambican Exclusive Economic Zone, and Natal. Dead Virgin Cones form the shallow marine sediments. They are carnivores and individuals can grow up to 102.1 mm [49].

There was also a very interesting study about some mussels in the Marmara Sea (i.e., *Vennus gallina*, *Ostrea edulis*, and *Pecten jacobaeus*), which reaches from Dardanelles up to Black Sea. Another Black Sea mussel which can be seen also in the Marmara Sea is *Mytilus gallovincialis*. Those shells were collected from the coast named as German Beach, in Heybeli Island (Greek name: Halki) (near Istanbul). An excellent cell culture study was also completed. Here, the inner and outer parts of the tested mussels were used. The most upper cell proliferation was observed for the *Pecten Jacobaeus* inner layer, while the higher alkaline phosphatase production was indicated for the material of the inner level of the Black Sea Mussel [34].

In another study related to mussels, the investigations were performed on the *Mytilus galloprovincialis* and *Ostrea Edulis* shells. They were collected from Portugal (Aveiro). The production of nano-powders, which presently represents an important task in the process to discover novel biomaterials, is usually attained from pure chemical reagents. However, recently, a number of companies have been commercially producing coralline HA nano-powders using raw materials with natural origin, such as from corals and a range of sea shells. It was reported by various groups that the usage of these nano-powders will allow to control the chemical and structural characteristics at nano-scale textures and hence the properties of biomaterials [50–56].

Snails

Cone snails represent a group belonging to predatory marine invertebrates, which can rapidly dispose venoms to either parasitic worms, molluscs, or fish preys. These venoms are quite complex and usually contain more than 1000 peptides called conopeptides (or conotoxins), with venom complexity in direct correlation with nutritional breadth. Most characterized conotoxins target ion channels situated in the peripheral and central nervous systems and muscle cells, this way contributing to a rich source of strong and selective molecules, able to cure a wide range of ailments [56, 64, 65].

Conus quercinus (Fig. 4a), also known as "oak cone" or "yellow cone," represents a sea snail species, a marine gastropod mollusc belonging from the *Conidae* family. The size of the shell ranges between 35 and 140 mm. The habitat of this species covers the Indo-Pacific (including Hawaii), Republic of the Marshall Islands, French Polynesia, Fiji, New Caledonia (in the Red Sea), the Indian Ocean (off Aldabra), Chagos, the Mascarene Basin, Madagascar, and Mauritius (off Eastern India), the tropical Indo-West Pacific and off Australia (Northern Territory, Queensland, Western Australia) [58].

Scallop (Fig. 4b) is a general designation for the abundant species of saltwater clams or marine bivalve molluscs belonging to the taxonomic *Pectinidae* family. The scallops represent a cosmopolitan family of bivalves, which are usually met in almost all of the world's oceans, but never in freshwaters. These species are skilled both to swim fast on short distances and to migrate some distance across the ocean's floor. One should note that, there are many species of scallops used as an excellent food source, while others are cultivated as aquaculture [56, 66].

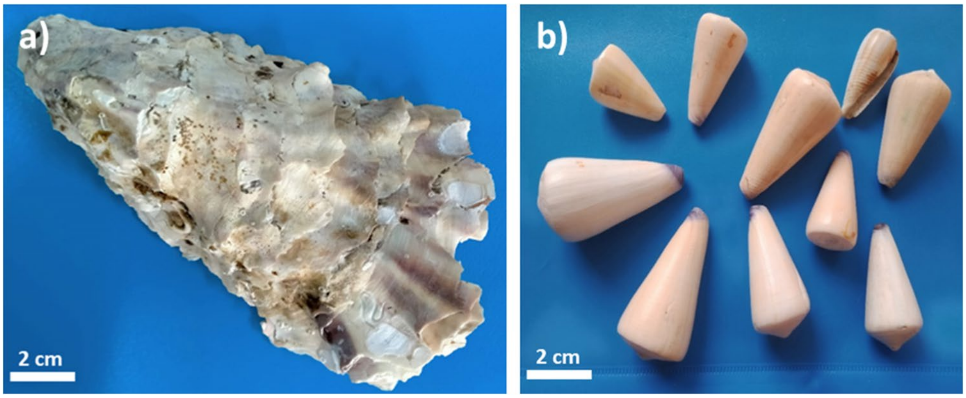


Fig. 3 **a** Photograph of a Pacific Kumamoto oyster (*Crassostrea sikamea*). **b** Photograph of a *Conus virgo*

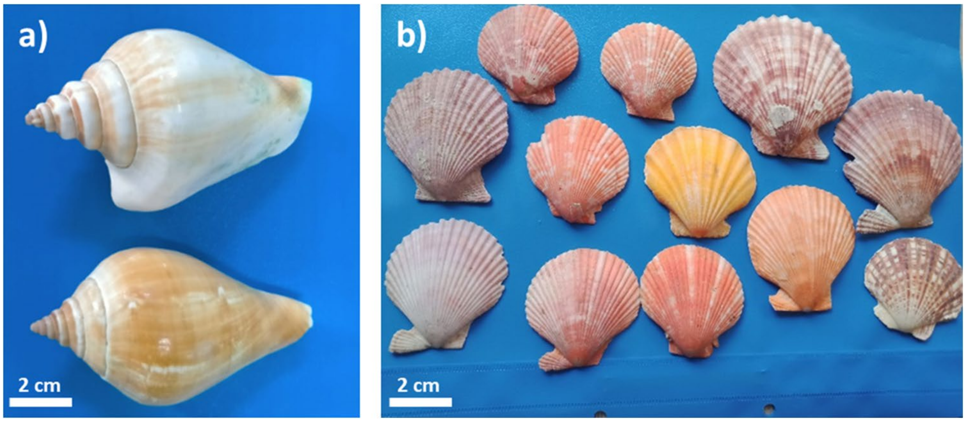


Fig. 4 **a** Photograph of *Conus quercinus*. **b** Photograph of *Scallops* (in various colors)

Aporrhais pespelecani, also known as "pelican's foot" or "common pelican's foot" (to distinguish it from congeners), represents a sea snail species, a marine gastropod mollusc belonging to the *Aporrhaidae* family (Fig. 5a and b). It lives both in the Eastern Atlantic Ocean, from Norway to the Mediterranean Sea, and in the Black Sea, below the low tide level, in the sublittoral zone, with depths in the range of 10−130 m, on either mud or muddy sands [59].

Bolinus brandaris, the purple dye murex, represents a prosobranch neo-gastropod, that lives on sandy or sandy-muddy bottoms, at depths around 200 m. It inhabits the Mediterranean Sea and the NE Atlantic Ocean, from Morocco (south as Tangier) to Portugal [60].

There is also another interesting tropical sea snail named "tiger cowrie" (i.e., *Cypraea tigris*). It is a typical sea snail, which lives in the Indo-Pacific area. It is one of the most common sea snails (mollusc) in the Pacific Ocean and emerges in large numbers in the tropical Indo-Pacific region (from Africa up to Hawaii). The shells of *Cypraea Tigris* are used to produce TCP, HA and nano-bioceramic structures by a very simple ultrasonic equipment and chemical synthesis method [61].

As shown by Gunduz et al. [62], in comparison to other bioceramic production methods, CaP nano-powders can be obtained using a simpler, less time-consuming and economical chemical agitation route (i.e., hotplate). $CaCO_3$ is the main component of the shells, accounting for a weight loss of ~ 45%, given by the equation:

$$CaCO_3(s) \rightarrow CaO(s) + CO_2(g) \tag{2}$$

The inferred results are in agreement with the ones reported by Lemos et al. [50]. Moreover, the detection of hilgenstockite and portlandite, two well-known CaPs used decades ago as ceramic biomaterials, was also reported [50].

Sahin et al. [53] conducted an interesting study on Iceland cockle (*Clinocardium ciliatum*) seashells. They are a species of bivalve mollusc belonging to the *Cardiidae* family, which can be found along the Atlantic coast of North America, ranging from Greenland (West Europa–East USA) up to Massachusetts. These creatures are living at depths of 10–159 m [53]. Thus, by applying a mechano-chemical route, α-TCP and β-TCP were fabricated from aragonite structures using sintering temperatures of 850, 1000, and 1200 °C, respectively. Both easy and economical techniques to fabricate sustainable TCP bioceramics were also evidenced [9, 63–66]. The main novelty of these studies, considering the source material, was the conversion of seashell wastes in beneficial bioceramic products [65].

Another interesting study was performed on a sea snail called "netted dog whelk" (i.e., *Nassarius hinia reticulatus*), inhabiting the Marmara Sea, Turkey. The sea snails originated from a local beach, near Istanbul. In general, their

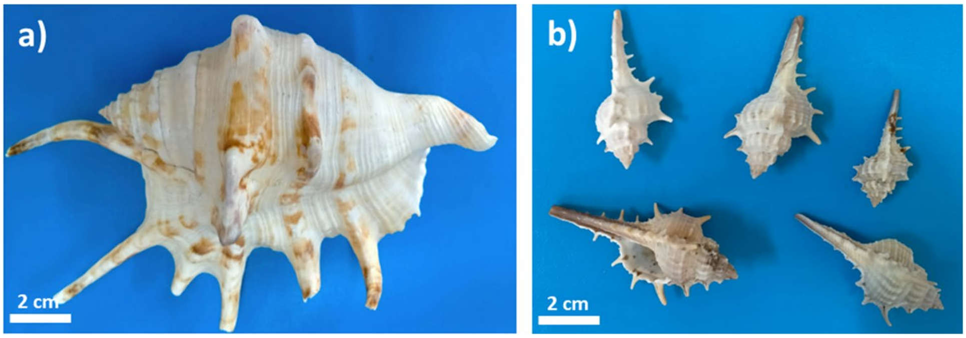


Fig. 5 **a** Photograph of *Aporrhais pespelecani*. **b** Photograph of *Muricidae Murrey scolopy*

typical habitation spreads from the shores of England up to Ireland coasts, through the Aegean Sea (including all Greek and west Anatolian coasts). Nevertheless, the *Cerithium vulgatum* shells can be easily distinguished from the *Nassarius hinnia reticulatus* ones, due to both the inferior length and diameter, and the brownish color of the latter [73].

Various approaches such as hydrothermal conversion using high pressures or chemical, hydrothermal and mechano-chemical methods were introduced to convert naturally occurring $CaCO_3$ (*e.g.*, aragonite and calcite) into apatite-based materials. These methods represent the most effective routes to obtain HA materials derived from calcitic-aragonitic structures, i.e., corals or other sea creatures (i.e., cuttle-fishes, sea urchins, shells, and/or snails).

Barnacles

Both marine structures and biogenic materials, along with a wide range of biomimetic approaches are currently used to fabricate novel biomaterials and successfully address the limitations of nowadays scaffold designs. Bioactive ceramics derived from sustainable marine-based biomaterials such as corals, sponges, sea urchins and shells, are functionalized as scaffolds able to adapt and progress in correlation with the environment, throughout the regeneration process [9].

A barnacle represents an arthropod, which belongs to the infraclass Cirripedia (*Subphylum crustacea*), in the subphylum Crustacean, being related to crabs and lobsters. These creatures inhabit exclusively the marine environments, and they usually live in shallow and tidal waters, typically in erosive areas. They are the only group of crustaceans which possess permanent external calcareous shells. These shells are retained throughout the life of the adult and they offer protection against biotic and physical environmental pressures in the seas. Moreover, both the barnacle's shell and the planktonic larval dispersal can equip Cirripedia with adaptive mechanisms to conquer and persist in widespread, varied, and physiologically stimulating environments [67].

Megabalanus tintinnabulum is a large-sized barnacle (Fig. 6). It has a barrel shape or it is narrowly with conical structure, up to ~ 5 cm tall and ~ 6.5 cm in diameter. It has a tropical origin, its habitat being related to West Africa and Indo-Pacific area. It spread to other parts of the world, being attached to the ships' hulls. Very interesting, these marine creatures were considered for centuries to be molluscs, due to their apparent possession of a shell. But in the nineteenth century researchers demonstrated that barnacles were actually crustaceans. They have the shrimps, lobsters or prawns as nearest relatives, in opposition to bivalve molluscs such as oysters and mussels. Recently, scientists found that barnacles are crustaceans and they are useful material to produce nano-bioceramic structures using a very simple method (i.e., mechano-chemical conversion route). The as-obtained purple barnacle-based bioceramics can be additionally studied for the production of a wide range of bioceramic materials that are appropriate for various medical applications [67].

The production of bioceramic materials derived from "giant purple barnacle" (*Megabalanus tintinnabulum*) is very important and priceless as a viable alternative in medical applications. Marine structures and converted CaP powders and sintered solid shapes can contribute to our economy and can reduce pain and suffering to many patients. In this respect, in the USA, the total cost with the repair and replacement of 280,000 hip, 700,000 vertebral and 250,000 wrist fractures was estimated at ~ US$10 billion per year [68–70].

Sea urchins

The sea urchin represents a very ancient seafloor-dwelling invertebrate. It belongs to the phylum of *Echinoderms*, which date ~ 520 million years ago, before the Cambrian

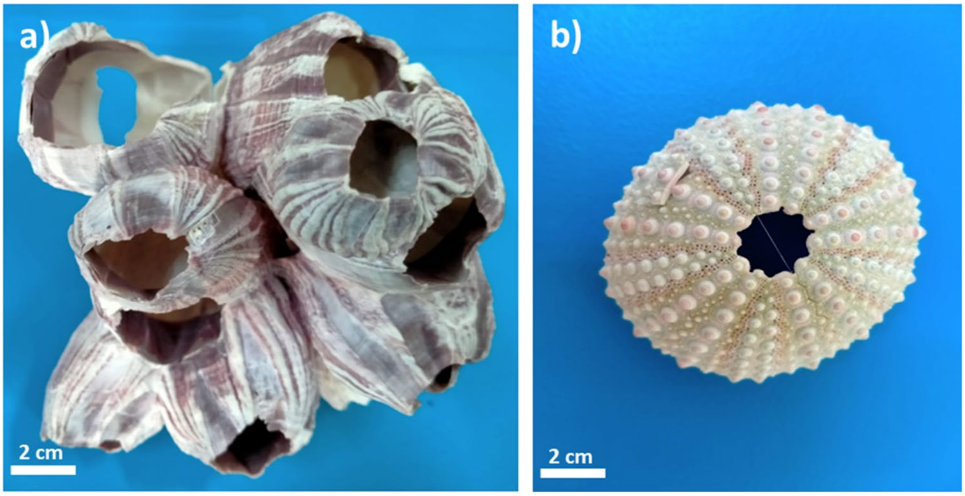


Fig. 6 **a** Photograph of a barnacle—*Megabalanus tintinnabulum*. **b** Photograph of a sea urchin—*Psammechinus miliaris*

period [68]. These marine creatures play an important role in both aquaculture and coral reef ecosystems, which assures their intense behavioral investigations [69]. An interesting sea urchine named *Psammechinus miliaris* (Fig. 6b) has a globular hard shell, somewhat flattened dorso-ventrally, and can reach a diameter of up to 6 cm. Its body is protected by short, equal-length robust spines and it inhabits both the eastern Atlantic Ocean (from Scandinavia south to Morocco) and the North Sea (but not seen in the Mediterranean Sea). *Psammechinus miliaris* is a typical omnivore which feeds on marine worms, hydroids, small crustaceans, molluscs, diatoms, macro-algae, and detritus (waste or debris of any kind). It can also eat both fresh and rotting kelp (*Saccharina latissima*), but the former is difficult to digest, taking longer time to pass through the gut. It demonstrated its effectiveness when eliminating fouling organisms from used salmon cages and oyster trays. It should be emphasized that the gonads of *Psammechinus miliaris* are occasionally eaten, in particular in the Mediterranean cuisine. They are small in specimens caught in the wild, but larger in individuals [70], being one of the many species of sea urchins which inhabit the oceans [71].

In general, the sea urchins are small, rounded, and spiny marine animals, which are living along the shallow rocky shorelines. The first threat related to these creatures is a direct contact with their dangerous spines. They are echinoderms, a phylum of marine creatures shared with starfishes, sand dollars and sea cucumbers. These echinoderms can be easily recognized due to their pentaradial symmetry (they possess five rays of symmetry), which can be simply detected on a starfish. This symmetrical system resembles to a water vascular one, whose general purpose is related to locomotion, transport of nutrients and waste, and respiration. These sea creatures possess tubular feet also known as "pedicellariae," used for their movement. It is worth to note that, in the case of "the flower sea urchin," even though the spines are short and inoffensive, some "pedicellariae" emerged into toxic claws.

It is also very interesting also to examine the structure of the spines of two sea urchins *Heterocentrotus mammillatus and Heterocentrotus trigonarius*. It was found that they mostly contain large-sized single crystals of Mg-rich calcite ($(Ca,Mg)CO_3$). It was demonstrated that the existence of Mg can stabilize the β-TCP structure (the addition of Mg also increases the transition temperature from β-TCP to α-TCP and decreases the solubility of β-TCP) [70–72].

Agaogullari et al. [21] conducted recently a study about a heart sea urchin, called *Brissus latecarinatus*. The name for this sea creature was first given by Leske in 1778. It is widely spread in the Indo-West Pacific and Hawaii area. Agaogullari et al. used this sea urchin for the production of bioceramics. Thus, hydrothermal and mechanochemical methods were applied for the powder fabrication of biocompatible and restorable CaP ceramics of TCP and monetite, which can be used as grafts in various tissue engineering applications. There is a very different sea urchin called "echinoderm Sputnik sea urchin" (*Phyllacanthus imperialis*). It seems to look exactly like a space satellite. Next to this sea urchin, one can also mention the *Trochidae Infundibulum concavus* mollusc. They are both used for the development of powders from calcium phosphate-based materials (as raw biomaterials for bone-scaffold applications) by using two simple routes, i.e., hotplate and ultrasound. It should be emphasized that, both methods are applied to convert, using atmospheric pressures, the aragonite from the heart urchin (*Brissus latecarinatus*), to CaP nano-powders, i.e., monetite and TCP. One can therefore conclude that, the powders produced from these marine structures can be further considered as potential candidates for bone grafting applications [73][73][73]**.**

Fish bones

Even though they can be easily collected from the fish processing industry, and despite the fact that they have a large potential to be converted into economically competitive and valued by-products, fish bones and scales are still considered as waste products only [76]**.** Popescu-Pelin et al. [77] have recently reported on fish bones as new biomaterials for medical applications. Within this study, these sustainable materials were demonstrated to exhibit a promising bone and cartilage regeneration potential. Moreover, using pulsed laser deposition to fabricate bi-phasic CaP coatings from these abundant natural resources (derived from sea bream and salmon fishes) was indicated to have a positive economic impact (i.e., fabrication of cheap implants). Next to the important economical aspect (i.e., the reduction of the production cost), the obtaining of apatites from biological, sustainable sources (i.e., bones) assures the conservation of almost the same compositional and structural characteristics of pristine materials, allowing for an improved biomimicry [77]. On this issue, the purity of the fish bones is the most important factor. Ecological problems and contaminants poured into the seas are a major obstacle because of the toxic elements; however, controlled growth of fish in properly maintained clean pools might reduce and even eliminate this issue.

Important information about the transformation of seashells and other calcite- and aragonite-based materials, presenting dense structures, into viable alternatives for implantology, was also indicated [78]. In addition, new published work shows CaP powder production directly from fish bones. Pujie Shi et al. reported on the production of HA bioceramics derived from "rainbow trout" (*Onchorynchus mkiss*), cod (*Gadus*), and salmon (*Oncorhynchus Keta*) fish bones. Using a simple thermal calcination route, the isolation of HA from these bio-wastes was indicated. In a comparative study between synthetic and naturally occurring HA, it was suggested that both the collagen and nano-HA (nHA) derived from the rainbow trout and salmon fish bones could represent low-cost and environmental-friendly resources of CaPs. Moreover, the crystallinity of nHA surprisingly was higher than carbonated HA [79], which was attributed to the used calcination temperatures.

Taking into consideration the growth of the global population and the subsequent rapid urban and industrial development, on one hand, and the progress of fishing technologies, on the other hand, the production from fisheries and aquaculture increased. An improved management of the fish wastes is therefore desired both to surpass these important problems, and to assure the framework for the future economic development [80].

One should stress upon that, the Giant European salmon fishes can grow over a meter in length, with an average-sized adult weighting more than 5 kg. Next to their remarkable presence is standing an amazing lifecycle: from the gravel of freshwater rivers, they travel hundreds, sometimes thousands of km out to the ocean to bulk up before returning back to their origin to breed and restart the cycle. The Romans named these fishes “the leapers,” considering their athletic ability to leap obstacles as they swim from the sea back to their spawning grounds upriver [81].

An important growth in the quantity of transformed fish wastes was indicated all over the world [82]. It was estimated that about two-thirds of the total amount of fish was discarded as wastes which consequently generated both economic and environmental enormous worries [83]. This is the main reason why, the aware discarding and recycling of these fish wastes represents an important problem that has to be urgently tackled. Along with the increased care for the circular economy, the exploitation of underused or waste marine materials is considered a viable approach for the production of biomaterials presenting high added value.

Atlantic salmon

The Atlantic salmon fish (*Salmo salar*), known as the king of fishes, has been admired starting from the stone age. This royal fish is now often related to untouchable (i.e., pristine) natural habitats, belonging to the rivers of the Scottish Highlands (Nova Scotia) and up to Canada. One could be surprised to find out that, the traveling paths of the Atlantic salmon fish (Fig. 7a) include many European cities. For instance, in the summer, if one will look down from the ancient city walls of Chester, UK, a shadow (i.e., the Atlantic salmon fish) moving below the surface of the River Dee can be seen [84].

The gilt-head bream (*Sparus aurata*), a fish with a golden head (Fig. 7b), belongs to the *Sparidae* family and it is widely found in the Mediterranean Sea, beside the Mediterranean countries, even at Britain coasts, Canary Islands, at Cape Verde and rarely at the Black Sea coasts [85].

European sea bass

As previously indicated, fish scales can be transformed into viable biological resources for the fabrication of natural bioceramics. In this respect, a route to obtain HA bone-scaffolds using European sea bass (*Dicentrarchus labrax*) scales was reported (Fig. 8a and b). In this study, the fabrication of nano-HA biomaterials was attained by a calcination method [84]. Thus, calcium-deficient HA ($CaOHPO_4(PO_4)_5OH$ ($Ca/P = 1.5$)) was obtained. One should note that the use as a bone substitute of

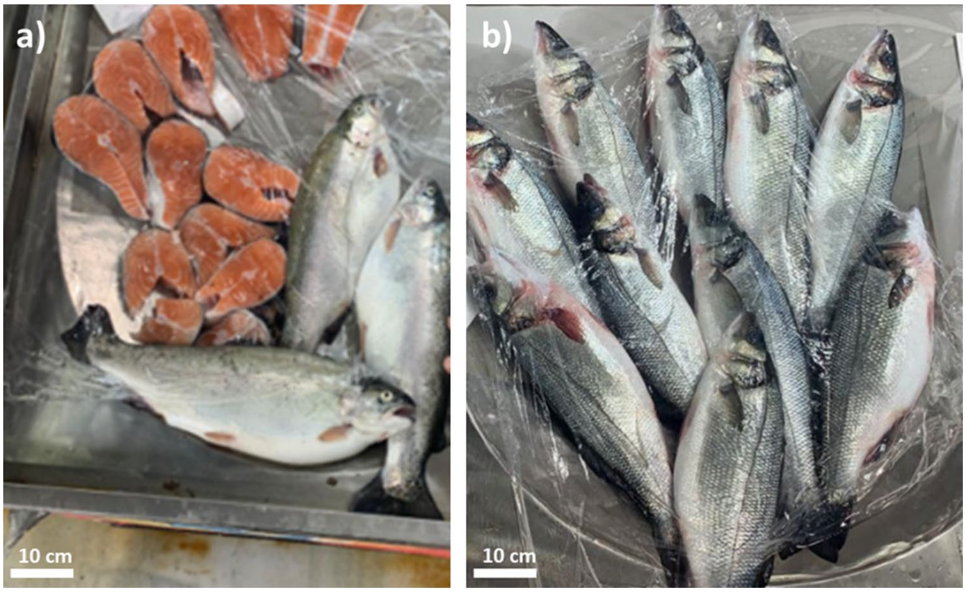


Fig. 7 **a** Photograph of an Atlantic salmon fish (*Salmo salar*). **b** Photograph of a gilt-head bream (*Sparus aurata*)

natural-derived HA, containing Mg, presents increased benefits in comparison to synthetic HA. It was demonstrated that the Mg incorporation into HA allows for an increased proliferation of cells, which was demonstrated to have a key-role in the healing process of bone fractures [91, 92].

The European sea bass represents one of the most well-known European fishes which are commercially farmed (i.e., pisciculture). This type of fish is also farmed in Turkey, Greece, Italy, Spain, Croatia, and Egypt, the annual world production exceeding 120,000 tons [86].

Atlantic Bonito

The Atlantic bonito (*Sarda sarda*) is the only fish inhabiting both the Atlantic (at both sides) and Mediterranean waters. One can distinguish it by the higher meristic characters, such as 50–55 vertebrae instead of 43–46, and 20–23 rays in the first dorsal fin instead of 17–19 [85].

It was demonstrated by XRD analysis that the obtained bioceramic material was made of ~ 67% HA and ~ 33% TCP. Therefore, the bones of this fish can be easily transformed to bioceramic materials which can be used in applications where partly resorbable and economic biomaterials with low carbon footprint are needed [86].

Calcination of fish bones is a good source for natural bioceramic production. It was reported that ~ 91 million tons of fish and shellfish are caught worldwide every year. The Food and Agricultural Organization (FAO) reports that 50–60% of that fish is used primarily as human food, while the rest of 40–50% is dumped to trash and has a negative impact on the environment [85]. It was concluded that *Sarda* has a plurality of spawning areas in the Western Mediterranean part, where the reproduction occurs at rather precise times. There is a gradient South-North in the reproductive season, in each area the spawning seems to last less than 2 months, generating well-identified cohorts, at least for the first 3 years of life. Ample migrations along the coast were ascertained by tag-recapture experiments, these migrations probably maintaining the mixing of the population [87].

Cuttlefish

The common cuttlefish (*Sepia officinalis*) is highly appreciated by consumers around the world, and it is traded with different presentations particularly in Japan, the Republic of Korea, Thailand, Indonesia, Italy, and Spain, being the species of cuttlefish with the highest commercial value [95, 96]. In the last decade, the world catches attributed to this species have registered numbers between 20,000 and 30,000 tons every year. The cuttlefish bone consists of two parts: a dorsal shield (external region) and an internal lamellar region [17]. Its hard and porous internal structure facilitates the buoyancy (Fig. 9.).

In a more recent study, HA biomaterial production was attained via hydrothermal transformation (HT) from aragonite. The HT was performed at 200 °C (~ 15 atm) for 4 h [90]. Rocha et al. [91] indicated that the HT of aragonite ($CaCO_3$) to HA bioceramic occurs according to the equation given in coral conversion, which was originally proposed by Roy and Linhea in 1974:

$$10CaCO_3 + 6(NH_4)_2HPO_4 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 6(NH_4)_2CO_3 + 4H_2CO_3$$

During the hydrothermal treatment for a rapid and efficient transformation of $CaCO_3$ to HA (at relatively low temperatures 200 °C), low pressures (~ 15 atm) are usually applied [91].

Sword fishes

Bone is one of the most remarkable biomaterials found in the animal kingdom, displaying large morphological and functional variability both within and across many species. While the largest loads borne by human bone originate from locomotion, bone structures are also used for hunting or fighting with other species, such as the antlers of deer, the horns of giraffes, or the sword (i.e., rostrum) of the swordfish. The swordfish (*Xiphias gladius*) rostrum presents a particularity, as it lacks the osteocyte network, which is critical for remodelling of human bones. Thus, it is unknown how the structure of the swordfish rostrum

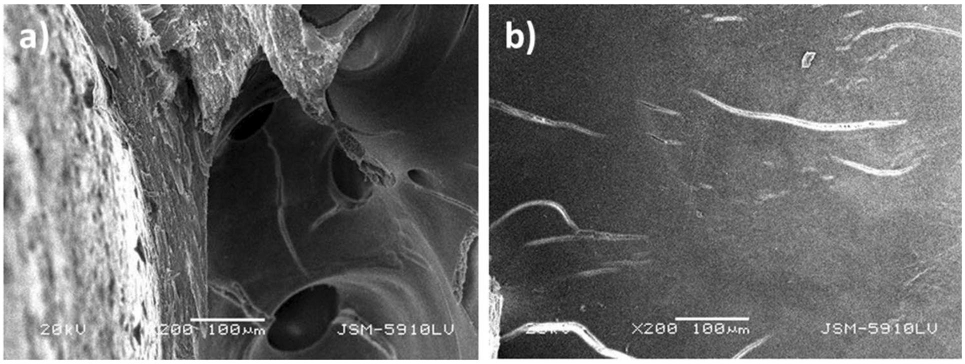


Fig. 8 **a** SEM image of an European sea bass bone graft. **b** Top-view SEM image of an European sea bass bone

Fig. 9 Photograph of a cuttlefish (*Sepia officinalis*)

generates and maintains strength and toughness to withstand the large biomechanical forces necessary for hunting (Fig. 10a and b). The sword of this fish represents a powerful model of lengthwise aging of bone, as indicated by a mineralization gradient and decreased crack-growth toughness [92].

Sharks

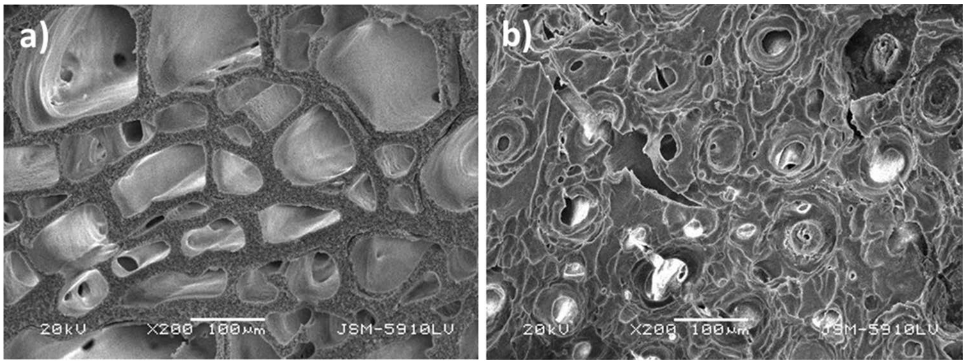
Sharks are fish! Not ordinary fish however. Sharks have a skeleton, but it is not made of bone, like most other vertebrates. Instead, their skeleton is made of a softer, more flexible material called cartilage, the same material found in human ears and nose [93]. The earliest known sharks date back to more than 420 million years ago [94].

The shark's body is covered by scales, known as dermal denticles or "skin teeth". Dermal denticles are heavy scales in comparison to other fish scales, which act as a suit of armor and add stability and strength. They compensate for the fact that a cartilaginous skeleton is not as protective as a skeleton made of bones [93]. It is known that, for amphibians and fish (*e.g.*, sharks), the outer part of teeth is denoted as enameloid, whereas in mammals and reptiles it is denoted as enamel. The interior of teeth consists of dentin, a bone-like phase of apatite nanocrystals and about 20 wt.% of organic matrix (mainly collagen). Dentin is a porous structure with µm-sized dentin tubuli. As in mammalian teeth, the structural building elements in shark teeth occur in a highly ordered hierarchical way. On the outside, hard and mineral-rich enameloid is present, whilst on the inside, softer and less mineralized dentin is observed. In contrast to mammalian teeth, the shark teeth contain fluoroapatite, $Ca_5(PO_4)F$, as biomineral phase with partial substitutions of phosphate by carbonate and of fluoride by hydroxide. Fluoroapatite (FA) has different mechanical properties than HA: it has higher bulk modulus, stiffness constants and elastic moduli [94]. In teeth, the incorporation of fluoride ions into the apatite lattice protects the tooth against acids. Although FA has a higher hardness compared to HA, the shark teeth enameloid (FA) was not harder than the enamel of human teeth (HA) [95]. Autografts are considered nowadays as the gold standard for the treatment of bone defects. Mario García-González *et al.* [96] evaluated in their study the efficacy of using a marine-originated bioapatite in the veterinary clinical field as a bone-grafting scaffold for cats and dogs. This bone shark-derived biomaterial was presented as a suitable bioceramic material candidate for orthopedic surgeries. The obtained preliminary results had shown that its use reduces consolidation time in dogs with fractures and arthrodesis. In addition, no adverse systemic or local reactions were observed. On the other hand, in the veterinary orthopedics field, the golden standard is still the utilization of fresh cancellous bone grafts for enhancing defect healing. However, over the past two decades, the application of artificial bone grafts has been augmenting [96].

Whales

The giant bones of whales (*Cetacea*) are the largest extant biomineral-based constructs ever known. The fact that such mammalian bones can grow up to 7 m long can

Fig. 10 **a** Cross-sectional SEM image of a sword fish bone. **b** Top-view SEM image of a sword fish bone



raise some questions related to differences and similarities with other smaller bones. There are 90 species of whales, some of them being very small, for example, the small harbor porpoise (*Phocoena*; 1 m, 55 kg), whereas others such as the blue whale (*Balaenoptera musculus*; 30 m length, 90 tons in weight) are known to be exceptionally large. The mandibles of blue whale are obviously the largest single skeletal element for any known vertebrate. Whale bones are very porous and very light. Despite the fact that there are a lot of reports about whale bones, information about in use of bioceramic materials is scarce. Even though catching whales for food consumption is unethical, their number decreased in the twentieth century mainly because of human inconsiderate hunting for food, and the environmental climate change and warming [97]. Whales have a great biomimetic potential. We can learn a lot of information from whales about their large-scale biomimetics. Marine life charities and wildlife tour operators have been reporting that a wider interest in and the empathy for whales has been growing incrementally in the world, which is an excellent news to save these giant creatures [98].

Marine algae

There are reports [99] in which it was demonstrated that HA can be also derived from marine algae (i.e., commercial product named Algipore®, by Friadent Company, Germany). This granulate pre-biomaterial was first processed by calcifying the marine algae (*Corallina officinalis*). The biomaterial processing involves pyrolytic segmentation of the native original algae and processing by hydrothermal transformation of the calcium carbonate ($CaCO_3$) into FHA [$Ca_5(PO_4)_3OH_xF_{1-x}$].

Felicio-Fernandes *et al.* [100] obtained biogenic materials from the algae of the *Rodophycophyta* division, collected in the coastal area of the Santa Catarina Island. These algae are characterized by a high content of $CaCO_3$ in their vegetative structure. The collected algae were selected in the laboratory for removal of greater impurities such as mollusc shells or small marine organisms. This material was washed with normal tap water and then dried in an oven at 80 °C, for 48 h. After drying the samples, a new selection was made, followed by a measurement of the dry weight. The present organic matter was digested through treatment with a dilute aqueous solution (10%) of sodium hypochlorite. The material was then washed until its pH was close to the physiological one. This white material formed by particles of 3 mm length (on average) was further dried in an oven at 80 °C for 30 h and then stocked for later analyses and utilization. The obtained material was considered as being entirely free of organic matter. The use of $CaCO_3$ from the algae was evaluated as 80% of the dry weight, having a remarkable value considering the natural origin of the material. They used two different methodologies for the HA synthesis, both involving hydrothermal reactions:

1. $(NH_4)_2HPO_4$ was dissolved in distilled water in the desired proportions. This solution was placed in the pressure vessel on top of the phycogenic $CaCO_3$.
2. $(NH_4)_2HPO_4$ was dissolved in an NH_4F (20 ppm) aqueous solution, and this solution alone was later run onto the phycogenic $CaCO_3$ for the synthesis.

The fact that synthesized HA is nonstoichiometric represents an advantage, since human bones themselves are formed of nonstoichiometric HA. Results have demonstrated the occurrence of carbonated type AB HA, which is almost the same as the one of the human bones. In addition of the study [100], extracted *Scenedesmus sp*. microalgae nutrients (phosphorus and nitrogen) via flash hydrolysis process, were recovered through two different precipitation/mineralization pathways to produce HA and dittmarite by the addition of calcium (Ca) and magnesium (Mg) as mineralizers via the HTM and AP processes, respectively. In this study, two pathways were successfully applied to *Scenedesmus* sp. microalgae to recover phosphorus in forms of value added bioproducts. Spherical shaped carbonated HA precipitated through the integrated flash hydrolysis-hydrothermal mineralization (FH-HTM) process. It was concluded that these approaches could bring a promising solution for nutrients management in algae cultivation and production of value-added bioproducts [101].

In another study, HA was produced from algae (*C. officinalis*) using a hydrothermal conversion method [30]. First, $CaCO_3$ and CaO were produced under 650 °C and 700 °C. XRD analysis was used for their detection. However, to produce HA using a hydrothermal process, attention must be paid to (1) removing organic matter, (2) decomposition of carbonate, and (3) preservation of the original algae's morphology, in the proceeding pyrolysis steps. The overall process produced a material of high purity with good reproducibility, using a simple and economic (low-cost) technique. This study demonstrated the potential to obtain environmentally compatible HA products derived from marine algae, processed under low-pressure conditions [108, 109].

Corallina officinalis is a beautiful seaweed, ranging its color from deep purple to pink color (or fully white if it is bleached). It is called "coral weed" because, like corals, undergoes a process called calcification. This proves deposits of $CaCO_3$ into the tissues of the seaweed. As a result, this seaweed is crunchy to touch, due to the $CaCO_3$ skeleton that forms inside [19, 110].

Starfish

If one tries to place a living starfish on a wet surface near the sea, it will quickly attach to it using his strong suction cups. If one tries to remove it, will find out that it will not be such an easy process. Starfish use seawater to steer their feet. The smooth area on top of the starfish body is used to filter the water. Its anus is on top, more precisely in the middle of the body, while its mouth is exactly opposite, on the underside of the body [105, 106]].

The sea stars (*Asteroidea: Echinodermata*) comprise a large and diverse group of sessile marine invertebrates (starfish or sea stars are star-shaped echinoderms belonging to the class Asteroidea), having seven extant orders. They are unique and treasured creatures found in the sea, and these fascinating species are the images of the seashore. They typically have a central disc and usually five arms, though some species have a larger number of arms. They have profound biological, ecological, cultural, pharmaceutical, and taxonomical significance [106].

Rodriguez et al. [107] presented an interesting study in which they synthesized HA from starfishes, using a hydrothermal method. They concluded that they succeeded to produce HA by using a simple, economical, and reproducible method by which a range of raw materials for biomaterial applications could be obtained.

Figure 11 shows the photograph of dried specimens of Knobby Starfishes (*Protoeaster*) which belong to the class *Asteroidea* [108]

The body of a Knobby starfish is calcified, and therefore, it is hard and heavy. It has tiny finger-like structures, which are called *papulae*. Those are seen on the upper side of the body when they are submerged. It has long tapered to rounded tip arms that are flexible enough and triangular, when observed in cross section.

The single row of knobs on the upper side of the arms is used for the identification of this species. The color, shape, and number of knobs vary depending on the starfish's body structure. The sucker shaped tipped tube feet emerge from under the arms. These can be either red or purple in color (in a fresh state, some of these knobs have a reddish color). The most common colors of the Knobby starfish are red, orange, or brown. However, one can encounter white, pink, blue, or green starfish also. Knobby starfish may look dangerous, because of the brightly colored knobs, nodules, and spines. But the fact is that, they are not venomous. They eat scavenges on dead creatures and other microorganisms. However, there are some other reports, which state that they feed on sponges, clams or snails. It is also said that, the knobby starfish hosts shrimps, scale worms, harlequin crabs and sea star crabs. Parasitic snails are also counted sometimes [109]. They are harvested in large scale from the wild for various purpose such as for the live aquarium trade, or for selling. Unfortunately, they are unlikely to survive long without proper and expert care. A few years ago, they were counted amongst the most common large starfish species of Malaya, but nowadays they are considered as an endangered species on the Red list of threatened animals of Singapore [110]. Beside all these, *Protoreaster nodosus* is known to regulate microbial and meiofaunal communities of sand and seagrass habitats

Fig. 11 Photograph of dried starfishes (Knoobby starfish)

and may have an important ecological role due to its large size. Despite its economic and ecological importance, the biology of this species remains poorly understood [109].

Marine crustaceans

The common marine crustaceans building a very large family, which covers all the seas, oceans, freshwaters, or lakes occur from barnacles, mantis shrimps, prawns and shrimps, cleaning shrimps and allies, lobsters and spiny crayfish, mud and coral "lobsters," hermit crabs, squat lobsters and allies, and crabs. All of them have a high content of calcium in their outer shell, which can be used to prepare HA. Most of the outer part consists of chitin. From chitin, chitosan can be produced, which is a very well-known biopolymer [111].

Crustaceans are forming a very large, diverse arthropod taxon which consists of crabs, lobsters, crayfish, shrimps, prawns, krill, woodlice, and barnacles. In the world, there are about 67,000 described species, with sizes ranging from 0.1 mm (i.e., *Stygotantulus stocki*) to the Japanese spider crab with a leg span of up to 3.8 m and a mass of 20 kg. Like other arthropods, crustaceans have an exoskeleton, which they molt to grow. They are distinguished from other groups of arthropods, such as insects, myriapods, and chelicerates, by the possession of two-parted limbs, and by their larval forms, such as the nauplius (larva) stage of branchiopods, and copepods. Most crustaceans are free-living aquatic animals, but some of them are terrestrial (*e.g.*, woodlice), some are parasitic (*e.g.*, Rhizocephala, fish lice, tongue worms) and some are sessile (*e.g.*, barnacles). The body of a crustacean is composed of segments, which are grouped into three regions: the cephalon or head, the pereon or thorax and the pleon or abdomen. The crustacean body is protected by the hard exoskeleton. The majority of crustaceans are aquatic, living in either marine or freshwater environments, but a few groups have adapted to life on land, such as terrestrial crabs, terrestrial hermit crabs, and woodlice. Crustaceans have also a rich and extensive fossil record [111].

Crab shells containing $CaCO_3$ are very abundant. Using wastes of crab shells (*Portunus pelagicus*), I Raya et al. [112] successfully synthesized HA, at an optimum temperature of 800 °C.

Extensive production methods and application of marine-derived bioceramics in medicine

Production methods of marine-derived bioceramics

There are a few methods successfully used nowadays for the production of HA from sustainable, marine resources, and in this section, we will concentrate on the most important ones. Thus, D. S. Gomes et al. [30] presented in their study a variety of techniques for the synthesis of HA, which can be broadly grouped into six main sets of methods:

1. Dry methods: involve solid state and mechanochemical reactions.
2. Wet methods: based on low-temperature chemical precipitation, co-precipitation, sol–gel route and hydrolysis.
3. Hydrothermal methods: use aqueous solutions of high temperature and high voltage, as hydrothermal, emulsion and microemulsion, and sonochemical.
4. High temperature processes: include combustion and pyrolysis.
5. Synthesis based on biogenic sources: can be extracted from fish bones, shells, eggshells, bovine bones, in the presence of biomolecules or bio-membranes.
6. Combination of the aforementioned techniques.

As reported, all these methods used for HA synthesis have different processing characteristics which determine different morphologies.

In another work [63], cleaned Atlantic Deer Cowrie shells were crushed and sieved, with final particle dimensions of less than 100 µm. The raw powders were suspended on a hotplate stirrer for chemical agitation. The temperature was kept at 80 °C for 15 min and then appropriate amount of H_3PO_4 was added by titration in the prepared solution to form calcium phosphate precursors. The obtained solution was stirred for 8 h, and left to dry at 100 °C for 24 h. Next, the resulting dried sediments were collected and heat-treated between 400 and 800 °C for 4 h, depending on the required specific CaP phase.

One could predict that 30% of hospital beds will soon be occupied by osteoporosis patients, and 20% of those suffering from an osteoporotic hip fracture do not survive in the first year after surgery. Better therapies for diseased and damaged bones are therefore needed. Human bones consist of ~ 70% of CaP mineral; therefore, CaPs are the materials of choice for repairing the damaged bone. To achieve this, the process of CaP biomineralization and the interaction of CaPs and biological environment in the body need to be fully understood. First commercial CaP bone graft substitutes were launched 40 years ago [113].

Tetracalcium phosphate, with the complex chemical formula $Ca_4(PO_4)_2O$, ($4CaO{\cdot}P_2O_5$), is the most basic of the CaPs, and has a Ca/P ratio of 2, making it the most phosphorus-poor phosphate. It is found as the mineral hilgenstockite, which is formed in industrial phosphate rich slag (called as "Thomas slag"). This slag was used as a fertilizer due to the higher solubility of tetracalcium phosphate relative to apatite minerals. Tetracalcium phosphate is a component in some CaP cements that have medical applications [114].

Application of marine-derived bioceramics in medicine

More than two million bone grafting procedures were performed annually worldwide, and this is the second most frequent tissue transplantation after blood transfusion. In this respect, autologous bone is still being considered as the gold standard. However, the concerns of limited supply and donor site complications are still maintained. Bone allografts dominantly share the second higher option for orthopedic surgeons and nearly one third of all bone grafts used in the world are allografts since they are available in various forms and large quantities. Orthopedic scenarios such as large segmental bone defect however may result in delayed union or even nonunion if improperly treated clinically [104].

The human bone anatomy has the architecture of a nanocomposite material, consisting of 60–70% mineral component, up to 30% organic components (mostly type I collagen) and the rest of 10% is water. The mineral component, usually defined as biological apatite, incorporates various substitutions [13]:

- Calcium (Ca^{2+}) can be substituted by Sr^{2+}, Ba^{2+}, Mg^{2+}, Na^{+}, or K^{+}.
- Phosphorus (P) can be substituted by C, As, V, or S.
- Hydroxyl groups (OH^{-}) can be substituted by carbonate groups $(CO_3)^{2-}$, fluorine (F^{-}), chlorine (Cl^{-}), or their place can remain vacant.

Bone grafts and substitutes possess osteoconductive and osteogenic properties to provide mechanical support and foster bone healing. Autologous bone grafting is often considered the gold standard and describes the harvesting of osseous matter and subsequent transplantation to a different site within the same patient [13].

The human skeleton possesses a unique restorative capacity, and bone adaptability allows for efficient repair to prevent fractures. The goal of surgical fracture care is to facilitate the natural regenerative process of bone and restore its function. Fracture care is accomplished by usage of modern bone grafts, bone substitutes, and orthobiologics that can augment healing via their osteoinductive, osteoconductive, and/or osteogenic mechanisms. Fracture healing is understood as both a local and systemic process [105].

Bone grafts can be classified in five main groups [112, 121]:

(a) Allograft-based bone graft involves allograft bone, used alone or in combination with other materials (*e.g.*, Grafton, OrthoBlast).

(b) Factor-based bone graft are natural and recombinant growth factors, used alone or in combination with other materials such as transforming growth factor-beta (TGF-beta), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and bone morphogeneic protein (BMP).

(c) Cell-based bone grafts are in use for cells to generate new tissue alone or are added onto a support matrix, for example, mesenchymal stem cells.

(d) Ceramic-based bone graft substitutes include CaP, calcium sulphate, and bioglass used alone or in combination; for example, OsteoGraf, ProOsteon, and OsteoSet.

(e) Polymer-based bone graft uses the degradable and nondegradable polymers, alone or in combination with other materials, for example, open porosity polylactic acid polymer.

On the other hand, dental bone grafts can be classified in five main groups:

1. Autograft, is the tissue taken from one operative site and grafted in another operative site within the same individual.
2. Homograft/allograft, is the tissue taken from one operative site in one individual and grafted in the operative site in another individual of the same species.
3. Heterograft/xenograft, is the tissue taken from one individual and grafted in the operative site of another individual of different species.
4. Syngensio grafts, is the tissue graft removed from blood-related relatives.
5. Orthotopic graft, is the tissue grafted into an anatomical site normally occupied by that tissue, for example, bone to bone and skin to skin.

Bone regeneration is a complex, well-orchestrated physiological process involving a number of cell types and intracellular and extracellular molecular signalling pathways. Bone grafts provide a structural framework for clot development, maturation and remodelling, that supports bone formation in osseous defects. These materials must possess biocompatibility and osteoconductivity, as well as the properties that support osteogenesis. An ideal bone graft should be nontoxic, nonantigenic, resistant to infection, easily adaptable, readily and sufficiently available to stimulate new attachment and able to trigger osteogenesis. The long-term success of dental implants also depends on the complex biointegration of these alloplastic materials, determined by the responses of the different surrounding host tissues. The osteoconductivity, osteoinductivity, and bioactivity of CaP materials has attracted significant interest, using various coating techniques, including plasma spraying, magnetron sputtering, electrophoretic deposition, sol–gel deposition, pulsed laser deposition, ion beam dynamic mixing deposition, electrospray deposition, biomimetic deposition, and electrolytic deposition [106, 115–119]**.**

Bone graft materials can be placed in different locations in dental and maxillofacial applications, such as the following: in alveolar sockets after post extraction, fillers of local bony defects due to trauma or infections, filler of peri-implant defects due to peri-implantitis, for vertical augmentation of the mandible and maxilla, and for horizontal augmentation of the mandible and maxilla [120].

The use of bone grafts for the reconstruction of intraosseous defects produced by periodontal disease dates back to Hegedus in 1923. Nowadays, periodontics aims to maintain the health of teeth and their supporting structures with the aim to periodically control the infection and to regenerate the lost supporting structures. Bone, the basic building block of the healthy periodontium, is affected in most of the periodontal diseases and can be managed either by mechanically recontouring it or by different grafting techniques, which encourages the regeneration in places where it was lost. Bone replacement grafts are mostly used to promote bone formation and periodontal regeneration. Bone grafting, placing bone or bone substitutes into defects created by the disease process, act like a scaffold upon which the body generates [113].

In dentistry, the most common use of bone grafting is for dental implants, to restore edentulous area of a missing tooth. In general, bone grafts are either used in block (such as from chin or ascending ramus area of lower jaw) or particulated, to be able to better adapt to a defect. The grafted, vascularized fibulas have been used to restore skeletal integrity to long bones of limbs in which congenital bone defects exist, and to replace segments of bone after trauma or malignant tumor invasion. The periosteum and nutrient artery are generally removed with piece of bone so that the graft will remain alive and grow when transplanted into a new host site. Once the transplanted bone is secured into its new location, it generally restores blood supply to the bone on which it has been attached [109].

Kumar et al. [121] used marine-derived bioceramics and composite bone grafts as a filler biomaterial for scaffolds to facilitate bone formation and promote wound healing. These grafts are bioresorbable and have no antigen–antibody reaction, and act as a mineral reservoir which induces new bone formation. They worked successfully for biomaterials in periodontal surgeries. Modern day periodontics aims to maintain the health of our teeth and they support structures with the main goal to control the infection and regenerate the lost supporting structures. The basic dogma of tissue regeneration is to stimulate a cascade of healing events which, if coordinated, can result in the completion of integrated tissue formation and may prove to be a huge step-forward in managing advanced periodontal disease and preventing our tooth loss. Bone grafting is one of the most commonly used options to treat large bone defects in periodontal regenerative therapy.

The use of dental implants for the rehabilitation of missing teeth determined increased treatment options for the patients. Maxillary sinus augmentation has been shown to be a predictable method to increase the posterior maxillary bone height and allows to place dental implants when the residual alveolar ridge is deficient in bone volume. Loss of teeth in the posterior maxillary area can lead to adverse consequences. It is not uncommon to observe severe maxillary sinus pneumatization, which reduces the implant prosthetic alternatives to replace missing teeth. In this anatomical situation, it can be very difficult to obtain effective primary stability. Maxillary sinus augmentation has been shown to be a predictable method to increase posterior maxillary bone height, and allows to place dental implants when the residual alveolar ridge is deficient in the bone volume [110].

Recent findings on shrinkage of key areas of the facial skeleton which contribute to the aging appearance of the face has determined a search for the most appropriate bone-like implant materials. Evidence that HA, in granular form, maintains volume in the long term supports its use in the correction of aging, in addition to its use in the correction of inherently deficient areas of the facial skeleton [111].

Osteoporosis is a disease characterized by low bone mass, deterioration of the bone tissue, and disrup disruption of bone microarchitecture. It can lead to compromised bone strength and an increase of the risk of bone fractures. Osteoporosis is one of the most common bone diseases in humans, representing a major public health problem. It is commonly found in Caucasians, and older people. Osteoporosis is a risk factor for fracture just as hypertension is for stroke. Osteoporosis affects an enormous number of people, of both sexes and all races, and its prevalence will increase as the population ages. It is a silent disease until fractures occur, which causes important secondary health problems and even death. It was estimated that the number of patients worldwide with osteoporotic hip fractures exceeds 200 million. It was reported that, in both Europe and United States, 30% women are osteoporotic, and it was estimated that 40% post-menopausal women and 30% men will experience an osteoporotic fracture in the rest of their lives [112].

In a recent preliminary clinical trial, it was reported that a mandibular repair was successful carried out and total integration of coralline HA graft into the bone was achieved, however further long term observations were suggested [122]. The images given in Fig. 12 show a large mandibular defect, before and after treatment with coralline HA. It was further reported that the defect healed well postoperatively, without any complications (Fig. 12).

The mandibular defect shown in the figure is large and could pose a significant functional problem. It is possible that, malocclusion and even proprioception can be the result of such defects. It was concluded that the coralline HA graft clearly restored the bone.

The exploration of the rich biodiversity in the marine ecosystem stands as an important aspect for the development of novel biomaterials for bone tissue engineering. Thus, marine biological materials are considered one of the most important resources in biomimetics, and their use as raw materials was recently reported for practical applications in both technological and biomedical fields. Despite their endless potential, these sustainable marine resources are still unexploited at their best as multifunctional biomaterials. In the next paragraphs, a general overview of the use of these marine materials (i.e., corals, shells, and fishes) for various biomedical applications is provided. A lot of work still needs to be done, but the increased researches in this direction give confidence that in the near future these resources will be considered viable alternatives to synthetic ones.

Corals

The use of coral-based bioceramics became a realistic solution to metal-based manufacturing [123], for various applications in either implantological or tissue engineering domains [124]. In addition, the structure of a coral might be chemically converted to CaP particles, to be used as drug carriers. In this respect, the transformation of *Tubipora musica* coral at 400 and 800 °C, respectively, resulted on one hand, in plate-like CaP nanoparticles (mostly monetite), and on the other hand, in spherical-shaped CaP nanoparticles (whitelockite and HA) [9].

The Scleractinian corals, i.e., *Porites* spp., were successfully converted to HA by hydrothermal and mechanochemical treatments [9].

The important properties of the coral skeletons determined their use as coral bone graft substitutes [125], and in applications aiming the osseointegration with the human bones [9, 130, 131]. Thus, an efficient in vivo bone formation at critical size defects in sheep using MSC-covered scaffolds from Acropora coral was reported [126].

In another study, murine preadipocytes grown on coralline skeletal material derived from *Porites lutea* corals were shown to differentiate into osteoblasts [127].

Positive effects on the activity of human osteoblast-like MG-63 cells grown on the scaffolds isolated from the coral *Goniopora* sp. were also demonstrated [128].

In a recent report, Gancz et al. evidenced that the biomaterials of coral origin can be used as strong scaffolds for

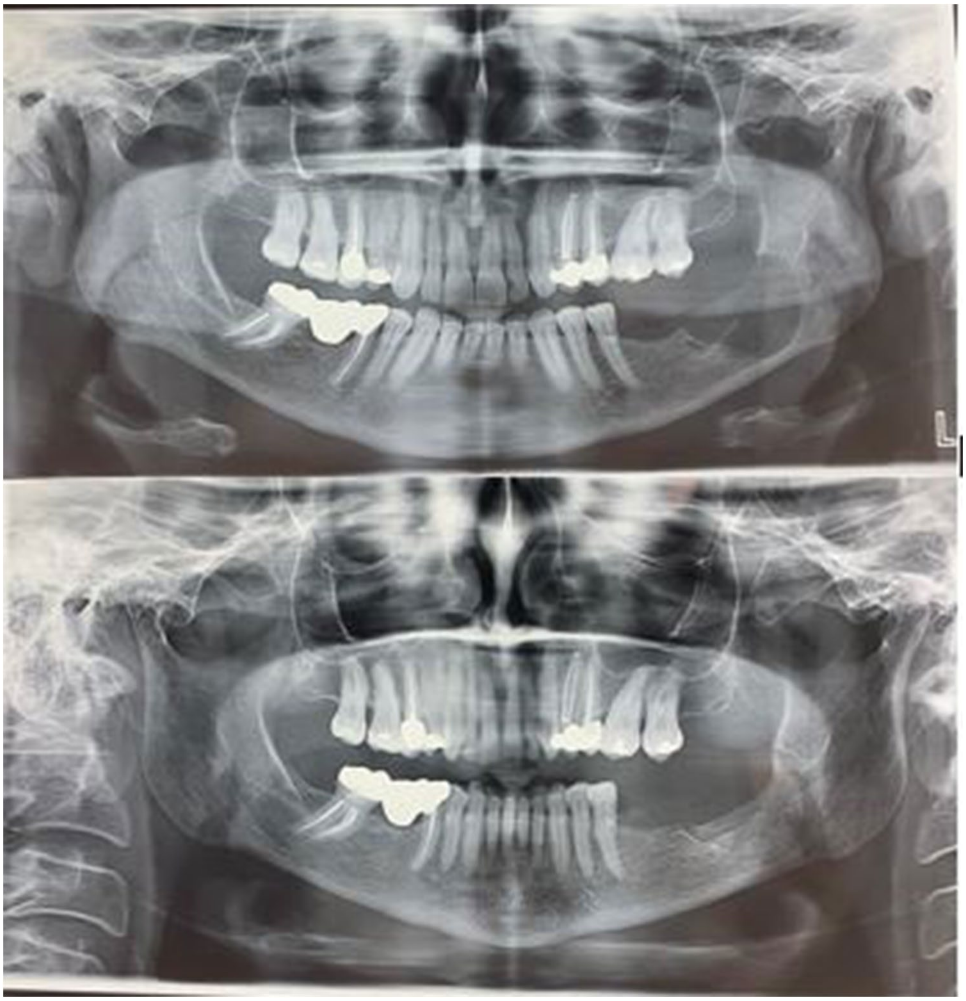


Fig. 12 Images of pre (i) and post (ii) treatment of the mandibular defects with coralline HA repair

tissue regeneration due to their ability to reduce rejection by inflammatory reactions [129].

Besides, octocorals were also demonstrated to retain high biomimetic and biomedical potentials [130].

The skeleton structure of black corals, i.e., *Parantipathes larix* [131] or *Cirrhipathes* sp. [132], was reported to contain chitin, which demonstrated its biocompatibility.

Koëter et al. [133] studied the intra-articular function of calcium carbonate skeletons derived from corals by using HA scaffolds to fill defects produced in the femoral trochlea of goats. Coral-derived HA scaffolds were therefore demonstrated to be effective as bone filler without causing inflammatory reactions at the implant site.

Considering that ceramics are brittle in nature, researchers found alternative solutions to be used as bone graft substitutes by the combination of two or more materials to enhance both their mechanical and osteoconductive characteristics. In this respect, Zhang et al. [134] observed in their study that, when incorporating lower concentrations of silver to coral-HA, improved results (in terms of morphology and cytocompatibility) were obtained. Moreover, cell morphology, adhesion and proliferation in MC3T3-E1 cells were also found to be dependent on the Ag + concentration, demonstrating remarkable biocidal behavior on both *Escherichia coli* and *Staphylococcus aureus*.

One should note that ceramic scaffolds can be also combined with growth factors. Thus, Nandi et al. [135] introduced BMP-2 or IGF-1 into coral-derived HA scaffolds and used these structures to fill bone defects in rabbits. It was therefore demonstrated that the growth factors determined significant improvement in bone healing. In similar reports, nano-HA/coral blocks were mixed with recombinant human VEGF and implanted in critical-size defects in beagle dogs. It was concluded that, these porous structures promoted neovascularization and bone growth at 3 and 8 weeks after surgery, thus improving bone healing and regeneration [136].

Coral exoskeletons were reported as precursor materials for drug delivery systems, increasing cortical and cancellous bone density, and thus offering a sustainable alternative to treat osteoporotic patients [137]. It was also demonstrated that, such type of materials can successfully be used in simvastatin delivery for prolong periods of time, along with an increase in the mechanical strength of bone and osteogenesis [138].

Despite all these improved characteristics, the protection of coral reefs [139] impedes the production of coral-based biomaterials at an industrial level.

Fishes

The in vitro biocompatibility and bioactivity results on HA derived from cuttlefish bones (i.e., *Sepia officinalis*) proved its suitability for clinical bone implants. Along with their low cost, availability, and ease of design recommend these scaffolds for various bone tissue-engineering applications [75]. Kannan et al. [140] fabricated HA from the same type of fish bone and substituted it with fluorine in various concentrations. The as-obtained structures were shown to maintain structural integrity even after being submitted to thermal treatments. Moreover, nano-sized crystallites were obtained, which had comparable sizes with bone apatites, being thus recommended for early bone growth.

Using freeze-drying method, Pallela et al. [141] developed a novel composite scaffold, made of chitosan, HA – derived from fish bone (i.e., Thunnus obesus) and a marine sponge (*Ircinia fusca*) collagen, and demonstrated that the scaffold had homogeneous dispersion of HA and collagen in chitosan matrix having 60–180 µm and 50–170 µm interconnected porosity. The results of in vitro testing indicated a superior cell proliferation in the case of composite scaffolds as compared to pristine chitosan, which advanced this type of scaffolds as promising biomaterials for tissue engineering applications.

By alkaline hydrolysis [142], nano-HA was obtained from salmon fish bones. Complex structural and morphological investigations testified the amorphous nature of the biomaterial, its nontoxicity and a nanostructure size in the range of 6−37 nm. Moreover, in vitro tests with mesenchymal cells demonstrated an increased bone mineralization, which indicated that HA derived from salmon bone is a promising biomaterial in tissue engineering [142].

Shells

Even though molluscan shells were primarily investigated as indicators for environmental transformation [143] and contamination [144], their applications are recently focused on biomechanics [145], biomimetics, and materials science [152].

Having calcium carbonate in their composition up to 99.9% of the mass, shell wastes were used as mortar [148]. It was therefore reported that crushed oyster shell small particles (i.e., 0.074–2 mm) were more suitable as sand substitutes in comparison to the large ones (i.e., 2–4.75 mm).

In a similar study [149], in comparison to the round and shorter particles of generally used limestone, the longer and prismatic-shape mollusc-based $CaCO_3$ ones were demonstrated to affect the mortar setting time and its mechanical properties.

Moreover, shell wastes were indicated as reliable sources of calcium in livestock feed supplements, with an important impact on animal bones and eggshells' strength [150].

Oyster and clam shells were also demonstrated to have beneficial effects for both eggshell strength and egg production rates [151].

Oyster shells (*Mytilus galloprovincialis* and *Ostrea edulis*) were converted to HA nano-powders by hydrothermal transformation. With a low cost and being easy available, these natural materials were demonstrated to possess an increased bone regeneration potential [50].

Concluding remarks

Nanosized HA particles are widely recommended in the field of implants, due to their structural and compositional similarity to natural bones, material strength, biocompatibility, and osteoconductivity. Additionally, it is possible to include significant elements in nano-HA to improve and incorporate better physical and biological properties. However, synthetic fabrication of nano-HA can lead to inclusion of nonwanted elements which under certain amounts can be regarded as toxic. It is worthy to note that, the utilization of marine source wastes as precursor materials for nano-HA synthesis is an innovative method to convert wastes into highly valuable materials if their purity during growth and fabrication can be adequately controlled. However, the control of dissolution and stability of the synthesized CaP, specifically nano-HA, in biological fluids are a major limitation until now. Thus, specifically grown and purified marine structures and their product nano-HA synthesis is and will continue to be an alternative to conventional synthetic approaches for yielding pure nano-HA particles and ceramics for use in implant fabrication and other biomedical applications [152].

It should be remembered that, the marine structures in addition to be a valuable source as a ceramic raw material, they are also an excellent source of organic matter that can further help in the medical field.

As stated earlier, the use of ready-made inorganic marine skeletons is one of the simplest potential solutions to major problems hindering the future development of regenerative orthopedics such as providing a frame work design and a potentially rich, accessible source of scaffolds and osteopromotive analogues and biomineralization scaffolding and proteins. It has already been shown that, coral and marine sponge skeletons can support self-sustaining musculoskeletal tissues and that extracts of spongin collagen and nacre seashell organic matrices promote bone mineralization. This should not be surprising given that the pivotal biomineralization proteins, which orchestrate bone morphogenesis, are also found in the earliest calcifying marine organisms. A reasonable number of natural organic compounds can be found in marine organisms. They have been reported to modulate various biological activities such as anti-inflammatory, antifungal, anticancer, antibacterial, antidiabetic, antiviral, as well as antioxidant.

Conclusions

Collecting raw marine materials derived from natural, sustainable resources is a very significant task for the extraction and/or recovery of beneficial biomedical composites. Biominerals (i.e., biosilica, calcium carbonates, and phosphates) have been well recognized and accepted to be of paramount importance in skeleton-genesis of various organisms including the ones which inhabit both the seas and the oceans on our Planet. If we spoke generally as the first and the last biggest market in general, we already know that the molluscan shells were collected and utilized for centuries as aquaculture by-products. It is generally accepted that already existing marine environments continue to represent an untapped source for the fabrication of biomimetic materials for future like using all kind of marine shells, corals and fish bones.

HA is one well-known biomaterial, which is widely applied in various medical and dental applications as a graft material. As stated earlier, bovine bones have been one of the biggest sources for natural HA production, but its fabrication can lead to very dangerous diseases (i.e., “mad cow” disease). Therefore, it was proved that HA derived from marine sustainable resources is much safer and easier to produce than bovine HA.

All these nanostructured CaP-based materials were advanced as viable materials for a wide range of medical applications, i.e., scaffolds for tissue engineering and carriers for the delivery of nonviral genes.

Last but not least, since the Earth’s available mineral resources are nowadays threatened and strained by the rapid demographic increase and economic growth, the immediate search for alternative resources is therefore critical and highly encouraged. In this respect, marine-derived materials were demonstrated to possess an enormous potential and impact in biomedicine. To our opinion, this systematic review could be considered as a valuable start point for the use of marine-derived materials as viable alternatives to synthetic bioceramics for future orthopedic, reconstructive and dental surgery applications.

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Declarations

Conflict of interest The authors declare no competing interests.

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