Medicines of the Sea

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Traducción

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Abstract

This article is about the importance of marine compounds for the development of drugs. It explains how marine organisms produce secondary metabolites with therapeutic properties for various diseases, such as cancer, parasitosis, and others. It also mentions the need to conserve and explore marine ecosystems to find new drugs. The article cites some examples of approved or in-study marine drugs, such as cytarabine, trabectedin, and ziconotide, and discusses their mechanisms of action, clinical applications, and limitations. Finally, the text highlights the potential of Mexico as a country with great biological and marine diversity.

Nature as a source of inspiration

It often happens that we overlook the origin of the things we use and enjoy because we are used to them. Such is the case with the medicines we use. Seeing them, arranged in order on the shelves of pharmacies and supermarkets, with their trade names so familiar and at the same time indecipherable, it is easy to lose sight of the fact that each one hides a fascinating story.

The sober packaging and the combination of white with pastel and metallic colors offer poor indications about the origin of the drugs. Taking this into account, it is difficult not to imagine that they are all synthetic products, the result of a group of people wearing white coats, breaking their heads by putting together different combinations of functional groups and residues, to arrive at a new active compound. But did you know that more than half of the medicines on the market have been inspired by natural sources?

Since ancient times, nature has played a very important role in the discovery and development of new substances applied to the treatment of major and minor ailments. We know that living things are not static systems, but struggle to adapt to an ever-changing environment. As a result of external factors found in that environment, or in response to competition with other organisms, many living things produce chemical compounds called secondary metabolites, which aim to give them adaptive advantages to survive adverse conditions. These compounds have different chemical characteristics than those produced in a laboratory, often more complex than we could imagine. If you

combine thousands of species of living things and the different conditions in which they live, it is no surprise how many naturally occurring compounds are discovered.

Among the best known naturally occurring drugs are taxol and vinblastine, used for cancer treatment, along with quinine and artemisinin, used to fight parasitic diseases. However, this time we will direct our readers to other spaces not so commonly referred to: we will talk about natural products with therapeutic applications from the marine environment.

The Path to Marine Me It often happens dicine

Herbal tradition is often cited as the root of the search for medicinal remedies in living beings. But there is another source of drugs that has a greater potential than terrestrial organisms, which, ironically, is less explored and known: marine environments.

Oceans cover more than 70% of the Earth's surface. Although they seem to be only large and almost empty bodies of water from the surface, they are actually the habitat of a huge diversity of organisms, from large mammals that travel long distances in their annual migrations, to countless microorganisms that are born and die to the rhythm of the currents, some of them never seeing the sunlight.

Looking more closely, we realize that the marine environment has unique physical and biochemical properties, often extreme and completely different from those on land. The high salinity and the pressures that can deform steel in the strange domain of the abyssal pits are examples. As a consequence, the organisms that inhabit these environments have to adapt not only to these factors, but also to the biological conditions of the specific ecosystem in which they live, such as their predators or competitors.

As we mentioned earlier, one of the most important adaptive mechanisms in nature is the production of secondary metabolites, which, unlike primary metabolites, differ for each species and are generated under certain conditions. For example, some organisms must produce compounds that protect them from the effects of UV light, while others will avoid being preyed upon or fight the settlement of other organisms in their immediate vicinity. Conversely, others will produce compounds to attract organisms that provide them with certain benefits, thus establishing close symbiotic relationships.

From an ecological perspective, compounds are produced as a defense or adaptation mechanism. Curiosity and experimentation reveal that those same metabolites can also have some effect in other organisms and microorganisms that they do not necessarily coexist with. This is the starting principle of the concept of marine medicines: metabolites different from terrestrial ones with antibiotic, antiviral, antiparasitic, anticancer, anti-inflammatory properties, among others. In addition, with new chemical structures and mechanisms of action.

The first studies to address the biological activity of marine compounds focused, in the early 1950s, on visible and easy-to-collect organisms. Such is the case of the Tethya crypta sponge, a decidedly

deceptive creature, if judged only by its appearance, and unobtrusive to the naked eye, which inhabits the shallow waters of the Caribbean Sea.

This new field of research allowed the characterization of two compounds: spongothymidine and spongouridine. After years of research, they led to the development of cytarabine (Ara-C), a compound that, by 1969, was approved for the treatment of leukemia. It became the first drug of marine origin with official approval. Ten years later, in 1979, the second marine drug came to market, vidarabine (Ara-A), the first drug against herpesviruses.

After the approval of these drugs, many years passed in which algae, sponges, stars, cucumbers, corals, and other marine organisms were studied. It was not until 2004 that two new drugs were marketed for the treatment of chronic pain and hypertriglyceridemia, isolated from a conical snail (Conus magus) and fish oil, respectively. Advances in science and technology enabled marine natural products research to benefit. For example, there was access to organisms that were previously completely unattainable, and improvements were also made to the efficiency of equipment for chemical and biological analysis. The omics sciences have been of great relevance to understand different aspects of the synthesis and discovery of new compounds, as they study the set of different aspects in biological systems, such as their genetic (genomics), protein (proteomics), metabolic (metabolomics) profiles, among others.

In the same way, in the nineties, we found a new field in the research of marine natural products: the metabolites produced by microorganisms. These small and almost invisible organisms were a promising source of new chemical compounds with potent biological properties, compared to many of the metabolites known up to that time.

Marine medicines on the market

The drug discovery and development process is a long, slow, and expensive journey. It requires a lot of investment and research efforts, but marine organisms have overcome these challenges at an incredibly fast pace. Between 1969 and 2021, 15 marine-based drugs were approved. Additionally, the growing interest of scientists in this new source of compounds with therapeutic potential is reflected in the ten drugs approved between 2011 and 2021. Of these, ten are for the treatment of different types of cancer, while three are for treating hypertriglyceridemia, and the other two correspond to an antiviral and an analgesic (Marine Pharmacology, 2023).

Among marine organisms, the invertebrates group (sponges, worms, cucumbers, corals, stars, hedgehogs and others) were initially considered the most prolific producers of compounds with relevant bioactive properties. Evidence of this are the 12 approved drugs, whose active compounds were first identified in sponges, molluscs and tunicates.

Currently, there are 38 more compounds in different clinical phases of study, which, depending on

the stage they are in, if they are approved, can take from one to fifteen years to reach the market. This means that there is still a long way to go before we see a more extensive and wide impact of marine medicines on everyday life. Therefore, clinical trials not only require a substantial investment of time but also resources and manual labor.

These drugs have various chemical classes, such as fatty acids, nucleosides, alkaloids, peptides, and antibody-drug conjugates. Most importantly, conjugates (with antibodies) are used as anticancer agents: the antibody binds to specific proteins or receptors on cancer cells, thus allowing the drug to enter and destroy those cells without harming healthy cells. As for drugs for the treatment of hypertriglyceridemia, they correspond to Omega 3 fatty acids, which decrease bad cholesterol and fats in the blood (such as triglycerides).

What is expected of marine medicine?

The systematic study of marine products has shown up to four times more chances of success in the discovery of new drugs, compared to other sources. So far, around 30,000 marine metabolites have been identified, of which a large number have properties against cancer cells, bacteria, fungi, viruses and parasites, as well as potential as treatment agents for metabolic disorders.

Among the limitations of the discovery of new drugs are, on the one hand, the small amount of active compound that is obtained from the natural source, which, in turn, limits the panel of experiments to be performed. On the other hand, its chemical complexity, which hinders its synthesis in the laboratory. To overcome these challenges, various strategies emerge, among which the exploration of cultivable microorganisms in the laboratory stands out, as it would represent a sustainable and potentially uninterrupted source of compounds.

It is interesting to note that since the chemical study of marine microorganisms began, it has been proven that a large part of the previously isolated invertebrate compounds are originally produced by the microorganisms that inhabit them. Often, organisms of larger size, or of advanced position in the food chain, become accumulators and even modifiers of compounds; that accumulation justifies that many times we identify a large part of the metabolites from them. This, without forgetting that the most easily accessible organisms were studied much earlier.

If we briefly focus this review on Mexico, it is possible to observe that, having a geographical location between the Atlantic Ocean (central-western) and the Pacific (central-eastern), this country enjoys a great marine biological and ecosystemic diversity. Furthermore, in terms of extension of coastlines and marine surfaces, it is the second best endowed worldwide1.

Who can say that new and unimagined compounds harbor the microbes, flora and fauna that these coastal areas call “home”? Of particular interest, of course, are also the less explored areas, such as the abyssal plains, underwater volcanic chimneys and twilight zones, in which their inhabitants move between the worlds of daylight and perpetual darkness throughout their lives.

Even though it is true that the habitats of these areas are extremely valuable, their potential for the discovery of active compounds highlights our responsibility to protect them and to motivate new generations to venture into the marine world, which holds great surprises and mysteries yet to be discovered. Undoubtedly, in the coming years we will see new medicines of marine origin coming to the market for the treatment of various diseases.

We thank readers for joining us on this brief dive into the world of sea medicines. We hope that what we have shared with you is a seed that will find fertile soil in the curiosity of your minds. We look to the future with the certainty that this seed will sprout and will be the inspiration to join the noble enterprise that is the scientific quest to understand, preserve and grow together with the marine ecosystems and the fascinating organisms that inhabit them.

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