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The Potential of Jellyfish in Cancer Therapeutics

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Abstract. Conventional cancer treatments (radiotherapy, chemotherapy, surgery) often cause toxic side effects, and their efficacy is limited by tumor microenvironment heterogeneity. Combining natural bioactive compounds with conventional therapy has emerged as a promising strategy to enhance treatment outcomes. Jellyfish-derived compounds, especially venom and collagen, show notable anti-cancer potential. Jellyfish venom contains pore-forming toxins that trigger apoptotic and necroptotic pathways, suppressing proliferation of multiple cancer cell lines. Jellyfish collagen offers high biocompatibility and low allergenicity, regulating immune responses and inhibiting tumor angiogenesis to improve therapeutic responses. Additionally, jellyfish fluorescent proteins aid tumor localization and distribution tracking in oncological research. Despite these advantages, clinical translation faces challenges: key anti-tumor toxins remain unidentified, dosage control is imprecise, anti-proliferative effects vary, and jellyfish exploitation poses ecological risks. Overall, jellyfish-derived compounds hold great potential as adjunct cancer therapies. Future work should focus on isolating core anti-tumor toxins, optimizing administration, and advancing clinical trials to enable standardized clinical application.

Keywords: Nature compounds, crude venom, collagen, cytotoxicity, apoptotic pathways

1. Introduction

Cancer treatment is a growing area of research, with the improvement of diagnostic methods and medical equipment. Currently, the main treatment methods of cancer are surgery, radiotherapy, and chemotherapy [1]. However, these conventional methods have toxic side effects. For example, chemotherapy can result in anemia, vomiting, inflammation and infections, and neurotoxicity [2]. Thus, current research is working on developing less-toxic methods of treatment that also increase the effectiveness of treating the cancer. Some current trends include combined therapies, targeted therapies, immunotherapies, and nanotherapies [1]. One of the most notable ones is combining natural compounds with radiotherapy and chemotherapy. These natural compounds, usually extracted from plants or marine species, have antitoxic and antioxidative effects that help to promote apoptosis, inhibit angiogenesis, induce cell cycle arrest, and prevent tumor metastasis [1]. Furthermore, natural compounds have fewer side effects, and are biodegradable, biocompatible, and more accessible compared to synthetic drugs [3]. Even more, natural compounds can be made into individual drugs to serve as alternative methods for cancer treatment. As of 2022, there are four marine-derived drugs that have been approved by the FDA. One of these drugs is Brentuximab-

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vedotin, extracted from sea hare Dollabella auricularia or from cyanobacteria [4]. This drug works by blocking the cell cycle from proceeding to the M stage, thereby inducing apoptosis. On February 11th, 2025, Brentuximab-vedotin was approved by the U.S. Food and Drug Administration (FDA) in combined therapies with lenalidomide and rituximab for treating recurring cases of large B-cell lymphoma. This reflects the potential of natural products as individual drugs and in combined therapy to reduce toxic side effects and improve patient outcomes.

Many marine organisms have bioactive compounds with anti-cancer effects. Jellyfish are abundant marine invertebrates currently under active biomedical research. This review will focus on jellyfish and their applications in the biomedical field for cancer treatment. Crude venom is a secondary metabolite found in jellyfish that inhibits the proliferation of cancer cells [5]. Jellyfish also contain collagen [5]. Jellyfish collagen is compatible with human collagen, and thus can be used in the research on tissue regeneration and inflammatory and immune responses [5]. Current research on jellyfish and their natural products can provide important insights on how natural products can be combined with other therapies to improve patient outcomes.

2. Jellyfish morphology and venom composition

Jellyfish belong to the phylum Cnidaria and the subphylum Medusozoa. Jellyfish are diploblastic organisms, comprised of two distinct cell layers: the outer epidermis and the inner gastrodermis. A defining feature of cnidarians, including jellyfish, is the presence of specialized stinging cells termed nematocysts. Nematocysts, encapsulated within cnidocysts, are densely distributed on the oral arms and body surface of jellyfish. They play important roles in biological functions such as prey capture, defense against predators, and other physiological processes.

The three components of the nematocyst are the operculum, capsule and threat. When there is a stimulus, the thread inside the capsule will quickly extend out and then penetrate the outside of the victim to deliver venom. Despite extensive research, the complete components of jellyfish venom remain unknown. Only a few bioactive substances have been identified so far. The first type of component is matrix metalloproteinases (MMPs), which break down the extracellular matrix [6]. MMPs are responsible for inflammatory responses, skin damage, and secondary infections [6]. They have been also linked to the growth of tumors, since they contribute to extracellular matrix (ECM) remodeling [7].

Another component of jellyfish venom are pore-forming toxins [6]. These enzymes have high cytotoxicity and lethality, able to perforate the cell membrane directly [6]. Other prominent groups of components include phospholipase A2 and serine protease; both have been shown to induce inflammatory responses and other pathological symptoms in venoms [6]. Components of jellyfish venom trigger apoptosis and necroptosis, two types of programmed cell death [8]. Both routes lead to programmed cell death, but they are different in terms of molecular mechanisms; apoptosis keeps the membrane of the cell intact, whereas necroptosis causes membrane disruption [9].

Chironex fleckeri is a species of box jellyfish and one of the most poisonous animals in the world. This species is an ideal model for studying the molecular mechanisms of venom-induced cell death [8]. Researchers inhibit specific components of the necroptosis and apoptosis pathways to investigate how these programmed cell death pathways contribute to the toxicity of Chironex fleckeri venom [8]. Inhibition of MLKL (mixed lineage kinase domain-like protein), a key component of necroptosis, reduced venom-induced cytotoxicity significantly [8]. MLKL inhibition was combined with caspase (a core apoptotic effector) inhibition to strengthen the anti-venom effect synergistically, and thus both necroptosis and apoptosis are thought to contribute to the toxicity induced by Chironex fleckeri venom [8]. Cassiopea andromeda and Catostylus mosaicus are other

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jellyfish species with similar cytotoxic mechanisms [10]. Jellyfish venom can induce programmed cell death, and thus is now being investigated as a new way to treat cancer.

3. Jellyfish collagen

Collagen is the most abundant structural protein found in animal tissue, responsible for mechanical strength and found in connective tissue [11]. A big part of the extracellular matrix is made up of collagen [11]. The basic structure of collagen has repeating Gly-X-Y units, and X and Y are mostly proline (Pro) and hydroxyproline (Hyp) [11]. This primary sequence folds into an α-helix and then forms a triple-helix tertiary structure [11]. Several triple helices are further organized into collagen fibers to provide support for the tissue [11]. The mesoglea is a gelatinous layer between the epidermis and gastrodermis of jellyfish, and it mainly consists of ECM components [11]. This layer maintains body structure by providing a support for cell adhesion and movement [11]. Collagen is also important for tissue regeneration and wound healing in jellyfish [11].

Jellyfish collagen is structurally similar to the types I and II collagen in vertebrates; however, jellyfish collagen has a different peptide sequence and a lower melting point [11]. Jellyfish collagen can also bolster the immune system and is free of the IgE-mediated allergic response [11]. Currently, most of the commercial collagen products are derived from mammals [11]. Jellyfish-derived collagen can be used as a safer option: they have good biocompatibility and a low risk of allergic reactions and zoonotic disease transmission [11].

Jellyfish collagen shows great potential for improving the effectiveness of cancer treatment. Collagen from Rhopilema pulmo, a kind of jellyfish that lives in the Mediterranean Sea, has been shown to regulate immune function and inhibit tumor angiogenesis [11]. This suggests the potential applications of jellyfish collagen in improving cancer therapeutic outcomes [11].

4. Anticancer effects of jellyfish venom on cancer cells

Accumulating evidence indicates that jellyfish venom exerts significant antitumor effects by initiating apoptotic signaling pathways in cancer cells and inhibiting their proliferation, thereby highlighting its potential as a novel antitumor agent.

4.1. Apoptotic pathways: intrinsic and extrinsic mechanisms

Caspases, a family of cysteine proteases, are crucial roles in the initiation and execution of programmed cell death [4]. The two pathways for activating apoptosis are the intrinsic (mitochondrial) pathway and the extrinsic (death-receptor) pathway. Both pathways activate initiator caspases, which then activate effector caspases (e.g., caspase-3 and caspase-7) to cleave intercellular components [12]. This results in DNA fragmentation, membrane blebbing, cell shrinkage and the breakdown of cells into membrane-enclosed spheres called apoptotic bodies [12].

The extrinsic pathway is triggered when a death ligand (e.g., tumour necrosis factor [TNF] or Fas ligand) binds to a death receptor on the cell surface [13]. Ligand binding induces the trimerization of the death receptor and subsequently recruits adaptor proteins at the cytoplasmic end [13]. Two essential adaptor proteins are Fas-associated death domain (FADD) and TNF receptor-associated death domain (TRADD) [13]. FADD recruits and activates procaspase-8 to form the death-inducing signaling complex (DISC) [13]. TRADD is also a protein that recruits the receptor-interacting protein kinase 1 (RIPK1) to form the ripoptosome complex [13]. Both complexes activate caspase-8, an initiator caspase that subsequently activates caspases-3 and -7 [12]. If RIPKI is not cleaved by

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caspase-8, RIPK3 will be activated, initiating the necroptosis pathway [13]. Crosstalk between the apoptotic and necroptotic pathways indicates that these two mechanisms work together to cause cell death in response to jellyfish venom; this is relevant for understanding jellyfish cytotoxicity and how it can be applied in cancer therapy.

The intrinsic pathway is activated by the internal stress signals that occur in the cell microenvironment, such as DNA damage, reactive oxygen species (ROS) accumlation, growth factor deprivation, endoplasmic reticulum (ER) stress and other disruptions [12]. These stress signals lead to mitochondrial outer membrane permeabilization (MOMP) [12]. Many mitochondrial proteins leaked out into the cytoplasm during MOMP [12]. One such protein is cytochrome c [12]. Cytochrome c binds to the scaffold protein Apaf-1 to form an apoptosome, and this wheel-shaped complex activates caspase-9, which in turn initiates the caspase cascade of caspases-3 and -7 [12]. Smac/Diablo is another protein released during MOMP that binds to cytoplasmic inhibitors of apoptosis proteins (IAP) and thus activates caspases [12].

Proteins of the BCL-2 family tightly regulate MOMP [12]. Based on the apoptotic function, proteins in the BCL-2 family are divided into three types [12]. The first group is MOMP-initiating proteins (e.g., BAX and BAK) that increase the permeability of the mitochondrial membrane [12]. The second group includes anti-apoptotic proteins (e.g., BCL-2, BCL-XL, BCL-W and MCL-1) [12]. These proteins inhibit BAX and BAK to prevent MOMP [12]. The third group of proteins (e.g., BIM, BID, BAD, PUMA and NOXA) have a single BH3 domain and bind to anti-apoptotic proteins to inhibits their function [12].

Some mutations in cancer cells allow them to evade apoptosis and divide uncontrollably. A few studies have found that caspase inactivation is required for the formation of cancer cells [9]. Cancer cells generally have an increased expression of anti-apoptotic proteins (e.g., BCL-2) [10]. Pro-apoptotic genes are also increased through transcription and translation alteration [10]. Furthermore, BCL-2 suppresses the expression of the tumor-suppressing gene p53 and reduces the activity of cell cycle regulation, DNA damage repair and apoptosis.

4.2. Jellyfish venom-induced apoptosis in various cancer cell lines

Jellyfish venom has been shown to induce apoptosis in a variety of cancer cell lines, with distinct species-specific and cell type-specific effects. In a study investigating the antitumor activity of Cassiopea andromeda and Catostylus mosaicus venom on human adenocarcinoma A549 cells, both venoms suppressed cell proliferation [10]. The dosage for optimal suppressive effects and minimized toxicity on human foreskin fibroblast (HFF) cells was determined to be 2mg/mL and 10mg/mL, respectively (three independent experiments, $P<0.05$) [1, 10]. Further analysis found that C. andromeda and C. mosaicus contained five and six antitumor compounds, respectively [10]. Treating cancer cells with the venom extracted increased the concentration of pro-apoptotic compounds (e.g., BAX, p53, cleaved caspase-3, cleaved caspase-8, and cleaved caspase-9), and decreased the concentration of anti-apoptotic compounds (e.g., BCL-2) and inactivated forms of caspases [10].

One major bioactive component found in C. mosaicus venom is citrinin [10]. Citrinin activates p21-activated protein kinase 2 (PAK2)-dependent signaling pathways, caspase-3, and caspase-9 [10]. As a result, there is ROS accumulation [10]. In addition, citrinin has high affinity for FADD, which activates caspase-8 [10]. These findings indicate that citrinin can activate both intrinsic and extrinsic apoptotic pathways in human cancer cells [10]. Other shared antitumor compounds found in C. andromeda and C. mosaicus venoms include 9,12-octadecadienoic acid methyl ester, heptadecane,2,6,10,14-tetramethylheptadecane and batilol [10]. Similar to C. andromeda and C.

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mosaicus venom, jellyfish venom extracted from C. tuberculata oral arms and whole C. marsupialis jellyfish inhibit the proliferation of lung adenocarcinoma A549 cells [14, 15]. Thus, venom extracts from other jellyfish species can exhibit similar antitumor activity, communicating the broad potential of jellyfish venom in cancer therapy.

Jellyfish venom also exerts selective antitumor effects in other cancer cell types. Venom from C. tuberculata and C. marsupialis also exhibited antiproliferative effects on melanoma A2058 cells [15]. In another study, researchers investigate the effect of C. andromeda venom on mitochondria in breast cancer cells [3]. The venom extract caused mitochondrial dysfunction; consequently, there was a drop in mitochondrial membrane potential (MMP), an increase in ROS, cytochrome c release, mitochondrial swelling, and a reduction in succinate dehydrogenase activity [3]. These internal signals finally triggered the intrinsic pathway of apoptosis [3]. Unexpectedly, only the cancer cells showed cytotoxicity. This demonstrates the potential of using bioactive compounds found in jellyfish venom to decrease the toxic side effects of conventional cancer treatment methods. Rhizostome jellyfish has also been found to inhibit the proliferation of MCF-7 breast cancer cells [3]. Enzymes, neurotoxins, pore-forming toxins and other components are thought to be the cause of cytotoxicity in jellyfish venom by inhibiting the adhesion and proliferation of cancer cells [3].

Anticancer activities of Nemopilema nomurai venom against HepG2 liver cancer cells have also been investigated. From research, it is found that the proportion of cancer cell death increases with an increase in both time and dose of venom administration [3]. N. nomurai venom reduced cell cycle progression, inhibited tumor cell proliferation, apoptosis, migration and invasion of tumors, and angiogenesis [3]. Thus, the jellyfish venom has the ability to target multiple oncogenic pathways. N. nomurai also has cytotoxicity in HCT116 colon cancer cells [3]. Venom affects the activity of mitogen-activated protein kinases (MAPKs) and caspases, required for cell cycle progression and apoptosis [3]. Another study shows that N. nomurai venom inhibits the proliferation of HT-29 colorectal cancer cells, while normal cells were not affected [3]. It further confirms the selective antitumor activity of jellyfish venom.

5. Advantages, limitations and future research directions

Jellyfish-derived bioactive substances have excellent prospects for advancing cancer therapy research. They provide insights on how cancer cells proliferate at the molecular level and how marine natural products can be used to enhance the efficacy of the current treatments. In addition to jellyfish, the bioactive components in sea urchins and sea anemones have also been investigated for their effects on cancer cell proliferation [15]. This emphasizes the broader significance of marine cnidarians in oncology research.

However, some defects and safety problems still exist in the application of jellyfish-derived bioactive substances for cancer treatment. First, it is difficult to control the jellyfish venom dosage. This is necessary to maximize cytotoxicity, while preventing an overdose that would be lethal. For example, in a preclinical study investigating the impact of C. andromeda venom on rats, multiple alterations occurred [10]. The rat experienced skin necrosis, hemorrhage, rectal and ocular bleeding, and behavioral changes (e.g., increased aggression) [10]. Therefore, although jellyfish venom has anti-cancer properties, it is important to precisely control the venom dosage. However, specific components of jellyfish venom are difficult to identify, and it is challenging to identify the optimal dosage to give to patients.

Furthermore, antitumor effect of jellyfish venom is not directly due to toxicity. Venom from the oral arms of C. tuberculata has shown good anti-proliferative effects on cancer cells, though it is not toxic to normal cells [15]. In contrast, highly toxic venom from C. marsupialis has shown negative

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effects on healthy human cells and is not suitable for cancer treatment [15]. Therefore, more research is needed to discover which jellyfish species has effective bioactive compounds for cancer treatment.

Jellyfish should be used sustainably so that harm to the environment can be avoided. Jellyfish are abundant and form blooms that disrupt power plant operations and fishing activities [15]. In addition, they can be obtained relatively easily as bycatch from commercial fishing activities [15]. However, jellyfish are important members of aquatic ecosystems. An exploitation in jellyfish could negatively affect aquatic organisms, depleting fish populations as well. Additionally, the jellyfish population changes with the seasons, so the source of bioactive compounds may be inconsistent.

At present, research on bioactive compounds from jellyfish venom is still in the preclinical stage, and most of the studies so far have only employed in vitro cell experiments and in vivo animal models to examine their antitumor effects [3, 10]. Future research should prioritize on the identification, isolation, and purification of specific antitumor compounds found in jellyfish venom. Furthermore, dosage control techniques should be optimized, and experiments should work to large-scale in vivo studies and clinical trials. This validates the safety and efficacy of jellyfish bioactive compounds for cancer treatment.

6. Conclusion

This paper summarizes the research progress of jellyfish-derived bioactive substances in cancer therapy. Jellyfish venom and collagen show remarkable antitumor potential, with venom exerting selective cytotoxicity on various cancer cells via apoptotic and necroptotic pathways, and collagen providing a safer alternative to mammalian collagen with immunomodulatory effects. Despite these merits, clinical translation is hindered by incomplete venom component characterization, dosage control challenges, ecological concerns, and insufficient preclinical/clinical data. Future research should focus on isolating specific antitumor molecules, optimizing delivery systems, and conducting rigorous trials to unlock jellyfish's potential as a marine resource for low-toxicity cancer therapies.

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