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Use of Synthetically Created Secondary Metabolites Generated from Marine Species as Epigenetic Biomarkers and Prospective Cancer Therapy

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Abstract

Seaweed, coral, and sponges are examples of sessile creatures that constantly adapt to the biotic and abiotic elements of the ecosystem. To maintain an ecological niche suited for life, this incredibly intricate and dynamic process frequently leads to various types of competition. As a defensive strategy against the outside environment, a large proportion of marine animals have acquired the ability to produce physiologically active compounds known as secondary metabolites. These organic compounds and their derivatives may have epigenome and disease-related epigenetic machinery modulatory effects. By facilitating the creation of complex chemical compounds with potential therapeutic ramifications, epigenetic alterations also serve as a type of environmental adaptation and give marine animals a competitive edge. By controlling important transcriptional factors associated with cancer's hallmarks through carefully orchestrated molecular mechanisms, bioactive compounds are able to interfere with epigenetic targets. These molecular interactions also create signalling interactions of the tumour microenvironment that are essential to cancer phenotypes. As epigenetic modulators, secondary metabolites originating from marine species and their synthetic derivatives are currently understudied. In this review, we emphasize their benefits and drawbacks as well as possible improvements to cancer therapy.

Keywords: Biomarkers; Cancer therapy; Secondary metabolites

Introduction

Marine ecosystems are a remarkable source of novel and structurally complex bioactive metabolites that are spontaneously created by various species and exhibit distinctive biological activity. Extreme environmental factors such low light, high pressure, ionic concentration, pH and temperature variations, nutritional shortages, and small living areas might be blamed for these characteristics [1]. Because of the high number of organisms coexisting in a small space, they are also highly competitive and complex, which leads to the evolution of adaptations and behaviours aimed at protecting the species, such as the use of chemical strategies that take advantage of the abundance of bioactive molecules produced by the secondary metabolism [2, 3]. Marine-derived metabolites come from several signal transduction pathways that have been triggered as a result of epigenome alterations in the producing species. Marine creatures' phenotypic and genetic changes are defined by a complex web of interdependent connections. Epigenetic changes, which might start adaptive biochemical processes in the species, complicate this interaction even further [4]. The maritime environment (defined by biotic and abiotic variables), in turn, exerts an inductive function on epigenetic, genetic, and phenotypic alterations with transgenerational repercussions on the species [5, 6], playing a fundamentally selective role in inherently altering animals. Secondary metabolites generated by several species may be excellent candidates for new natural compounds with potential pharmacological action for the treatment of cancer since the reprogramming of epigenetic states can be brought on by environmental exposures in the marine ecosystem [7]. New marine-derived compounds were isolated and characterised [8-10], some of which have potential anticancer activities. These compounds were isolated and characterised using cutting-edge chromatographic isolation and purification techniques, pharmacological screening techniques, and numerous spectroscopic approaches for structural investigation. The epigenome of the organism and any possible epigenetic changes have a significant impact on the chemical composition of isolated molecules, revealing a complicated and interrelated system of information exchange. With a focus on their significance as epigenetic modulators producing posttranscriptional, inductive (produced by the organism's metabolism), and induced (produced by changes in the marine environment), modifications, we describe the therapeutic potential of marine-derived secondary metabolites and their synthetic derivatives in cancer in this review. In view of the immense heterogeneity that distinguishes both the organisms themselves and their habitat, we also talk about the difficulties associated with finding novel natural and synthetic marine bio-compounds with anticancer potential. In terms of development, research, and transmissibility of marine technology, this study also emphasizes the sustainable use of marine resources as producers of high yields of value-added biomolecules for the pharmaceutical industry in the direction of more sustainable economic growth.

Anticancer activities of marine-derived secondary metabolites with inductive and induced epigenetic modifications

A subfield of genetics known as epigenetics is based on the coexistence of intricate biomolecular systems that coordinate genetic information in the nucleus and ultimately govern gene expression, which is passed down through generations. The external environment's disturbances further condition all of this knowledge. In the absence of changes in DNA sequence, epigenetic modifications to gene function are persistent during mitosis. Typically, environmental perception mechanisms work by changing chemical markers that are naturally present in the genome. "Epigenetic markers" are a type of DNA

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function barcode that may be used to identify whether a gene is active or quiet in cancer. Changes in gene expression and the activity of transcriptional regulators can both be directly influenced by altering and reprogramming epi-signals, with subsequent consequences on the functionality of cells and tissues. Along with genetic abnormalities, which are a feature of many cancers, epigenetic dysregulations affecting DNA methylation, histone modifications, and microRNAs add another level of complexity and influence the development of tumours and phenotypic changes. These epi-alterations are further controlled by specialized protein machinery known as "chromatin writers, readers, and erasers," which can modify and have reversible effects on the epigenome. Due to their capacity to add modifications to DNA and histones, DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), histone methyltransferases (HMTs), and lysine/arginine methyltransferases (KMTs/RMTs) are all writers; readers, able to "read" and subsequently interpret covalent modifications, include: bromodomains, which are specific for ace The PWWP domain can bind DNA and methylated histones, whereas plant homeodomains attach to methylated histone H3 [11-14]. TET proteins, histone demethylases, histone deacetylases, protein phosphatases, and deubiquitinating enzymes, which remove methyl, acetyl, phosphate, and ubiquitin groups from DNA and histones, are examples of erasers.

The PWWP domain can bind DNA and methylated histones, whereas plant homeodomains attach to methylated histone H3. Erasers include the TET proteins, which eliminate DNA and histone modifications, as well as the histone demethylases (HDMs), histone deacetylases (HDACs), protein phosphatases, and deubiquitinating enzymes, which eliminate the methyl, acetyl, phosphate, and ubiquitin groups from the histones and other proteins, respectively [15-17]. Bioactive molecules with epigenetic activity isolated from marine sources represent a viable alternative to conventional therapies for use in extensive preclinical assessments and the advanced stages of clinical studies because modern medical approaches are based on the personalization of human healthcare. Additionally, attempts are being undertaken to find more physiologically active and effective compounds due to some infections developing resistance to pharmaceutical treatments and the ineffectiveness of conventional chemotherapies. Sessile creatures are far more vulnerable to environmental changes in marine settings and have sophisticated survival techniques. These organisms also have a very dominating combination of biotic and abiotic elements, which influences the synthesis of secondary metabolites with essentially unique chemical-physical properties. The complicated interaction between secondary metabolites and epigenetic processes, which in turn helps animals build defensive systems that are passed down through generations, adds even another layer of complexity. Antioxidant, antibacterial, antiviral, anticoagulant, antidiabetic, anti-inflammatory, antihypertensive, and anticancer actions are only a few of the favourable qualities that secondary metabolites can have for human health. Additionally, the environment around them, particularly instances of climatic stress or predator assault, has a significant impact on their natural biological processes. Only for certain species have computational systems employing knowledge-based algorithms or sequence-based prediction been able to pinpoint the genes in charge of producing these natural chemicals. These genes are often found in certain biosynthetic gene clusters (BGCs) in the genome that also include the necessary enzymes for the production of regulatory structures and secondary metabolites. It is not always possible to anticipate marine species BGCs and, consequently, their link with the generation of secondary metabolites, because to the vast genetic and epigenetic heterogeneity among them. For instance, certain chromatin remodelling proteins may constantly turn on or turn off certain genes over time. To better understand the relationship between the production of metabolites and the genes that produce them, cutting-edge technologies are emerging, such as those involved in triggering the activation of silent BGCs, which include changes in growth conditions (for example, temperature and pH) or genetic engineering-based approaches.

Sustainability and health

Potentially effective anticancer medications derived from different marine species are not always abundant in the environment and do not always retain the same functional characteristics over time in terms of chemical-physical structure and biological potential, which restricts their characterization. Prior to being utilized as medications, these molecules must be subjected to exacting standards and processes developed on the fly, as well as to rigorous scientific study and quality control. The circumstances of the marine environment, which have a vital influence on development, research, and novel approaches used in marine biotechnology, are one of the factors that affect their production. Since its preservation offers significant advantages for human health, the sea must be seen as both an environment to be utilized and a resource. Apart from human activity, factors such as climate change, nutrient availability, and predator attack have a significant impact on the production of bioactive compounds. For these reasons, we are working harder than ever to improve sustainability, well-being, and health, both in terms of environmental protection and socioeconomic factors.

Polyphenolic compounds

One of the primary categories of secondary metabolites originating from the marine environment is (poly)phenolic compounds. Their production varies among taxa, growth circumstances, geographic location, and abiotic/biotic variables, and they are present in a variety of pelagic creatures. The presence of one (in the case of phenolic acids) or more (in the case of polyphenols) aromatic rings attached to hydroxyl groups in their structures, which provide highly potent antioxidant characteristics, allows us to identify these compounds from one another. Their bioactivity is also connected to further enzymatic inhibitory effects, as well as to anti-inflammatory, anti-cancer, and anti-diabetic activities, all of which have positive impacts on human health. Additionally, because they exhibit intriguing epigenetic molecular mechanisms that control gene expression as well as DNA damage and repair, their function as scavengers of singlet oxygen and free radicals as well as reducing and chelating agents is a very promising area for the study and treatment of cancer.

Alkaloids

Natural substances known as alkaloids have a nitrogen-heterocyclic structure. Marine alkaloids, which mostly originate from marine animals including sponges, algae (green, brown, and red), coelenterates, and tunicates, specifically have an amine nitrogen group and a carbon ring. The anticancer, antiviral, antimalarial, antifungal, and anti-osteoporosis capabilities of these metabolites are among their many characteristics. Marine alkaloids can be employed as lead chemicals for structural alteration or as chemotherapeutic agents.

Isofistularin-3 (Iso-3) is a potential natural chemical that belongs to the class of brominated alkaloids (BAs) and is derived from the sponge Aplysina aerophoba. This substance shares structural similarities with the well-known bromotyrosine derivative PsA. Together with a library of chemicals, iso-3 was tested for its DNMT1 inhibiting actions in vitro. A molecular docking prediction analysis of the compound's conformational structure revealed an inhibitory interaction between

DNMT1 and DNA via a conserved CXXC motif that affects binding activity via positively charged residues. The absence of HDAC inhibitory action in BAs is due to the absence of a thiol linker moiety. In lymphoma cells, iso-3 was demonstrated to have anticancer potential by causing cell cycle arrest, morphological alterations, authophagy, and both caspase-dependent and independent cell death.

Cyclic Peptides

Secondary metabolites originating from marine organisms are a rich supply of multi-structured peptides with special properties that can control cancer epigenetic processes. The bulk of these substances are derived from nature, and their ring-shaped backbone has been exploited in creative ways to create more potent and targeted medicinal medications. As epigenetic-like anticancer drugs, depsipeptides and cyclic tetrapeptides (CTPs) are the major topics of discussion in this area. Depsipeptides are non-ribosomal peptides in which the matching ester is used in lieu of one or more amine linkages. These derivatives, which are abundant in the marine environment, frequently contain non-protein amino acids. Because of how easily they can be synthesized, many structural combinations that may be used to find the most potent anticancer medicines may be created. For instance, amine groups might become esters to improve their lipophilicity and cellular permeability. Contrary to depsipeptides, CTPs have a very complicated structure made up of four amino acids connected by eupeptide bonds. As a result, they are particularly challenging to synthesise. L, D, and cyclic amino acids are specifically found in CPTs, and they help to lower the cyclic tension that is connected to CTPs. To create innovative and more bioactive molecular structures, a variety of biochemical techniques have been developed, along with substantial investigations of three-dimensional structures by X-ray crystallography and NMR. The epigenetic function displayed by marine-derived cyclic peptides demonstrating potent anticancer activity. The epigenetic function played by marine-derived cyclic peptides with potent anticancer and anticancer-associated biological activities is discussed in the following subsections. This role might have significant health consequences for people.

Discussion

Resistance to medication therapies and relapses are two downsides of anticancer therapy, thus one of the key goals is to identify and characterise novel medicines. The multidisciplinary process used to develop new drugs with anticancer activity typically starts with the discovery and extraction of novel bioactive molecules from natural sources. These molecules are then subjected to preliminary assessments of their biological activity, toxicological testing, and chemical and biotechnological synthesis. The inability to isolate natural biomolecules sometimes prevents the creation of promising medicines due to the difficulty in locating marine-derived natural chemicals and gathering adequate amounts for clinical and preclinical investigation. The aspects of the discovery of new marine-derived anticancer bio-compounds highlight the variability that characterises the organisms themselves and their surrounding environment, which have not previously been extensively discussed, even though the epigenetic role of natural compounds has been discussed in previous studies.

Natural marine compounds have distinct chemical, physical, and biological properties that are not present in the terrestrial environment, but the characteristics of already characterised molecules can be used to create new chemical synthesizes and molecularly model novel products with improved anticancer activity. The quantity and distribution of species in nature as well as the health of ecosystems are influenced by natural marine bio-compounds that are formed in tandem with biological systems and have the potential to be unique mediators of cancer's epigenetic processes. The idea of environmental sustainability, which is closely related to the pressing need to lessen the ecosystem's impact on natural resources and the need to protect the marine environment in order to maintain and preserve biodiversity and avoid, to the greatest extent possible, the loss of ecosystem functions, is another crucial factor. Marine biotechnologies are increasingly focusing on the construction of new techniques based on the assessment of the sustainability of organisms sampled for use in the future in conjunction with new selection criteria.

Conclusion

Marine organisms create secondary metabolites with highly varied chemical, physical, and biological properties as a result of biotic and abiotic influences, which further complicates attempts at study and development in this area. More than 10 marine-derived drugs are now in advanced clinical stages, and the majority of these are manufactured. Additionally, new and sophisticated technologies enable the biotechnological production of these molecules through gene cluster manipulation or cloning techniques, overcoming a number of challenges such as those related to environmental risks associated with the potential loss of genetic resources caused by the overharvesting of producer organisms. Identification and biosynthetic characterization of natural marine compounds, particularly those derived from secondary metabolism, are currently of great interest for the creation of new epigenetic drugs because they may serve as active principles (lead compounds) or be biochemically equivalent to active compounds (biosynthetic analogues). The control of gene expression is significantly influenced by a number of marine chemicals with anticancer action that can modulate microRNA and epigenetic processes such DNA methylation, acetylation, and histone methylation.

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Conflict of Interest:

The authors declare no conflict of interest.

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