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Compounds isolated from corals: a potential therapeutic strategy in bone diseases

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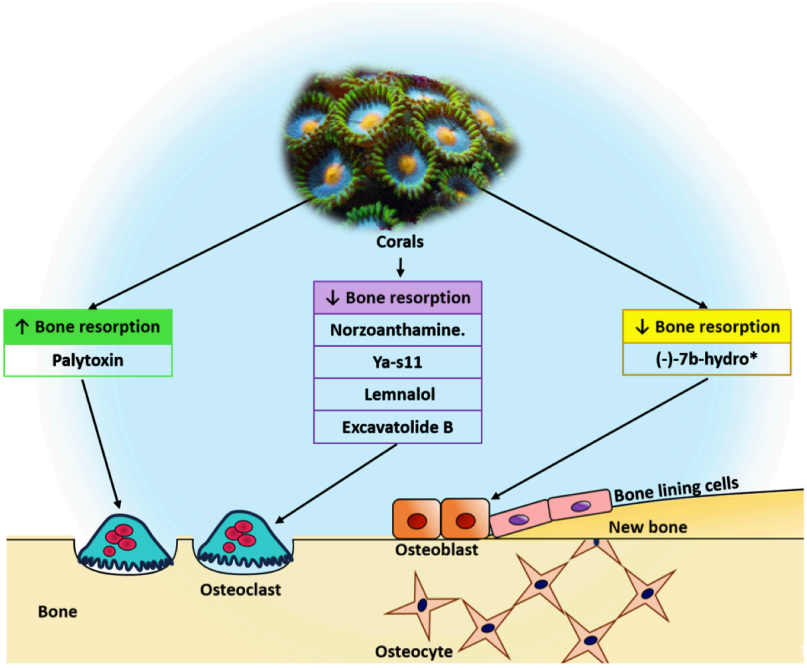
GRAPHICAL ABSTRACT



Patricia Juárez is an assistant professor working at the Biomedical Innovation Department at the Center for Scientific Research and Higher Education (CICESE) in Ensenada, Baja California, México. Her interests focus on translational research for the study and treatment of bone metastases and bone disorders.

Brenda Iduarte is an MSc student at the Biomedical Innovation Department at the Center for Scientific Research and Higher Education of Ensenada (CICESE). Her research project aims to characterize the effect of compounds derived from marine organisms (i.e. corals, sea snails, and sponges) in bone remodeling and osteoporosis.

To cite this article: **B Iduarte, P Juárez . Compounds isolated from corals: a potential therapeutic strategy in bone diseases. HubLE My Mentor & I. DOI: 10.13140/RG.2.2.35753.95847**

ABSTRACT

The ocean provides food and shelter to diverse marine species, and it is an exceptional storehouse of potential bioactive natural products that need to be explored.

Many marine organisms live in extreme conditions, and they have needed to adapt to complex habitats. As a result, they produce a wide variety of unique active molecules that are used as a defense against predators or to capture their prey. Many of these molecules have biological activity, and they have been described as potent anti-cancer, anti-microbial, anti-inflammatory, anti-oxidant and anti-hypertensive agents.

Our goal is to identify some compounds that can inhibit bone resorption, as well as compounds that increase bone formation, in patients with osteoporosis who have low bone mass and are at risk of fractures. Although many studies aim to characterize natural compounds that can be used for the treatment of cancer, there has been less focus in the area of bone and bone diseases. For this reason, we are excited to contribute to the development of this field and, hopefully, very soon to have potential new drugs for the treatment of patients that suffer from these diseases.

Introduction

Bone is a dynamic tissue, which is constantly regenerated during our life to regulate and maintain its strength and integrity. This process is known as bone remodeling. To be carried out, it requires the action of bone cells coordinated by signaling molecules. There are three types of bone cells: the *osteoblasts*, cells responsible for producing and mineralizing the components of the bone matrix, the *osteocytes,* which are osteoblasts that kept on differentiating and became trapped within the bone matrix and function as mechanosensors, and the *osteoclasts,* the bone resorbing cells.[1,2]

Bone cells coordinate bone remodeling by communicating with one another through either direct cell contact or signaling molecules.[1] However, these mechanisms can be interrupted by diverse factors which trigger different bone pathologies, including osteopetrosis, Paget's disease, bone metastases and osteoporosis.[3]

Conventional therapy in bone diseases

In recent years, treatments for bone diseases have focused on anti-resorptive or anabolic therapies. The most common anti-resorptive drugs are bisphosphonates, which induce osteoclast apoptosis, and denosumab, an anti-RANKL antibody which inhibits the recruitment and activity of osteoclasts in the resorption area. Analogs of parathyroid hormone and parathyroid hormone-related protein (teriparatide and abaloparatide) are the only approved anabolic therapies.[4,5]

Despite the positive results that have been obtained, we must improve these therapies and solve important questions, such as the optimal duration of treatments, and the safety of their long term administration. These therapies can increase bone mass to a certain point and, once they are suspended, the bone mass decreases again, meaning that the effects are not permanent. For example, in the case of denosumab, bone density declines rapidly once the treatment is suspended and bone turnover markers increase above baseline.[6] Another example is teriparatide: sustained administration increases bone resorption, whereas intermittent dosage increases bone formation. This limits the therapeutic effect, and some patients with reduced bone mass or suboptimal response to teriparatide still have very low bone mineral density after treatment.[4]

Currently, the maximum recommended duration for anabolic therapy is 2 years and for anti-resorptive treatments (bisphosphonates) 5−10 years. This shows

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that the treatments are palliative. None is appropriate for all patients, and they still have no long-lasting effect on the specific molecular mechanisms of bone diseases. Therefore, their use presents physicians with a dilemma: when to use them for maximum benefit, whether it is safe to repeat them, and for what duration.[4,7] So we must continue searching for new therapeutic agents, which requires elucidating the molecular mechanisms of the diseases that affect bones.

The ocean as a source of new therapeutic drugs

The oceans cover more than 70% of the surface of the Earth, providing a vast space for the diverse marine lifeforms.[8] Many marine organisms have adapted to complex habitats exposed to extreme conditions (i.e. high temperature or salinity, absence of light) and, as a result, produce a wide variety of secondary metabolites, not present on the landmass.[9] Others use small peptides or high molecular weight proteins as means of defense against predators, to decrease the excessive growth of other organisms or to capture their prey.[8]

With the development of technology, it is possible to extract a large variety of compounds such as peptides, alkaloids, nucleosides, peroxides, terpenes, fatty acids, sterols, carbohydrates, amino acid derivatives, cyclic peptides and polyketides from tunicates, marine sponges, seaweeds, nudibranchs, bryozoans, corals or sea snails, among others.[10,11] Many of these compounds are associated with anti-cancer, anti-microbial, anti-inflammatory, anti-oxidant, anti-viral, anti-tuberculosis and anti-hypertensive properties.[12,13]

Cytarabine and vidarabine were the first drugs of marine origin to be approved by the US Food and Drug Administration (FDA), in 1969 and 1976 respectively, and both compounds were isolated from the Caribbean sponge *Tethya crypta*.[14] Cytarabine is a synthetic version of a cytosine arabinoside. It acts by arresting the cell cycle during the S phase and inhibits DNA synthesis by preventing the activity of DNA polymerase.[15] Cytarabine is used for the treatment of leukemia. In 2017, a combination of daunorubicin and cytarabine, encapsulated in liposomes, was approved for the treatment of some types of acute myelocytic leukemia.[16] On the other hand, vidarabine is an anti-viral agent. It is a synthetic version of an adenine arabinoside, and is used in the treatment of herpes virus infection.[14]

An extended period of time passed before a new marine compound was approved again for use in patients. In 2004, ziconotide, a synthetic version of the ω-conotoxin MVIIA (ω-MVIIA) started being used for the treatment of severe chronic pain. This conotoxin was isolated from the venom of the sea snail *Conus magus*.[17]

In 2015, trabectedin was approved by the FDA, for the treatment of liposarcoma and leiomyosarcoma, two subtypes of soft tissue sarcoma. This compound is a partially synthetic analog of an alkaloid isolated from the marine tunicate *Ecteinascidia turbinata*.[14]

Currently, new compounds of marine origin are in clinical phase III trials. For example, eribulin mesylate (an analog of the marine natural product halichondrin B, initially extracted from marine sponges) is a microtubule-depolymerizing drug. Eribulin treatment resulted in a survival advantage for patients with metastatic or locally advanced breast cancer.[18] Soblidotin is a synthetic derivative of dolastatin 10, a compound originally isolated from the sea hare *Dolabella auricularia*. It induces the collapse of the vasculature inside tumors, in addition to its tubulin inhibitory activity.[19] Tetrodotoxin is a potent neurotoxin of marine origin but, at an adequate dose, it is a strong analgesic to treat pain in patients with cancer.[20] Promisingly, as a consequence of the large number of

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compounds that have been isolated and are under study, it won't be a surprise if we see a rise in approved drugs from marine origins over the coming years.

The vast range of compounds isolated from marine organisms shows very particular chemical and biological characteristics. However, because these species, compared with terrestrial species, are practically inaccessible, it is probable that many compounds that could be used to treat diverse human diseases, or as molecular bases for the development of new drugs, are still unknown.[8]

Corals as a potential source of bioactive compounds

The Cnidaria phylum includes organisms that are among the most venomous animals. The species of this phylum are divided traditionally into Hydrozoa, Scyphozoa, and Anthozoa. The Anthozoa class includes sea anemones, hard corals, soft corals and sea pens.[21] Soft corals have been studied extensively for their secondary metabolites, such as terpenoids (especially diterpenoids), which exhibit a wide range of biological activities.[8]

Some of the metabolites extracted from soft corals have been evaluated as anti-inflammatory compounds, and as anti-cancer agents on different cell lines derived from melanoma, leukemia, breast, colon or lung cancer, resulting in promising results. Surprisingly, although bones are commonly affected by the metastasis of some of these cancers, none of the isolated metabolites have been evaluated for their efficacy in bone metastasis.

A coral toxin with the potential to induce bone resorption

Palytoxin is an unusual and highly toxic metabolite produced by soft corals of the genus *Palythoa*, and initially isolated from *Palythoa toxica*. The mechanism of action of palytoxin has been widely studied, and its properties are exerted through a variety of processes, among them binding to the Na^+/K^+ ATPase on the cell membrane, converting it into an ion channel, and increasing the permeability of the cell membrane to Na^+.[8] In addition, palytoxin induces a significant increase in levels of mRNA that encodes proteins related to inflammation in cells of the immune system, suggesting that this toxin has the potential for proinflammatory activity.[22] When the effect of palytoxin was evaluated on mouse calvarias cultured *ex vivo*, it proved to be a potent inducer of bone resorption at low doses.[23] Therefore, palytoxin could be used for the treatment of diseases where bone formation is increased (Figure 1).

Compounds isolated from corals that can inhibit bone resorption

(−)-7β-hydroxy-8α-methoxydeepoxysarco-phytoxide

This metabolite is a cembranoid, a molecule that includes a cembrene ring composed of 14 carbon atoms and which belongs to the terpenoid family. It was isolated from the soft coral *Sarcophyton mililatensis*. The cembranoids are biologically active metabolites that are used by corals as a defense system against predators and have been mainly studied for their anti-tumor effect. In the search for new agents that induce bone formation, the effect of cembranoid (−)-7β-hydroxy-8α-methoxy-deepoxysarcophytoxide was evaluated on MC3T3-E1 cells (osteoblast precursors), demonstrating that it can increase alkaline phosphatase activity, collagen synthesis and calcium deposition.[24] This study suggests that this metabolite induces the differentiation of osteoblast precursor cells and the activity of

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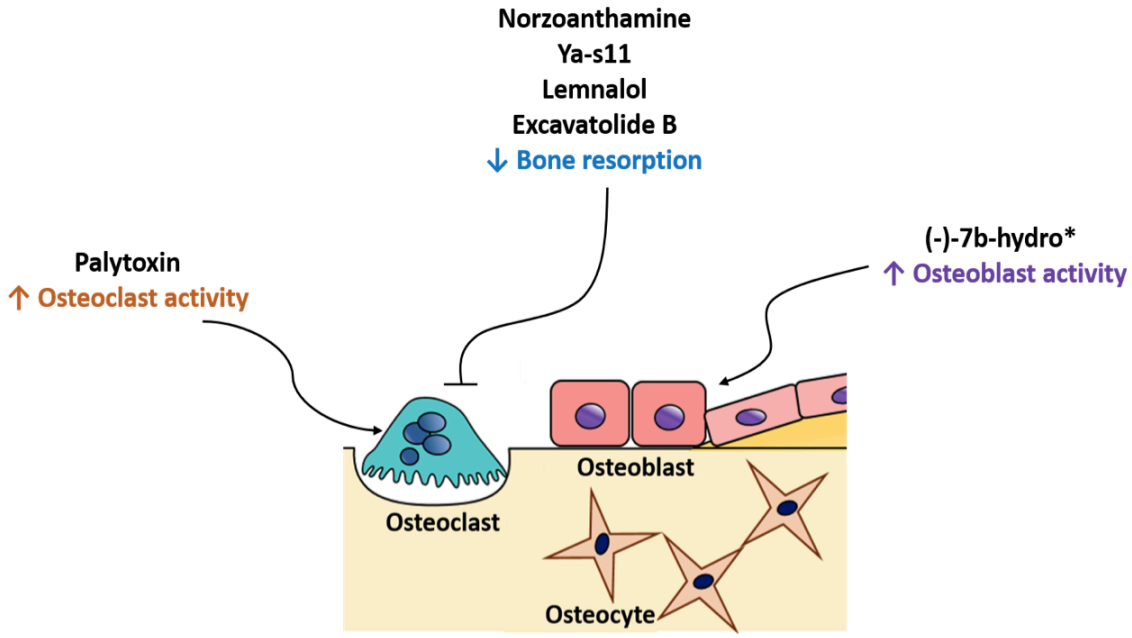

Figure 1. Coral and bone remodelling. Corals are marine organisms from which various compounds such as (−)-7β-hydroxy-8α-methoxydeepoxysarcophytoxide (7b-hydroxy*) and 11-epi-sinulariolide acetate (Ya-s11) are isolated and used as therapeutic agents in the treatment of bone diseases.

osteoblasts, and that this compound could be used to increase bone formation, although more studies are required to confirm this (Table 1).

Norzoanthamine

In 1995, an alkaloid of the zoantamines group named norzoanthamine was extracted from the soft coral *Zoanthus* sp.[25] Since then, possible applications for this molecule have been sought, and it has been shown to induce the aggregation of human platelets.[26] Studies of its mechanism of action showed that norzoanthamine protects collagen fibers, elastin and albumin from cleavage by proteases.[27] In addition, it aggregates with the collagen, increasing the deposition of hydroxyapatite.[28] These effects of norzoanthamine could explain why it prevented a decrease in bone mass and bone strength in ovariectomized mice.[29] Given that collagen is one of the main components of the extracellular bone matrix, norzoanthamine's protective activity on collagen fibers make this a molecule with potential application in conditions where bone loss is increased, such as osteoporosis.

11-epi-sinulariolide acetate (Ya-s11)

Ya-s11 is also a cembranoid, isolated from the soft coral *Sinularia querciformis*. Ya-s11 significantly inhibits the expression of proinflammatory proteins induced by nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2) in the murine macrophage cell line RAW264.7, stimulated by lipopolysaccharide (LPS). In a model of adjuvant-induced arthritis (AIA) using female Lewis rats, Ya-s11 reduced the extent of the disease.[30] Ya-s11 decreased the expression of osteoclast-related proteins such as cathepsin K, matrix metalloproteinases-9 (MMP-9), tartrate-resistant acid phosphatase (TRAP) and tumor necrosis factor-α in ankle tissues of AIA-rats, in a dose-dependent manner, leading to a decrease of bone destruction due to

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Table 1. Compounds isolated from corals that can modulate bone cell activity.

Compound	Coral extracted from	Effects
(−)-7β-hydroxy-8α-methoxydeepoxysarcophytoxide	*Sarcophyton mililatensis*	Induces the differentiation of osteoblast precursor cells and the activity of osteoblasts *in vitro.*[24]
Palytoxin	*Palythoa toxica*	Stimulates the production of prostaglandin E2, and the release of calcium from neonatal mouse calvariae via inhibition of the Na^+/K^+-ATPase in bone cells.[22,23]
Norzoanthamine	*Zoanthus* sp.	Accelerates the formation of hydroxyapatite crystals and enhances collagen release. Limits the bone loss and the decrease of bone strength in ovariectomized mice.[28]
11-epi-sinulariolide acetate (Ya-s11)	*Sinularia querciformis*	Inhibits the expression of proinflammatory proteins in RAW264.7 cells stimulated by lipopolysaccharide (LPS) and downregulates the expression of osteoclast-related proteins in the joints of rats with adjuvant-induced arthritis.[30]
Lemnalol	*Lemnalia cervicorni* and *Lemnalia tenuis*	Decreases the expression of the osteoclast-related genes tartrate-resistant acid phosphatase, cathepsin K, matrix metalloproteinases-9 and transforming growth factor-β1, suggesting a modulation of osteoclastogenesis. Inhibits bone loss in a mouse model of gouty arthritis.[32]
Excavatolide B	*Briareum excavatum*	Inhibits the differentiation of RAW264.7 cells into osteoclasts, induced by LPS Decreases osteoclast differentiation *in vivo*.[34]

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arthritis.[30] Although the authors suggested that it could be a compound for the treatment of AIA, it could be evaluated in other models of bone diseases where bone destruction is increased.

Lemnalol

Lemnalol is a sesquiterpenoid that is produced by the soft corals *Lemnalia cervicorni* and *L. tenuis.* It was shown to have anti-inflammatory properties by inhibiting the expression of the proinflammatory proteins iNOS and COX-2.[31] Therefore, its effect was evaluated in a model of gouty arthritis. Gouty arthritis is an inflammatory disease that can cause bone erosion. Lemnalol was shown to decrease the expression of the osteoclastic markers TRAP, cathepsin K and MMP-9, and of transforming growth factor-β1 (TGF-β1), suggesting a modulation of osteoclastogenesis. Treatment with lemnalol decreased bone loss derived from gouty arthritis. It could probably be used in other diseases with increased bone resorption.[32]

Excavatolide B

The diterpene excavatolide B was isolated from soft coral *Briareum excavatum*. It is known that, as a bioactive molecule, it can generate anti-inflammatory and analgesic effects.[33] Therefore, it was evaluated in the context of rheumatoid arthritis, where the chronic inflammation leads to an increase in bone resorption in the joint space, due to the activation of osteoclasts. The study found that excavatolide B inhibits the differentiation of RAW264.7 into osteoclasts, induced by LPS. Also, it decreases osteoclast differentiation in different models of arthritis induced by adjuvant or by type II collagen, leading to the conclusion that excavatolide B reduces osteoclastogenesis via the downregulation of the inflammatory factors interleukin-17A and macrophage colony-stimulating factor to influence the MAPK and HO-1/HMGB-1 pathways *in vivo*.[34]

Although the previously mentioned compounds have been evaluated mainly in inflammatory diseases, they demonstrate a potential in the regulation of bone cells (Figure 1). Therefore, they should not be ruled out as agents with therapeutic potential in bone diseases

A little more about corals

In addition to a large variety of metabolites with biological activities and therapeutic potential, corals could also contribute to bone health thanks to their very own 'skeleton'. A large group of corals that includes the genera *Porites, Goniopora, Acropora* and *Lobophylia* comprise an extended network of channels and pores, made of spicules of carbonates of lime or silica. This structure forms an internal skeleton that mimics the architecture of our spongious bones. For this reason, it was postulated that coral skeleton could be used as a replacement for human bones. Upon implantation, it would be repopulated by blood vessels and bone cells, leading to the formation of new bone.[35] Another study implanted human bone marrow mesenchymal cells, modified to express basic fibroblast growth factor, into porous coral scaffold.[36] It was successfully repopulated by bone and endothelial cells, and the authors found evidence of deposition of collagen type I and II. An alternative is its conversion to hydroxyapatite and fusion with nanocoatings of hydroxyapatite to strengthen the bone replacement against compression.[35]

Perspectives

Despite the considerable scientific advances of our era, there continues to be a growing need for new therapies for pathologies that affect bones (osteoporosis, bone metastasis, osteoarthritis, osteosarcoma). Marine organisms such as corals offer a wide range of new, unique compounds that could serve as new therapies. That's the reason why, in our laboratory, we are studying the effects on

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bone regeneration of compounds isolated from corals, sea snails or algae.

CONFLICT OF INTEREST

None reported.

ACKNOWLEDGEMENTS

The authors would like to thank the *Center for Scientific Research and Higher Education of Ensenada* (CICESE) and the *Consejo Nacional de Ciencia y Tecnología* (CONACYT) for their funding support. The authors are also particularly grateful to Damian Loera (Department of Communication, CICESE) for his invaluable help to realize the associated video.

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