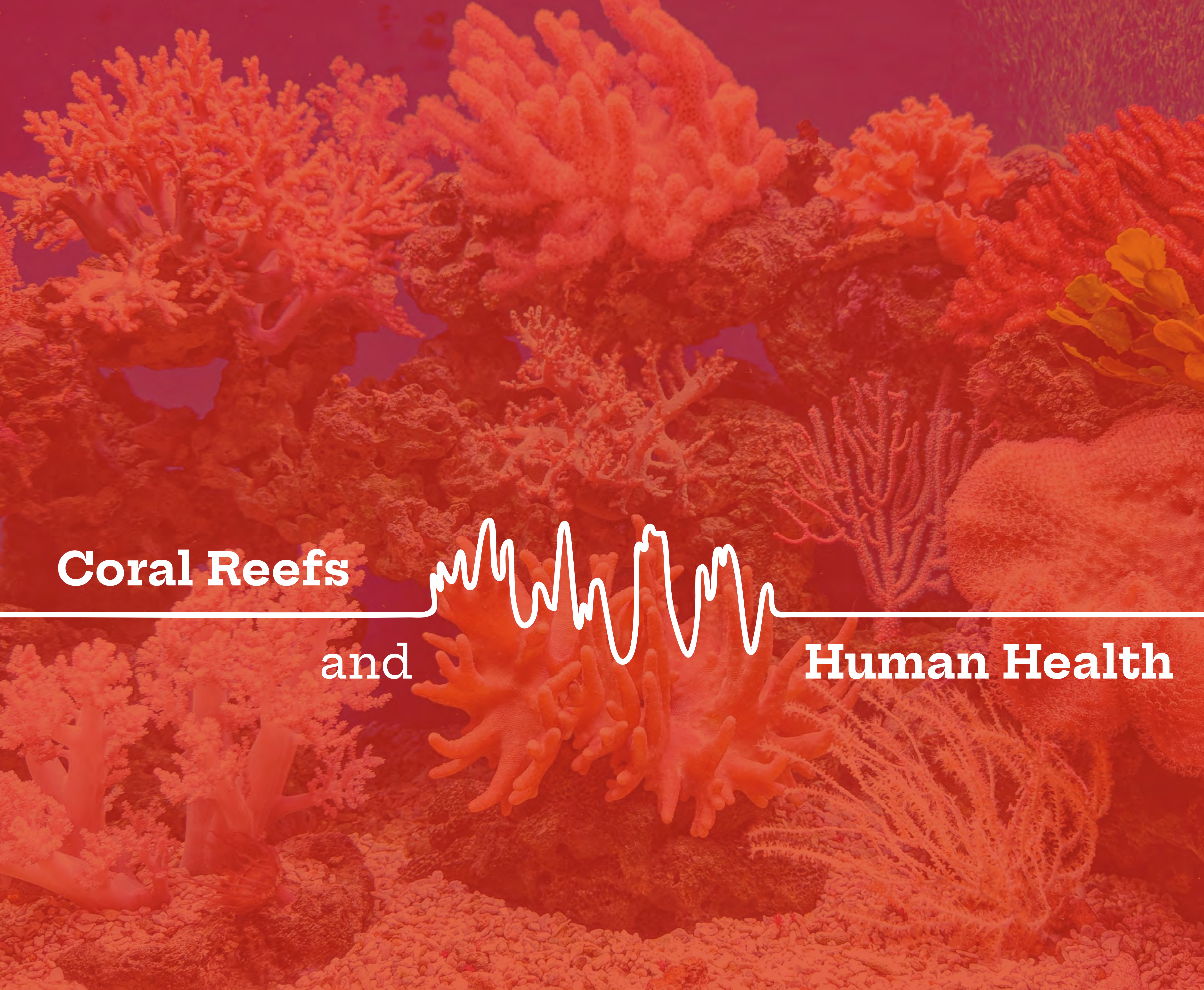


Coral Reefs and Human Health

CENTRE SCIENTIFIQUE DE MONACO

ICRS International Coral Reef Society

With the support of

PRINCE ALBERT II OF MONACO FOUNDATION

Designed by Science Crunchers

“The seaweed is always greener…”

Picture a forest of upside-down jellyfish-like animals anchored through delicate, stone skeletons that mirror roots of trees, flat and cone-shaped mushrooms or dense, dome-like hedges; all reaching upwards towards the sun light, but themselves shining in all colours of the rainbow. A myriad of animals call such coral forests their home, ranging from tiny free-swimming and ever so colourful nudibranchs to large, cosmopolitan fish such as Giant Travellies, Manta rays and Whale sharks.

Coral reefs are the marine equivalent to rainforests. They cover about 0.1% of the ocean floor, but support about a third of all life in our oceans. Unsurprisingly, and very much similar to rainforests, humans have valued coral reefs as a source of food and novel resources for drugs, as barrier to storms and floods and as a recreational space, long before appreciating them for their ecological significance. Particularly, medical research profits from the rich treasure trove that are coral reefs. However, it is only with a growing understanding of the role of coral reefs and their associated habitats like sea grass beds in biogeochemical processes on a global scale, such as regulating climate or providing a nursery for commercial seafood species, that we have started to recognise an interdependence between human and coral reef health. This reciprocity between human and ecosystem health is recognised under the concept of “One Health”. Here we will explore what untold treasures lie within coral reefs and how we can benefit from their riches without spoiling their natural state: to plunder pearls without crushing oysters.

Coral Reef derived Marine Natural Products

Coral reefs are a bountiful source of marine natural products (MNP). MNPs are chemical compounds or substances produced by living organisms, such as those used in anti-predator defence or to stun, subdue or outright kill one's own prey. The marine snail (*Conus magus*), for instance, may look beautiful from afar, but its venom (injected through a dart-like structure at the base of its muscular foot) packs a punch that paralyses its prey and careless humans alike. For centuries, such substances were utilised as basis for medicines and novel drugs.

However, while many natural products derived from terrestrial organisms exist, such as morphine (isolated from poppies *Papaver somniferum*) or penicillin (from the fungus *Penicillium notatum*), MNPs still seem to be underutilised. This is surprising given that the biodiversity on coral reefs rivals that of terrestrial ecosystems. In fact, our oceans likely hold a plethora of unknown chemical compounds used by marine organisms to answer the same question medicine poses: How to survive better and for longer?

New chemical structures derived from MNPs may fuel drug discovery and development. New drugs are in high demand given the diversity of novel (e.g., SARS, MERS, COVID-19) or re-emerging (e.g., vaccine-derived poliovirus) disease outbreaks. Moreover, evolved antibiotic resistance in bacteria of common diseases, such as skin-infections caused by methicillin-resistant *Staphylococcus* strains, can make traditional treatment options less reliable and increasingly threatens lives. Nevertheless, challenging approval processes and the struggle to secure decent financial returns caused a decrease in the number of approved drugs in the past decades compared to previous ones. Yet, precedents for the application of MNPs in commercially available cosmeceutical, nutraceutical, biomedical and pharmaceutical drugs exist and coral reef derived MNPs will continue to feature highly among ingredients in novel drugs.


Mantis shrimp waiting patiently


Nudibranch bustling around corals


Coral polyps with tentacles


Cone snail stalking prey

The coral reefs are laboratories of life with cryptic chemical compounds hidden behind their natural beauty

Coral reefs: the medicine cabinet of the sea

Seafood is a rich source of nutrition providing vital elements for a healthy diet, such as essential fats, vitamins, minerals or high-quality proteins containing important amino acids. Aside from the nutritional value, reef organisms offer the pharmaceutical industry a wealth of opportunity. For example, omega-3 fatty acids, which are found in much higher quantity in seafood, are known as 'nutraceuticals' (i.e., food components with medical or health benefits). Some of them, like DHA (Docosahexaenoic fatty acid), are associated with a reduced risk of suffering from cardiovascular diseases (e.g., heart attacks). Ingredients like these are the reason why seafood products are considered so crucial to the human diet. Further applications in the food industry include the use as natural additives, preservatives, antioxidants, for colouring or as gelling, emulsifying and stabilizing agents. Others are marketed as dietary supplements and prebiotics.

MNPs are also widely used as bioactive ingredients in cosmetics, offering a wide array of reported medical benefits, such as creams and lotions for skin and hair care. UV protection, for instance, is vital even for organisms living submerged below the waves. Corals, which live in shallow sun-lit environments require a way to protect against the harsh tropical sun, particularly during frequent exposure at low tide. Ingeniously, the corals' symbiotic algae (think the chloroplasts of plants) works overtime to not only biosynthesise sugars but an active substance, called Mycosporine-Like Amino Acids (MAA), that coats corals and protects both algae and host from UV radiation. Corals, thus, offer inspiration and solution to the problem of UV radiation. MAAs are now patented as a UV filter. Other coral reef-derived MNPs in the cosmetics industry include active antioxidants, anti-ageing compounds, and even those stimulating the growth of your eyelashes.

Colourful coral reef community

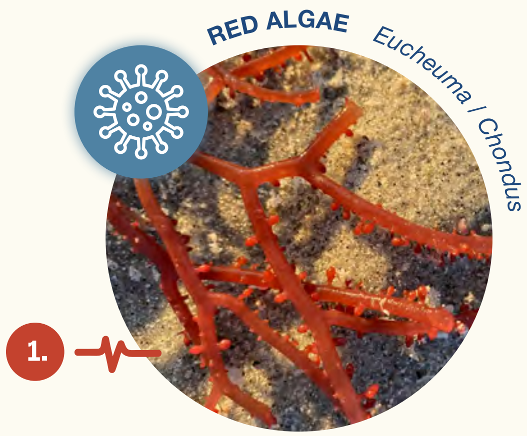
90% of the currently available drugs with a marine origin are from coral reef ecosystems

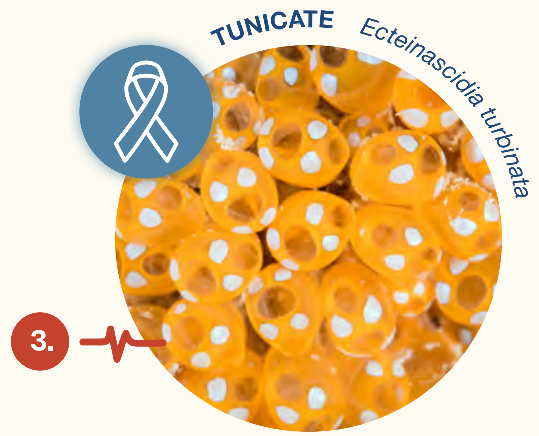
It is further expected that the diversity of organisms living on coral reefs evolved a similarly diverse repertoire of solutions to many of life's challenges, including cancer, bacterial and viral infections or losing a limb. The pharmaceutical industry reaps the benefits from diverse coral reefs by accumulating libraries of until then unknown chemical compounds and careful investigations of unsuspecting victims stung or hurt by reef inhabitants just going about their business can lead to the discovery of toxins or other chemical substances. The biological diversity on coral reefs is directly linked to the diversity of chemical compounds with potential medical application. Since realising the potential of coral reefs for medical research, the main therapeutic focus is concerned with cancer, but other areas such as antivirals, pain relief, obesity treatment or a remedy to combat Alzheimer's are also being trialled. Out of the 10 drugs from a marine origin currently on the market, 9 are from coral reef ecosystems. Three became drugs without any need for modification of the original natural molecule, whilst many others need optimisation. This statistic illustrates that biologically diverse coral reef ecosystem by contrast to that of the open ocean, which is commonly compared to baren deserts on land, may yet harbour a number of undiscovered chemical compounds.

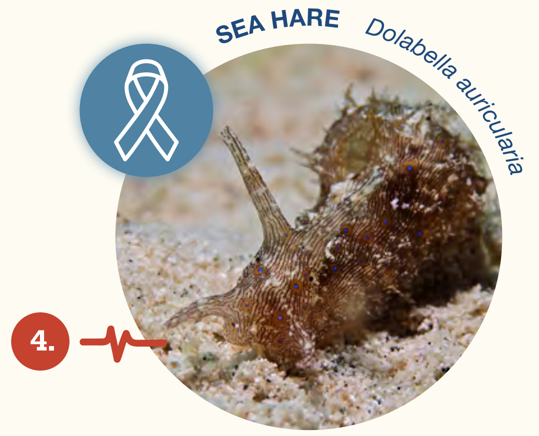
Besides those currently available, there is a robust and active pipeline of compounds in different stages of clinical trials. One of particular interest is Plitidepsin or dehydrodidemnin B. Marketed as Aplidin®, the cyclic peptide pliditepsin is extracted from an ascidian (*Aplidium albicans*) and exhibits antitumoral, antiviral and immunosuppressive properties. Aplidin® was initially marketed as a cancer medicine to adults with multiple myeloma and with at least three prior cancer treatments. In 2004, it was labelled as an 'orphan medicine' to treat rare diseases but marketing authorization was refused in 2016 after confirming that the risks of Aplidin® outweighed its benefits.

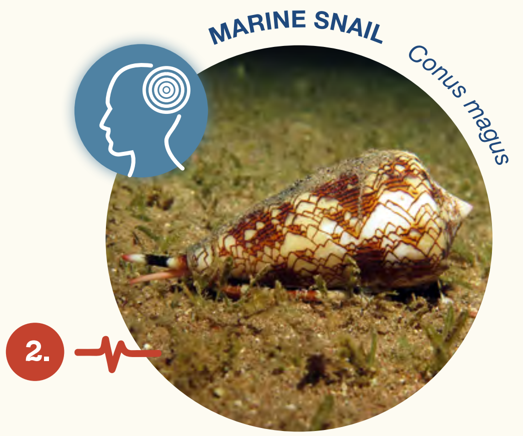
More recently, eEF1A proteins made headlines as they interact with several viral proteins that enable enhanced viral replication, even in novel viruses such as the coronaviruses (Sars-Cov-2). Pliditepsin was proposed to block these proteins, avoid virus replication and thereby its spread. In April 2020, clinical trials started testing effectiveness and safety of Aplidin® on patients with COVID-19. By mid-October promising results confirmed the drug's security and efficiency in reducing viral load of up to 70% in COVID-19 patients administered with the MNP drug. The drug is now advancing through to define upcoming steps with regulatory agencies in order to start phase III studies.

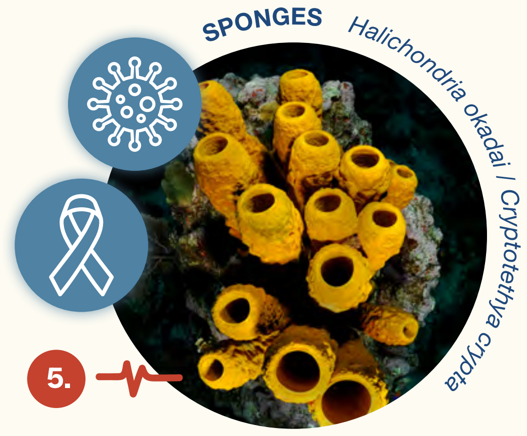
Approved drugs from natural products or derivatives from coral reefs organisms











THERAPEUTICAL AREAS:

Anti-viral

Cancer

Neuropathic pain

1. Iota Carrageenan (Carragelose®)

Iota carrageenan is a polysaccharide (long chain of carbohydrates), that is extracted from edible red algae (genus *Eucheuma/Chondrus*), which inhabits tropical rocky and sandy reef environments just below the tide mark. The carrageenan molecule forms curling helical structures even at room temperature, which gives them gelling, stabilizing and thickening properties that are widely used in the food industry. Its structure and electronic charge are also responsible for its antiviral properties. The nasal spray Carragelose® is sold as an over-the-counter drug against early symptoms of the common cold since the large, negatively charged Iota carrageenan compound traps positively charged respiratory viruses. Hence, Carragelose® creates a protective physical anti-viral barrier in the nasal cavity and prevents the infection from taking hold and the virus from replicating.

2. Ziconotide (Prialt®)

Ziconotide was inspired by ω-conotoxins. In nature, ω-conotoxins are found in the venom of the marine cone snail (*Conus magus*). These predatory cone snails employ a venomous harpoon, called a toxoglossan radula (often referred to as a snail's tongue) to take down prey as large and fast moving as fish. But even larger victims such as humans can suffer a rapid death from the venom. Interestingly, the sting causes an almost painless death – which actually led to the discovery of Ziconotide in the first place. Under the trademark Prialt®, the synthetic Ziconotide is marketed to manage severe chronic pain that is associated with neuropathies, AIDS or cancer. The research into the active compound found that conotoxins block cellular channels in the brain and spinal cord. This action inhibits the release of neurotransmitters and thereby provides relief for patients with severe neuropathic pain.

3. Trabectedin (Yondelis®)

Trabectedin was originally isolated from the Caribbean sea squirt (*Ecteinascidia turbinata*), yet in fact, it is actually the result of a symbiosis between the tunicate and its microbial symbiont (*Andoecteinascidia frumentensis*). Because of its low extraction and isolation yield the long-term commercialization seemed impractical and economically unfeasible until 1996 when a collaboration between a Spanish company and the Harvard chemist E. J. Cory developed a solution. The new method synthesised the compound using a semi-synthetic route involving an antibiotic (safracin B) as a starting material. Under the trademark Yondelis®, trabectedin is currently used as chemotherapy medication for advanced soft-tissue sarcoma and ovarian cancer. The compound interferes with cell division and DNA repairing mechanisms, severely affecting tumour cells.

4. Dolastatin 10 and brentuximab vedotin (Adcetris®)

Dolastatins were first isolated from a curious animal known as a 'sea hare' (*Dolabella auricularia*). Strictly speaking Dolastatin is not directly synthesised by the sea hare per se but produced by the cyanobacteria that the sea hares ingest. Dolastatin 10 shows potent anti-cancer activity in cell studies but it was too toxic to be used directly as a drug. However, it served as an important starting point to develop brentuximab vedotin – an agent used to treat Hodgkin's lymphoma without the aforementioned toxic side effects. Marketed as Adcetris®, brentuximab vedotin is one of the first antibody drug conjugates, a dolastatin 10 synthetic analogue linked to an antibody that specifically targets Hodgkin's lymphoma cells. This specificity ensures highly effective delivery of the drug.

5. Cytarabine (Cytostar-U®; DepoCyte®)

The MNP cytarabine has a supposed function in a defending the Caribbean sponge (*Cryptotethya crypta*). Sessile sponges are widely considered as drug treasure houses as they produce a whole array of antibacterial, antiviral, antifungal, antimalarial, antitumor and immunosuppressive compounds. Particularly, due to its antitumor properties, cytarabine has actually been used for decades as a key cancer drug treatment. Currently, it is the best approach for treating cancers of white blood cells such as myeloid leukaemia, non-Hodgkin's lymphoma and meningeal leukaemia. The component enters cells and inhibits the synthesis of DNA. Since rapidly dividing cells (as is the case with cancerous cells) require DNA replication to proliferate, they are disproportionately affected by cytarabine. Interestingly, cytarabine is unable to cross the blood-brain barrier, limiting its action in the brain. To overcome this barrier, the delivery system needed to be modified, which resulted in the creation of DepoCyte®, which releases cytarabine gradually and prolongs concentrations in the cerebrospinal fluid.

Corals – not only the backbone of the reef

Aside from the use of coral derived MNPs in drug development, coral skeletons are handled as alternative bio-implants in the case of bone loss since the 1980ies. Coral bio-implants are easily tolerated by patients and quickly resorbed and replaced by newly formed bones. Orthopaedics also recognises the potential of proteins extracted from the coral skeleton to aid in bone regeneration.

Lastly, coral organisms are non-conventional model organisms in scientific research that help us understand basic physiological or pathological processes. Cnidarians (which includes reef-building corals and free-floating jellyfish) can live for several hundreds to several thousands of years. Understanding ageing in different organisms can help understand how and why we age the way we do. Besides, the intimate relationship between algae and corals (and even other reef inhabitants such as nudibranchs) transforms these animals into Plant/Animal chimeras. Having algae so close means coral polyps experience a massive gradient in oxidative stress, ranging from full hypoxia during a sunny day when the algae excretes oxygen as side product of photosynthesis to anoxic conditions at night due to the lack of sunlight that fuels photosynthesis during the day. How corals deal with this amount of oxidative stress may shed some light on how some pathologies such as cancer in which oxygen plays a key role progress.

Coral grown on artificial structure

Like many marine invertebrates (such as sea stars), corals can regenerate from isolated body parts into fully functional organisms

Size Matters

Although over 20.000 MNPs are known, the number that is pursued and pushed through the drug discovery pipeline to be eventually commercialized is significantly lower than this. The initial search for MNPs can often make do with small amounts of wild organisms - enough to evaluate the chemical and biological nature of compounds. However, the amount needed to progress toward preclinical and clinical trials, and then commercialization, is substantially higher. Only at this stage, slow and limited natural production comes a significant drawback to large-scale application of many MNPs.

Yet, technological advances and synthetic MNPs inspired by organic compounds may enable future large-scale operations. Some companies produce *in vitro* coral proteins using biotechnology without having to harvest the coral itself. This is in theory possible for many MNPs and means that the drug pipeline of pharmaceutical and cosmetic industries can advance without exploiting the ecosystems sensitive to disturbances. Another viable approach is aquaculture. Coral aquaculture is already well-established and could provide the required biomass. This approach is already being used by some to produce novel drugs. Finally, coral micropropagation and advances in *ex situ* coral spawning techniques can also help in solving the biomass supply problem. Micropropagation uses an organism's tissue to generate clones that will eventually develop into a whole organism. Spawning of corals has now been cracked and can occur far from the corals' natural home, in London for example, and *ex situ* spawning labs are now cropping up all around the world increasing supply of young coral (larvae). These approaches are highly attractive for biomedical studies on coral or coral reef inhabitants because once they are grown up and maintained in a healthy state, a relatively high number of organisms can be reared in limited space.

One Health

Apart from the inspiration and source for natural products aimed at improving our overall well-being, coral reefs are of special ecological importance for our planet. They harbour an incredible diversity of life and indirectly and directly impact our health in more ways than we can imagine. They pose a physical barrier to storms for example, which are expected to increase in frequency and severity with climate change. Particle-feeding coral reef inhabitants such as sponges or ascidians also play key roles in water purification, turning wastewater or even sewage into the clearer water characteristic of the tropical reefs. Coral reefs and associated seagrasses beds even have been shown to directly keep humans out of harm's way by reducing free-floating pathogens by up to 50%. Furthermore, coral reefs are the main source of income to many coastal communities, offering delicacies such as sea bream or rock lobster to local and international customers. Such ecosystem services amount to a colossal value for human society.

However, local and global impacts threaten the health of coral reefs on a global scale, which in turn, impairs their potential to provide these services and be a source of novel MNPs. It is therefore fundamental to take actions to protect existing reefs and attempt to re-build already degraded habitats. Stressors such as overfishing, pollution and climate change have all been shown to increase instances of disease and large-scale coral die-offs. Coral bleaching is by far the most visible sign that the balance on coral reefs is tipping. Triggered by heat stress, that puts the otherwise peaceful symbiotic relationship between coral and its symbiotic algae to the test, corals whiten.


Sun-lid coral garden

One can liken this to the algal 'tenant' not being able to pay its rent and the coral 'landlord' evicting its algal buddy as a consequence. However, the algae is the breadwinner in this relationship. If temperatures remain high and no new algal tenants are found the coral soon starves and dies. Dead coral skeletons can then easily be taken over by seaweed that soon start to compete with other corals for space, smother newly settled corals and make the habitat less attractive for other reef inhabitants. As reef inhabitants begin to disperse, many of their jobs become vacant and services such as grazing on seaweed and transporting sediment are understaffed. This initiates a positive feedback that slows or hinders reef recovery after disturbances and eventually leads to a depauperated, less diverse ecosystem. This way humanity will not only loose a stunningly beautiful ecosystem but an unknown number of yet cryptic chemical compounds.

This reciprocity of human and ecosystem health was already understood by the Greek physician Hippocrates. But it took humanity another ~ 2300 years to recognise that we not only have the power to destroy ecosystems such as coral reefs, but equally protect their future – and with theirs our own. Today, global measures range from marine protected areas to active restoration programs on degraded reefs. Programs such as the World Coral Conservatory (WCC) project connects an international community of science centres, research laboratories, public aquaria, stakeholders and national administrations with the aim to increase the conservation and restoration of coral systems. The key realisation here is that the state of our ecosystems reflects back on human well-being. Returning to drug discovery, it is therefore not a big logical leap that keeping ecosystems pristine, whether on land or "under the sea", offers a richer diversity of yet to be discovered chemical compounds.

Preserving a healthy and biologically diverse coral reef community will ensure the discovery of novel chemical compounds well into the future

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