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Review Article

Exploring the seas for cancer cures: the promise of marine-derived bioactive peptide

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Abstract: Marine environments harbor a wealth of bioactive peptides with potential anticancer properties, sourced from diverse organisms like tunicates, sea sponges, and mollusks. Through isolation, identification, and modification, peptides such as Stylisin and Papuamides have shown enhanced activity and progressed to clinical trials, underscoring their therapeutic promise. Enzymatic hydrolysis emerges as a favored method for peptide extraction from marine proteins, with sponges identified as particularly rich sources. Compounds like Jaspamide and Homophymins exhibit potent cytotoxic activity against cancer cells, highlighting their therapeutic potential. Additionally, peptides from ascidians and mollusks, including Aplidine and Kahalalide F, demonstrate significant anticancer properties. The study delves into peptides affecting apoptosis, microtubule dynamics, and angiogenesis inhibition, offering insights into potential cancer treatment mechanisms. Marine-derived peptides hold great promise as valuable candidates for novel anticancer therapies, with ongoing research aimed at unlocking their full therapeutic benefits.

Keywords: Marine bioactive peptides, anticancer potential, enzymatic hydrolysis, cytotoxic activity, apoptosis, angiogenesis inhibition

Introduction

The vast expanse of the seas, covering 70% of the Earth's surface, hosts an extraordinary diversity of life, constituting approximately 75% of all living organisms. Within this marine realm lies a treasure trove of natural products with immense therapeutic potential. Recent years have witnessed a burgeoning interest in bioactive peptides derived from marine sources, obtained either through natural processes or enzymatic methods. These peptides not only provide essential nutrition but also exert profound physiological effects on bodily functions [1].

Marine organisms, ranging from sponges to bacteria, exhibit remarkable biochemical and physiological adaptations to their environments, thriving in conditions of darkness, cold, and high pressure. Marine bioactive peptides, derived from marine organisms like fish, algae, and mollusks, exhibit a range of significant biological functions [1, 2]. Key among these are their antioxidant properties, which help combat oxidative stress and prevent chronic diseases. They also possess antimicrobial activities, making them effective against various pathogens. Additionally, marine peptides show potential in anti-inflammatory, anticancer, and antihypertensive applications, making them valuable for health and therapeutic uses. In particular, marine invertebrates and bacteria are known for synthesizing secondary metabolites with diverse biological activities, including anti-inflammatory, antimicrobial, and anticancer effects [3].

Marine bioactive peptides are mainly extracted from fish, mollusks, crustaceans, and algae. The extraction process typically involves enzymatic hydrolysis, where specific enzymes break down proteins into peptides [3]. This is followed by purification methods such as ultrafiltration, chromatography, or membrane separation to isolate the desired peptides. These techniques ensure that bioactive peptides with specific functions are efficiently obtained from marine sources [4, 5].

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The rich biodiversity of the marine environment has spurred intensive research into the medicinal potential of marine products. Extracts from various marine organisms, such as tunicates, sponges, and mollusks, have yielded a plethora of bioactive peptides and depsipeptides with promising anticancer properties. Some of these compounds have advanced to different stages of clinical trials, while others, like Aplidine, have already entered the commercial market [4].

This article aims to provide a comprehensive review of recent studies on marine peptides, delving into their diverse biological activities and exploring their potential for developing novel therapeutic compounds [5]. With cancer treatment being a primary focus, the prospect of marine peptides as valuable pharmaceutical agents represents an area of significant interest and holds promise for future advancements in medicine.

Apoptosis stimulating peptides

Apoptosis is indeed a critical mechanism of programmed cell death, playing a vital role in preventing cancer. This natural process has been evolutionarily conserved to ensure the elimination of harmful or non-functional cells [6]. As our understanding of apoptosis deepens, there is great promise for advancing cancer treatments and improving patient outcomes. Apoptosis can be triggered by chemical agents, presenting a promising perspective for cancer treatment. In mammals, two main pathways mediate apoptosis, both involving the activation of caspases: the external signaling pathway and the internal (mitochondrial) pathway. Various molecules can stimulate apoptosis or serve as apoptosis inhibitors. The development of anticancer peptides targeting these molecules has become an important strategy for cancer prevention [14]. A key strategy to initiate apoptosis is inhibiting the Bcl2 gene, which functions as an inhibitor of apoptosis, while inducing the Bax gene, an inducer of apoptosis. By modulating these genes, the process of apoptosis can be initiated and regulated. Caspases play a significant and influential role in both apoptotic pathways. By targeting these essential molecules and pathways involved in apoptosis, researchers are exploring innovative approaches to develop effec tive anticancer peptides and therapies. Understanding the complex mechanisms of apoptosis has paved the way for novel treatments and interventions in cancer prevention and treatment [7]. The ongoing advancements in this field hold great potential for improving cancer management and patient outcomes.

In the mitochondrial pathway of apoptosis, cell death is initiated when certain apoptosis-stimulating molecules that reside in the space between the inner and outer mitochondrial membranes are released into the cytosol. This release causes the outer mitochondrial membrane to become permeable. As a result, pro-apoptotic factors like cytochrome c are released from the mitochondria, leading to the formation of the apoptosome complex and the subsequent activation of caspases in a cascade reaction. In this process, about 18 proteins from the Bcl2 family play a central and essential role in regulating apoptosis. Some of these proteins, like Bax, are pro-apoptotic, promoting cell death, while others, like Bcl2, inhibit apoptosis, preventing cell death. Jaspamide, the cyclic depsipeptide mentioned earlier, induces apoptosis in cells exposed to it more than in normal cells that are not exposed to this peptide. Jaspamide triggers apoptosis by activating caspase 3 and reducing the expression of Bcl2 protein while simultaneously increasing the levels of Bax protein. This imbalance in the Bcl2 family proteins enhances the pro-apoptotic signaling, ultimately leading to programmed cell death. These findings highlight the potential of jaspamide and similar compounds in cancer research and therapy. By targeting the mitochondrial pathway and modulating the Bcl2 family proteins, researchers can develop promising strategies for inducing apoptosis in cancer cells and potentially halting cancer progression [2]. The study of jaspamide and its effects on apoptosis sheds light on the intricate molecular mechanisms involved in programmed cell death, paving the way for further advancements in cancer treatment.

Studies have revealed that sumocystinamide A and phycocyanin C possess the ability to activate apoptosis-related caspases in various cancer cells. Sumocystinamide A can stimulate both intrinsic and extrinsic pathways of apoptosis, with its more effective mechanism being the activation of caspase 8. This activation leads to the initiation of apoptosis, triggering

programmed cell death in cancer cells. On the other hand, phycocyanin C induces caspase-dependent apoptosis by causing the release of cytochrome c from the mitochondria to the cytosol when added to HeLa cancer cells [8]. This release of cytochrome c is a crucial step in the apoptotic process, ultimately resulting in cell death. Furthermore, phycocyanin C has been found to activate multiple caspases, including caspases 2, 3, 6, 7, 8, and 9, when added to HeLa cells. This activation of caspases further amplifies the apoptotic signaling, promoting cell death in cancer cells. N-JUN terminal kinases (JNK) and mitogen-activated protein kinases (P38MAPK) play essential roles in regulating and coordinating cellular responses to various types of cellular stress, including cancer. In cancer, uncontrolled cell proliferation is a significant hallmark, and JNK and P38MAPK help monitor the cell division cycle by regulating cell cycle progression at different points through transcription-dependent or transcription-independent mechanisms [3]. Interestingly, JNK and P38MAPK have also been observed to have significant effects in viral cancers, highlighting their versatile roles in cellular responses and potential implications in cancer research and treatment. The study of these peptides and the involvement of JNK and P38MAPK in apoptotic pathways sheds light on the complex molecular mechanisms involved in cancer cell death. By understanding these processes, researchers can develop targeted therapies to induce apoptosis in cancer cells and combat cancer effectively [9].

The effects of JNK and P38MAPK in regulating apoptosis depend not only on the type of stimulus but also on the strength and duration of the generated signals. These signaling pathways can have complex and context-dependent outcomes, leading to diverse cellular responses, including apoptosis. The mechanism of action of compounds involving JNK and P38MAPK, such as Aplidin, often involves damage to the outer mitochondrial membrane, leading to the release of cytochrome c into the cytosol [10]. This release of cytochrome c triggers the activation of caspases, initiating the apoptotic process. Aplidin, a cyclic depsipeptide from Aplidium albicans, has been found to exhibit sensitivity in skin, breast, and lung cancer cells at low concentrations. It induces apoptosis through multiple pathways, including cell cycle arrest and inhibition of protein synthesis. Upon exposure to Aplidin, oxidative stress is initiated, leading to rapid and continuous activation of the JNK and P38MAPK pathways, along with related protein kinases. This activation cascade, occurring within minutes after Aplidin application to human HeLa cancer cells, results in the release of cytochrome c from the mitochondria and subsequent activation of caspases 3 and 9, driving the mitochondrial pathway of apoptosis.

The cytotoxic function of Aplidin is mediated through the involvement of protein kinase C delta, which plays a critical role in transmitting the apoptotic signal in response to Aplidin treatment. Many marine peptides, including Aplidin, have been shown to induce apoptosis in cancer cells, and this process can be investigated using various indicators such as DNA fragmentation, nuclear shrinkage, and cell membrane swelling or edema. These indicators collectively provide valuable insights into the occurrence and extent of apoptosis induced by these peptides [10]. The study of marine peptides and their ability to induce apoptosis opens up new avenues for potential cancer treatments. Understanding the intricate mechanisms involved in apoptosis can aid in the development of targeted therapies that exploit the specific vulnerabilities of cancer cells, providing hope for improved cancer management and patient outcomes. Indeed, while some marine peptides like sansalamide A, cyclooxazoline, and virenamides A-C have shown potential to activate apoptosis in certain cancer cells, the exact mechanisms of their actions remain to be fully elucidated [11]. Despite their promising anticancer activity, the specific targets and effectiveness of these peptides are yet to be clearly identified. Sansalamide A, a depsipeptide extracted from a marine mushroom, has demonstrated anticancer activity, but the detailed molecular pathways it engages to induce apoptosis in cancer cells are not fully understood. However, one of its analogues has shown the ability to arrest the cell cycle at the G1 phase in human pancreatic cancer cell lines CD18 and ASPC-1. This cell cycle arrest hampers cancer cell proliferation and is a potential mechanism underlying its anticancer effect. Cyclooxazoline, another marine-derived peptide, has displayed the ability to

halt the cell cycle of HL-60 leukemia cells at the G2 or M phase. Additionally, it has shown the ability to inhibit cytokines, which are molecules involved in cell signaling and immune responses [12]. These activities may contribute to its potential to induce apoptosis in cancer cells, but the exact targets and pathways involved require further investigation. Viranamides A-C, a group of three linear tripeptides extracted from the ascidian Diplosoma virens, have demonstrated cytotoxic properties. Studies have shown that these peptides act as topoisomerase II inhibitors. Topoisomerases are enzymes involved in the regulation of DNA topology, and inhibiting their function can lead to DNA damage and cell death. The inhibition of topoisomerase II by viranamides likely contributes to their cytotoxic effects and potential for inducing apoptosis in cancer cells. While the anticancer potential of these marine peptides is promising, more research is needed to fully understand their specific mechanisms of action and identify their molecular targets. These studies will be crucial for the development of targeted therapies and the utilization of these peptides as potential agents in cancer treatment [13]. Continued investigation and exploration of marine peptides may uncover valuable insights that can lead to the development of novel and effective anticancer drugs in the future.

Peptides affecting the alignment between microtubules and tubulins

Microtubules are intracellular organelles made of monomeric protein units called tubulin. These organelles play several essential roles, including the separation of chromosomes, maintaining the cell's shape, and facilitating the displacement, movement, and distribution of organelles within the cell. Drugs that affect the balance between microtubules and their constituent tubulins, specifically those targeting the polymerization and depolymerization of microtubules, are considered a type of anticancer medication. Some compounds with the ability to bind to tubulins are important in medicine and oncology and have been widely studied. Among these compounds are vinca alkaloids, such as vincristine and vinblastine, which inhibit cell division by attaching to tubulins and preventing the polymerization of microtubule strands and the formation of the division spindle. This mode of action has also been observed in other natural substances. Therefore, there is a strong need to develop the synthesis of natural anti-mitotic analogs that, like vinca alkaloids and toxins, interact with tubulins and inhibit their polymerization [14]. Dolastatin 10, a linear pentapeptide consisting of several different amino acid subunits, was extracted from the marine mollusk Dolabella auricularia. They are one of the mollusk class members with the most potential for producing peptides. Bai and his colleagues reported that dolastatin 10 inhibits the growth of L1210 leukemia cells in the culture medium. Preliminary studies showed that the use of dolastatin 10 in high concentrations causes the formation of a dense mass of tubulins, preventing the assembly of tubulins into microtubules. This action is achieved through GTP hydrolysis. A tripeptide component of dolastatin 10 effectively inhibits tubulin polymerization and induces GTP hydrolysis [15]. It is not known whether this tripeptide inhibits the binding of vincristine to tubulins or inhibits nucleotide exchange. Vitilevuamide B is a 13-amino acid peptide extracted from two ascidian plants named Didemnum cuculiferum and Polysyncranton lithostrotum. Vitilevuamide has a highly positive effect on inhibiting the polymerization of tubulins. It has been proven that vitilevuamide exhibits non-competitive inhibition when binding to tubulins, similar to vinblastine. Furthermore, vitilevuamide stabilizes the binding of colchicine to tubulins, effectively preventing tubulin polymerization. Other peptides derived from marine sources, such as Diazonamide A, Scleritodermin A, Hemiasterlin, Desmethoxymajusculamide C, and Milnamide D, have also demonstrated the potential to inhibit tubulin polymerization in various cancer cells. Diazonamide A is a cytotoxic peptide extracted from the sea ascidian Diazona angulata, while Scleritodermin A is a novel cyclic peptide obtained from the sponge Scleritoderma nodosum. In laboratory conditions, this peptide exhibits cytotoxic properties against human tumor cells and effectively inhibits the polymerization of tubulins. Hemiasterlin is a natural tripeptide extracted from the sea sponges Auletta and Siphonochalina sp. [15]. By binding to natural dynamic microtubules, it disrupts and causes the depolymerization of microtubules. One of the analogs of hemiasterlin, known as HTI-286, not only inhibits tubulin

polymerization but also induces the destruction of microtubules. HTI-286 is utilized as a drug with the potential to inhibit multicellularity, along with several other drugs classified as anti-microtubule agents. Desmetoxymajusqualamide C is a novel cyclic depsipeptide obtained from the cyanobacterium Lyngbya majuscule. Its role in combating HCT-116 human colon cancer cells has been demonstrated by its ability to disrupt the microtubule network effectively.

Angiogenesis inhibitory peptides

Angiogenesis is a process during which new blood vessels are formed. This process involves a series of changes, including vascularization instability, endothelial cell proliferation, displacement, and the formation of new blood vessels. Vascularization plays a critical role in the growth, development, and mobility (metastasis) of most cancerous tumors. The endothelial growth factor (VEGF) and its receptor VEGFR-2 (Flk-1/KDR) are key players in the vascularization of tumors. Inhibiting the VEGF-VEGFR-2 pathway and its intracellular signaling can potentially hinder tumor growth. These signaling pathways involve VEGF induction, extracellular phosphorylation, ERK1/2-dependent signals, protein kinase B serine/threonine protein kinase family (Akt), and hypoxia-inducible factor alpha (HIF1α) [16].

Neovastat (AE-941) is a compound extracted from shark cartilage, specifically from the cartilage of the shark species Squalus acanthias. This compound exhibits direct inhibitory effects on the growth of cancer cells and impedes vascularization. Researchers led by Lee have discovered that Neovastat modifies and inhibits both VEGF and the HIF2 alpha pathway. Furthermore, novel linear polypeptides with a molecular weight of 15,500, extracted from the shark cartilage Prionace glauca, have demonstrated potential anti-angiogenic activity. These polypeptides show promise in inhibiting the formation of new blood vessels [17]. Another compound, mycothiazole, is a combination of polyketide-peptide that hinders HIF1 hypoxic signaling in tumor cells, which is a HIF1-dependent target of VEGF gene expression. Studies have revealed that mycothiazole selectively disrupts mitochondrial respiration in the NADH ubiquinone oxidoreductase complex.

Peptides with anti-tumorigenic activity with unknown mechanisms

There are numerous peptides, such as patellamides, that have been found to inhibit tumors through unknown mechanisms, likely involving cytotoxic induction. Due to the complexity of their actions, an exact mechanism for their anti-tumor activity cannot be provided at present. Many peptides, including Styelin D, Eusynstyelamid, Lissoclinamides, botryllamides, and Mollamides, have been extracted from ascidians and show cytotoxic potential, but the specific mechanisms of their actions have not been fully elucidated [18]. Acetylin D is an antimicrobial peptide derived from the blood cells of the ascidian Lissoclinum patella, and it exhibits cytotoxic activity against cancer cells. Several marine peptides have been identified for their anti-tumor activity, each targeting different objectives. For instance, Statin 10 not only inhibits the bundling of microtubules but also induces apoptosis by reducing the level of Bcl-2 and increasing the expression of p53. On the other hand, the mechanism of action for Aplidin involves multiple pathways, including inducing cell cycle arrest, inhibiting protein synthesis, and displaying anti-angiogenic activity.

Medicinal applications and perspectives of peptides derived from marine organisms with anticancer potential

Currently, the number of natural products is on the rise; however, only a very small fraction of these compounds are commercially available. Among the vast number of peptides identified from marine organisms, only a limited few have been extensively studied in clinical trials, which will be further explored in the article by Mohabi et al. published in 2014. Some of these peptides have been introduced as antitumor drugs following successful clinical trials that demonstrated their efficacy. For example, Cemadotin, a peptide derived from a marine mollusk, and Aplidine, a potent apoptosis-inducing depsipeptide extracted from Aplidium albicans tunicate, are currently undergoing phase II clinical trials. Additionally, Kahalalide F, which has shown promising anti-tumor activity, is currently in phase III clinical trials for the treatment of lung, prostate, and skin cancer [4]. **Figure 1** shows the structure of Kahalalide F. Various factors have limited the extensive

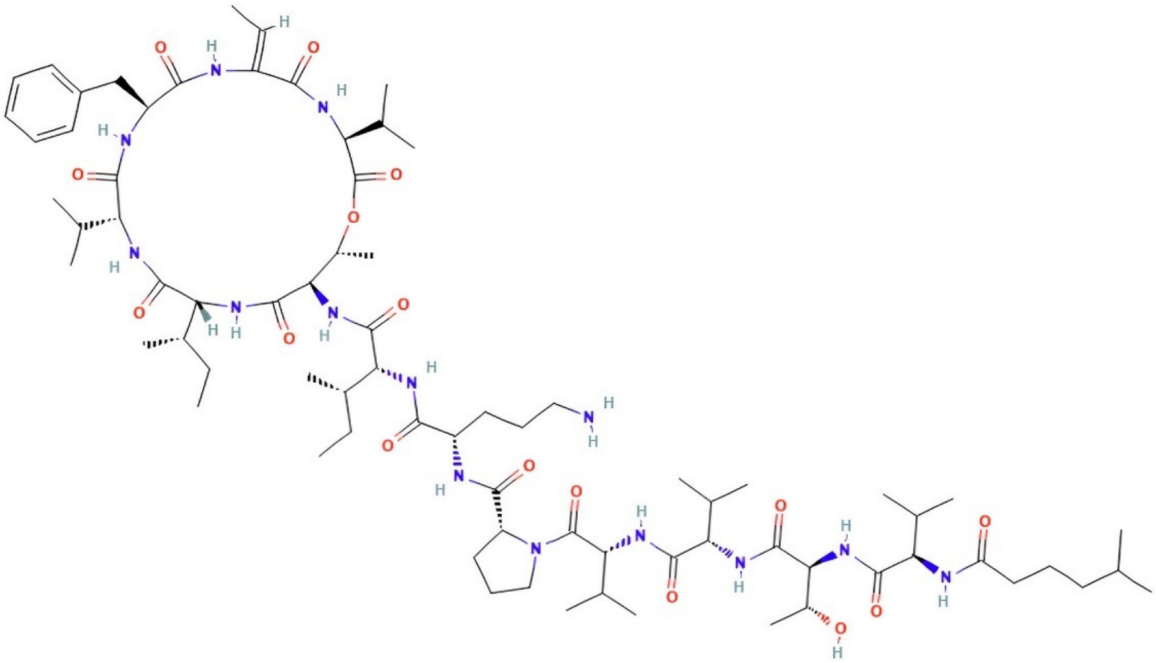

Figure 1. The structure of Kahalalide F.

research on bioactive peptides from marine organisms. These factors include the scarcity of sufficient compound quantities, challenges related to accessing the sources of samples, difficulties in isolation and purification methods, and ecological considerations. Nevertheless, ongoing research continues to unveil the potential of marine peptides in various therapeutic applications. Indeed, chemical synthesis plays a crucial role in determining the structure of marine peptides [1]. However, it can be challenging to synthesize sufficient amounts of these compounds, posing a problem in studying their biological activities. Furthermore, conformational issues have been found to significantly influence the biological activity of these molecules. An alternative approach to obtaining bioactive compounds with anticancer properties is through the enzymatic hydrolysis of marine proteins. Peptides derived from this process have demonstrated antioxidant and antiproliferative activities [19]. By utilizing specific enzymes, it becomes possible to select precise cleavage sites in the protein sequence, which can further influence the biological activity of the resulting peptide. Nonetheless, more research is necessary to fully elucidate the structures of bioactive marine peptides and to determine their specific types of activity, including how they interact with the cancer cell cycle. Integrating genomics with biosynthesis may prove to be a promising strategy for efficiently producing marine natural peptides and advancing their potential therapeutic applications. This integrated approach could open new avenues for harnessing the potential of marine peptides in combating various diseases, including cancer. Progress in the fields of genomics, proteomics, and metabolomics can have a significant impact on the identification and production of peptides as anti-cancer factors. Finding the DNA sequences that encode bioactive peptides will be a crucial achievement for the synthesis of these compounds.

Conclusion

The future of marine bioactive peptides research looks promising, with ongoing efforts aimed at fully elucidating their mechanisms of action and optimizing their therapeutic efficacy. Advances in genomics and proteomics are expected to enhance peptide identification and synthesis, potentially leading to the development of novel anticancer drugs. Continued exploration of marine peptides underscores their significance as valuable assets in the

fight against cancer, offering hope for improved treatment outcomes and enhanced patient well-being.

Disclosure of conflict of interest

None.

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