Cancerworld

From sea bed to bedside: Tapping the cancer pharmacy beneath the waves

Adriana Albini / 15 September 2021

Around 80% of life on our planet is found in ecosystems located within the almost 300 million cubic miles of ocean that cover the earth. Among its many wonders, the ocean is a treasure trove for medical sciences, providing knowledge and molecules, sometimes leading to discoveries that rise to patent production and even Nobel prize coronation.

Our knowledge of marine biodiversity remains minuscule, however. So far, we have explored only around 20% of our ocean waters, as they are difficult and costly to access. We have discovered no more than one in ten of the 2 million or more species that are estimated to live there (not to mention innumerable species of meiofauna – animals <0.5 mm– micro-organisms and bacteria).

Drug discovery in the marine environment has advanced much more slowly than in the case of land-based plants. Only 9,000 marine natural products have been screened for potential therapeutic value so far, and of these, only 16 have been marketed – 11 of them for cancer indications.

The future looks optimistic, however. According to the marine pharmacology/pharmaceutical pipeline website, as of August 2021 there were 30 marine-derived compounds in the clinical pipeline, five in phase III, nine in phase II and 16 in phase I. As to the preclinical pipeline, in the period 1998–2017, research found more than 1,000 marine chemicals with antibacterial, anticoagulant, anti-inflammatory, antifungal, anthelmintic (against parasitic worms), antiplatelet, antiprotozoal, antiviral and anti-tumoural properties.

Overcoming some of the obstacles that have held back exploring the pharmacological potential of natural marine products could be important in accelerating the discovery of new anti-cancer drugs. Also important is the need to take urgent steps to end pollution, climate change and all that

threatens the diverse ecosystems of our oceans.

Nature's pharmacy

From its very dawn, humanity has recognised the health properties of food and plants. Prehistoric humans ate soil – a practice known as geophagy – probably copying the self-medicating behaviour of animals, and there is some evidence that our ancestors knew the healing benefits of plants such as yarrow and mallow as far back as 60,000 years ago. Ancient Western and Eastern medicine extracted drugs from natural sources in a variety of ways, including comminution (pulverising), infusion or decoction (soaking or simmering flowers, leaves, roots and bark in liquid), maceration (chewing), etc.

The oldest written evidence of the use of plants for preparation of medicinal drugs can be found on a 5,000-year-old Sumerian clay slab from Nagpur, in central India. The Chinese book *Pen T'Sao*, written by Emperor Shen Nung ca. 2,500 BCE, includes 365 drugs from plants, minerals and animals. As the active ingredients of compounds were not identified until a couple of centuries ago, throughout history, pharmacology was based mainly on success and failure, experience, and tradition.

Today 60% of prescribed drugs can still be tracked back to products from nature, almost exclusively land-based and of plant origin.

Self-defence: the secret behind plant-based drugs

All organisms communicate with each other. To escape danger and combat predators, many animals can move and warn their own kind, or their adversaries – most commonly using body language, motility and sound. Plants, on the other hand, cannot run away. So they talk to each other or defend themselves through chemistry.

Plants produce biochemicals, called allelochemicals, to protect themselves against pathogens, competitors, and predators that want to eat them. Allelochemicals are a subset of secondary metabolites (fragments of biological molecules). While primary metabolites derive from the main function of an organism – that is, from growth – secondary metabolites have different functions, including defence. When a plant must defend itself, it produces a secondary, repellent or poisonous, metabolite. The poisons triggered by defence can have great utility from a pharmacological point of view; we humans can use them to fight our own 'poisons', such as infectious diseases (antibiotics), tumours (antigrowth drugs) or pain (analgesics), or to normalise circulatory aspects.

Marine organisms produce metabolites that are similar – though not the same – as those produced by terrestrial plants. Marine life has been around for more than 3 billion years longer than life on land, and can be found even at depths of 16,000 kilometres or more. Coral reefs are the most biologically diverse ecosystems on the planet, with more than 90,000 described species. The vast and mysterious treasure trove beneath the sea, therefore, presents a huge untapped potential for finding new drugs that could help treat all manner of diseases.

> The slow or non-motile organisms are the most likely to lead us to new drug discovery, as they must produce metabolites to fight predators

To adapt to different and extreme conditions, marine organisms have evolved with an extensive diversification of structures and functions. This represents a major source of attraction for the entire scientific community in the field of biomaterial research. It is the slow or non-motile organisms that are most likely to lead us to new drug discovery, as they must produce secondary metabolites to fight predators, compete for space, and prevent other organisms from settling on them. From marine sponges and ascidians to mussels, barnacles, crustaceans and more, marine organisms have shown to be potential sources for commercially important novel biomaterials.

From sea bed to bedside

The development of a new medical drug starts from the study of the disease processes and pathways, at a cellular or molecular level, to identify targets for new treatments. The search for molecules and compounds that act on such target can then begin.

Usually, when a terrestrial plant or marine organism is deemed to have therapeutic capabilities, it is administered in its entirety to cells or small laboratory animals. Meanwhile, a screening is made; the sample is separated into fractions (clusters of molecules that are separated by chromatography techniques), then biological tests are carried out. If the tests show that some metabolites decrease the growth of tumour cells, for example, a selection is made, and fragmentation continues until an almost pure compound is obtained. Mass spectrometry analysis is then carried out to measure the molecular weight and, through other analyses, such as infrared or nuclear magnetic resonance (NMR) spectroscopy, the structure can be understood.

Scaling up and stressing out

One of the problems that arise from the extraction of marine organisms, such as algae, is the difficulty in obtaining them in large quantities. As the metabolite is active at very low concentrations, many kilograms of algae would be needed to obtain just a nanogram of drug. One solution can be to build a bioreactor to produce large quantities of the required organism, algae or – more easily – bacteria (bacterial proliferation is simpler).

Alternatively, we can call upon organic chemistry for a laboratory synthesis of the molecule. If we know everything about the molecule of interest, we can now produce a synthetic derivative. This derivative is then tested to check that the biological properties exist and are reproducible in further tests. Through genomics, modern biology allows us to investigate and highlight any differences between chosen molecules.

Marine organisms produce metabolites that are similar to those produced by terrestrial plants – similar yet different. Using genomic techniques, for example, we can take a bacterium that lives in the sea, we make it proliferate in the laboratory, we characterise the metabolites, and we sequence the genome.

Modern biochemistry makes great use of information technology. For instance, by entering the genomic sequence in bioinformatics programs we can discover the difference between a terrestrial plant and a marine organism, or between two marine organisms. Depending on the ecosystem in which the bacterium develops, it will have diversities. For example, there are several isoforms of the popular dietary supplement spirulina, from fresh or salty water, depending on the area of origin. Some have already been tested, and are in the experimental phase I or II.

We can recreate an ecosystem in vitro and compare two fighting

organisms as in an arena, to stimulate the production of secondary metabolites

Normally it is defensive chemicals produced by an organism – or bacteria living in a mutually beneficial relationship with it – that are the source of a new medicinal drug. This poses a problem, since an organism on its own grows without danger and therefore produces mainly primary metabolites. But we can recreate an ecosystem in vitro and compare two fighting organisms as in an arena, to stimulate the production of secondary metabolites. If we have an organism that experiences a challenge, secondary metabolites will be stimulated. We can also change conditions, such as the amount of light or the proportions of one organism in relation to another.

Early successes

The first success story in marine-derived medicine dates back more than 50 years, with cancer patients the beneficiaries. In 1969 the US regulator, the FDA, approved the novel drug cytarabine or cytosine arabinoside (ara-C, marketed as Cytosar-U, Depocyt) for use as an anti-cancer drug enhancer in patients with leukaemias and lymphomas. The drug, still used for those indications, is a structural analogue of spongothymidine and spongouridine. Used with chemotherapy and radiotherapy, it enhances cancer cell destruction by suppressing DNA synthesis.

The story of its discovery began almost 25 years earlier, in the shallow waters of Elliot Key, Florida, where an organic chemist, Werner Bergmann, collected specimens of a previously undescribed sponge that was later taxonomised as a new species, *Tectitethya crypta*. Other sponges of the same species he also found in the waters of Bimini Islands – a chain of islands that are part of the Bahamas, located about 80 kilometres east of Miami.

Bergmann was studying sterols and steroids (the larger families of cholesterol and cortisone) at the time, and boiled his specimens in acetone to separate these lipids from the sponge. Instead, he recalled, a "rather copious amount of a nicely crystalline material" formed in the acetone. It was a new compound, a nucleoside that was similar, but not identical, to thymidine. In honour of his sponge, he named it 'spongothymidine'. Together with his team, Bergmann continued to study *Tectitethya crypta* for several years, and isolated another compound, spongouridine.

These two nucleosides are formed by bacterial colonies living within the sponge, rather than by the sponge itself. In nature, the sponge uses chemicals produced by the bacteria to prevent organisms such as barnacles from growing on its surface. In exchange, the bacteria are allowed to settle and take nutrients from the sponge, in a mutually beneficial relationship. Spongothymidine and spongouridine proved to have antiviral and anticancer properties.

Less than ten years after the approval of cytarabine, a second marine-derived drug, vidarabine (ara-A, marketed as Vira-A), was approved in 1976 for the treatment of *Herpes simplex* virus. After that no further compounds of marine origin were approved for almost 30 years. Of the 16 marine-derived drugs on the market in September 2021, only four were approved before 2010.

Picking up speed

The past decade, however, has witnessed success stories of ground-breaking ('wave-breaking?') medicinal drugs developed from natural products in the sea – mainly but not exclusively, for the treatment of cancer.

The best-known is **ziconitide** (SNX-111, marketed as Prialt). Discovered in the 1980s, it is a synthetic analogue of the natural peptide omega-conotoxin MVIIA, obtained from a snail species living in tropical waters, mostly off the coasts of Australia and Southeast Asia. *Conus magus*, or the magical cone, is an extremely toxic marine snail with a deadly weapon to administer its poison – a harpoon-like device which it launches at passing prey, paralysing and killing them in less than 15 seconds. A single drop of this poison would be sufficient to kill three humans, but synthesized and heavily diluted, it acts as a strong pain killer, 100–1,000 times more potent than morphine. It can be delivered intrathecally in hospitals to people who are terminally ill and in severe pain, which includes some cancer patients. Ziconotide acts by reversibly blocking N-type calcium canals on the spinal cord. It was approved by the FDA in 2004, and by the European regulator, the EMA, in 2005. as an analgesic agent for the management of chronic pain.

Eribulin mesylate (trade name Halaven) is a synthetic analogue of halichondrin B, first isolated from the Japanese marine sponge *Halichondria okadai* in 1985. It gained FDA and EMA approval in 2010 and 2011 respectively, for the treatment of metastatic cancer and liposarcoma. It is a microtubule polymerisation inhibitor, like taxol and taxanes. It has no effect on depolymerisation, and it sequesters tubulin into non-functional aggregates. Eribulin can be effective in patients with disease that is resistant to other tubulin-targeting agents.

Trabectedin (marketed as Yondelis, ET-743) is a synthetically produced anticancer agent derived from the Caribbean marine tunicate *Ecteinascidia turbinate*. It gained marketing authorisation from the EMA in 2007, under 'exceptional circumstances', receiving full approval in 2015. FDA approval came that same year, and the drug is now used in more than 70 countries for the treatment of relapsed soft tissue sarcoma and platinum-sensitive ovarian cancer. Trabectedin has a unique mechanism of action. It binds covalently to the DNA minor groove to initiate cytotoxic activity. Other multi-target mechanisms of action of trabectedin include important effects within the tumour microenvironment; in particular, trabectedin possesses indirect anti-inflammatory and anti-angiogenic activity via tumour-associated macrophages, and high-specificity modulation of various transcription factors.

Brentuximab vedotin (trade name Adcetris) is an antibody-drug conjugate (an antibody joined to a chemotherapy drug), derived from the anti-mitotic compound dolastatin 10. Dolastatin 10 was obtained from the nudibranch (sea slug) *Dolabella auricularia*, a native of the Indian Ocean. Adcetris gained FDA approval in 2011 for the management of relapsed or refractory Hodgkin lymphoma and systemic anaplastic large-cell lymphoma, with approval from the EMA coming the following year. The approval was extended five years later, by both FDA and EMA, to include patients with cutaneous T-cell lymphoma who have received prior systemic therapy, and again, a year later, for the treatment of adults with previously untreated stage III or IV classical Hodgkin lymphoma, and certain types of peripheral T-cell lymphoma, in combination with chemotherapy.

Tapping the vast unexplored marine pharmacy

Given the many encouraging results and the vast potential, it is surprising that there should be so few marine biodiscovery projects at national or international level. It is literally vital to understand the chemical properties of the ocean, as the marine environment supports most of life on our planet. Chemical ecology is important in the drug discovery process.

> We need to better understand the natural function of secondary metabolites, so as to manage and protect them better and find

new applications

To exploit secondary metabolites in a sustainable way, we need to better understand their natural function. We will then be able to manage and protect them better and find new biotechnological applications for these important natural products in the future.

Pharmaceutical companies need to be convinced that there are economically viable ways to get adequate supply of the source material. Various methods, such as aquaculture, cell culture, microbial fermentation, and genetic engineering, all look very promising, but drug companies are currently reluctant to invest funds in the development of general models for biological supply of marine products.

Public awareness of marine-derived pharmaceuticals also needs to be improved, not least as part of efforts to preserve the health of our delicate ocean ecosystems. We have spent too long exploiting our seas as a dumping ground for pollutants and taking more from them than can be replenished. Already 90% of big fish populations have been depleted, and 50% of coral reefs destroyed. A recent paper published in the Nature publication *Scientific Reports* notes that, "Marine forests (i.e. seascapes dominated by habitat-forming seaweeds) are among the most productive ecosystems in temperate rocky coasts, enhancing biodiversity, ecosystem functioning and habitat complexity. However, multiple anthropogenic stressors interacting at both local and global scales increasingly threaten these iconic ecosystems."

We need the ocean for our survival, and now the ocean needs us to act for its protection. The United Nations founded World Oceans Day in 2008, and on 8 June every year a different topic is addressed. The theme for 2021 was 'The Ocean: Life and Livelihoods', focussed on the wonder of the ocean and how it is our life source, supporting humanity and every other organism on Earth.

The coronavirus pandemic has made us think more about 'One Health' – a concept focused on the interconnections between people, animals, plants and our environment that determine our health which is now officially recognised by the G7. There is no human health without a healthy ocean.

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