# Marine Products in Colorectal and Pancreatic Cancers Treatment

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Gastrointestinal cancer refers to malignancy of the accessory organs of digestion, and it includes colorectal cancer (CRC) and pancreatic cancer (PC). Worldwide, CRC is the second most common cancer among women and the third most common among men. PC has a poor prognosis and high mortality, with 5-year relative survival of approximately 11.5%. Conventional chemotherapy treatments for these cancers are limited due to severe side effects and the development of drug resistance. Therefore, there is an urgent need to develop new and safe drugs for effective treatment of PC and CRC. Historically, natural sources—plants in particular—have played a dominant role in traditional medicine used to treat a wide spectrum of diseases. In recent decades, marine natural products (MNPs) have shown great potential as drugs, but drug leads for treating various types of cancer, including CRC and PC, are scarce. To date, marine-based drugs have been used against leukemia, metastatic breast cancer, soft tissue sarcoma, and ovarian cancer.

Keywords: marine natural products ; colon cancer ; pancreatic cancer

## 1. Introduction

Gastrointestinal cancer refers to malignant of accessory organs of digestion, and it includes colorectal cancer (CRC) and pancreatic cancer (PC). In 2020, 1.9 million new CRC cases and 0.9 million CRC deaths were estimated worldwide [1]. The CRC incidence is higher in developed countries; however, the number of cases is increasing in non-developed countries every year [2]. PC is a malignant tumor that usually occurs as a pancreatic adenocarcinoma. It has a poor prognosis and high mortality, with an estimated 5-year relative survival of 11.5% [3].

Cancer care usually requires teamwork by doctors in multiple disciplines who combine different types of treatments. Treatment options depend on several factors, including the type and stage of cancer, possible side effects, and overall health. The treatment options for CRC and PC are surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy [4]. Only about 20% of people diagnosed with PC are able to access surgery due to late stage diagnosis, at which point the disease has already spread. External beam radiation therapy is the type of therapy used most often to treat PC [5]. Medications are also given individually or as a cocktail as part of the treatment plan [5]. Drugs used in chemotherapy induce severe side effects that greatly affect the life quality of patients, including weakness, hair loss, nausea, vomiting, diarrhea, abdominal cramps, mouth sores, dry mouth, and numbness [6]. Therefore, there is an urgent need to identify new chemical targets and active compounds with higher selective potency or new cellular targets.

Natural products, which are chemical compounds produced by organisms, have been used for centuries as remedies for various illnesses. Since ancient times, humans have utilized natural products from various sources, such as plants, marine organisms, and microorganisms, for diverse applications.

## 2. Marine Natural Products (MNPs) with the Potential to Treat Cancer

MNPs are compounds isolated from marine microorganisms and phytoplankton, algae, sponges, mollusks, tunicates, echinoderms, mangroves, and others. Since the 1970s, marine organisms have played an important role in the discovery of novel biologically active compounds, and MNPs have become a source of bioactive secondary metabolites with the potential to treat diseases, including cancer [7][8][9].

The screening of 3019 compounds from the MNPs library identified that four compounds have potential therapeutic anticancer activity through the mammalian target of the rapamycin pathway (mTOR). mTOR regulates different cellular processes including cell growth and cell proliferation [10]. In addition, marine compounds such as glycosides, alkaloids, saponins, lipids, terpenes, ribose, steroids, xanthones, ethers, lignins, coumarins, carbazoles, azaphilones, nucleosides,

polyketides, and quinones have been shown to have high cytotoxic activities against 121 mammalian cancer cell lines including breast, colon, melanoma, lung and pancreatic human tumor cells [11].

Furthermore, recent studies investigated scalarine, a compound isolated from different marine sponges, and demonstrated that it can reduce the level of the receptor for advanced glycation end products (RAGE) and inhibit autophagy in human pancreatic cell lines (PANC-1 and MIA PaCa-2). RAGE has lately become a chemotherapeutic target for both treatment and chemoprevention. RAGE seems to be a key regulator of the inflammatory, stress, and survival pathways that contribute to PC carcinogenesis, chemotherapy resistance, increased proliferation, and a high risk of metastasis. It has been shown that PC tumors express RAGE, but not the surrounding epithelial tissues [12].

To date, MNPs from different marine species of sponges, tunicates, mollusks, and cyanobacteria have been approved as anti-cancer marine molecules, including Cytosar-U®, Depocyt®, Halaven®, Fludara®, Arranon®, Yondelis®, Adcetris®, Polivy®, Farydak®, Aplidine®, Zepzelca™, Blenrep™, Aidixi™, TIVDAK™, and PADCEV™ [13][14][15]. These drugs have several side effects including severe ones such as a fast or slow heart rate, difficulty breathing, high blood sugar (hyperglycemia), peripheral neuropathy, neutropenia, leukopenia, hypoesthesia, increased conjugated blood bilirubin, decrease in platelets (thrombocytopenia), low blood cell counts, infusion related reactions, and muscle pain (myalgia). In addition, several MNPs are currently being evaluated in different phases of human clinical trials [16][17]. In addition, recent in vitro, in vivo, and clinical studies have shown several marine compounds such as alkaloids, peptides, terpenoids, poly saccharides, and carotenoids have antitumor effects on CRC [18]. However, many MNPs are toxic and their use was terminated in clinical studies. Therefore, continued efforts in the field of marine drug discovery are expected to reveal more potent bioactive compounds with diverse mechanisms of action.

## 3. Mechanisms of Action of MNPs in CRC and PC

### 3.1. Induction of Apoptosis through Caspase Activation

Some MNPs were found to affect CRC and PC cells through caspase activation pathways. Caspases are protease enzymes that have essential roles in programmed cell death (apoptosis) [19]. Caspases-2, -3, -6, -7, -8, -9, and -10 are activated during apoptosis. Caspases-2, -8, -9, and -10 are called apical or upstream caspases, and are responsible for initiating caspase activation cascades. Caspases-3, -6, and -7 are called downstream caspases, and are responsible for the actual destruction of the cell during apoptosis [20]. During activation, apical caspases distribute death signals and activate downstream caspases in a cascade-like manner [21]. Downstream caspases then cause direct cellular structures disintegration, cellular metabolism disruption, cell death, inhibitory proteins inactivation, and additional destructive enzymes activation [22]. For example, marine sponge metabolites ilimaquinone and ethylsmenoquinone were found to activate caspase-3 and induce apoptosis via this pathway [23].

Many apoptosis-inducing stimuli activate caspases through one of the following three major pathways: (i) the mitochondrial pathway (intrinsic pathway), (ii) the death receptor pathway (extrinsic), and (iii) the cytotoxic T lymphocytes/natural killer cells (CTL/NK)-dependent pathway [20] (**Figure 1**).

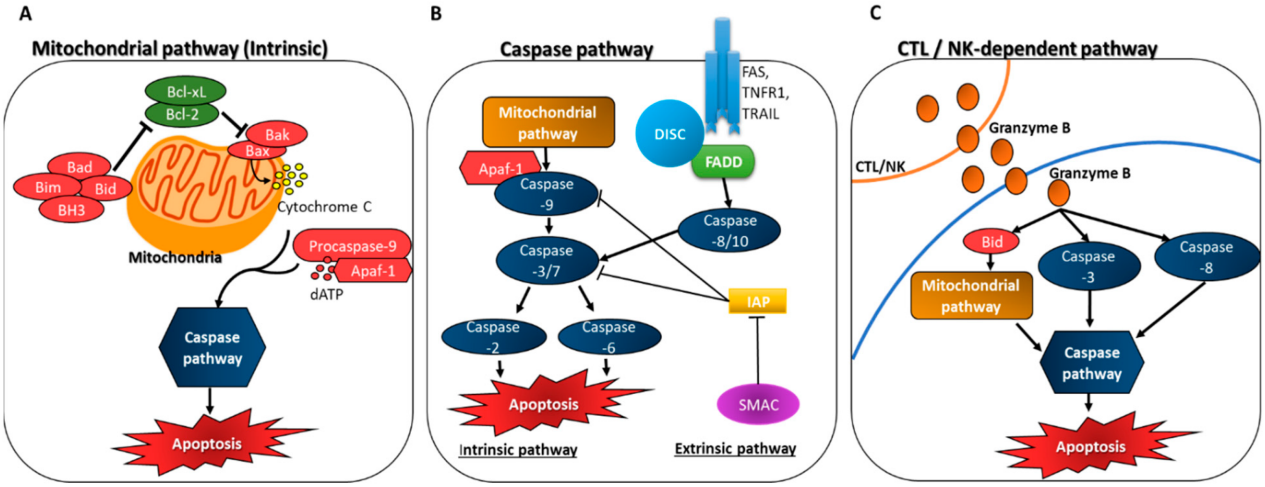


**Figure 1.** Three major pathways that induce stimuli that activate the caspase apoptosis pathway: (**A**) Mitochondrial pathway (intrinsic); (**B**) Caspase pathway; (**C**) CTL/NK dependent pathway. Bcl-extra-large (Bcl-xL); Bcl-2-associated X protein (Bax); Bcl-2-antagonist/killer (Bak); Bcl-2 associated agonist of cell death (Bad); Bcl-2 interacting mediator of cell death (Bim); Bcl-2 homology-3 (BH3); BH3-interacting domain death agonist (Bid); Apoptosis protease-activating factor-1

(Apaf-1); Deoxyadenosine triphosphate (dATP); Death-inducing signaling complex (DISC); FAS- associated death domain protein (FADD); TNF receptor 1 (TNFR1); TNF-related apoptosis-inducing ligand receptors (TRAIL); inhibitor of apoptosis protein (IAP); Second mitochondria-derived activator of caspases (SMAC); Cytotoxic T lymphocytes/natural killer cells (CTL/NK).

### 3.2. Inhibition of Anti-Apoptotic Factors

One mechanism of resistance to apoptotic stimuli in cancer cells involves the overexpression of the IAP family of proteins. IAPs include X-linked IAP (XIAP), cellular IAP-1 (cIAP-1), and cIAP-2 [24][25]. These proteins have been shown to prevent apoptosis by binding to caspases, including initiators and effectors, and thereby protecting them from cleavage and activation [25][26].

Kim et al. reported that the fucoidan extract from brown algae attenuated the levels of XIAP and survivin, which are members of the IAP family [27]. Additionally, Zhang et al. found that libertellenone-H (LH) isolated from Arctic marine fungi inhibits the thioredoxin (TRX) system, which leads to cellular stress and cell death in human PC cell lines [28]. The TRX system is expressed in all living cells and has a variety of biological functions related to cell proliferation and apoptosis. It also is a key part of the antioxidant system that defends against oxidative stress. Moreover, the TRX system plays critical roles in the immune response, virus infection, and cell death by interacting with the thioredoxin interacting protein [29]. The TRX system also helps tumor cells evade apoptosis by directly binding to the apoptosis signal regulating kinase and the tumor suppressor gene phosphatase and tensin homolog (PTEN) [30][31].

### 3.3. Interaction of MNPs with Tubulin to Cause Anti-Mitotic Activity

Microtubules are elements of the cytoskeleton and play important roles in many cellular functions, including intracellular transport, motility, morphogenesis, and cell division [32]. Microtubules are heterodimers composed of α-β subunits that assemble to form the protofilaments of the tube [33]. The polymerization and depolymerization of microtubules are critical processes for cell division machinery. Checchi et al. showed that disrupting these processes with microtubule binding drugs could be a useful tool to inhibit cell proliferation [34].

Leiodermatolide, a MNP isolated from a deep-water sponge, has a cytotoxic effect on human PC and CRC cells. It induces cell cycle arrest and apoptosis, and it affects the microtubules required for spindle formation and chromosome segregation [35]. Another compound, PM060184, isolated from the marine sponge *Lithoplocamia lithistoides* is considered to be a tubulin binding agent with potent anti-tumor activity [36].

### 3.4. Suppression of Cell Cycle Progression

The cell cycle is a four-stage process in which the cell increases in size (G1 stage), copies its DNA (S stage), prepares to divide (G2 stage), and undergoes mitosis (M stage). The cell cycle is controlled at three checkpoints. The integrity of the DNA is assessed at the G1, G2, and M checkpoints, and the cell cycle is regulated by a family of enzymes called the cyclin-dependent kinases (CDKs) [37].

### 3.5. The Role of NFκB and p53 in Apoptosis

NFκB is involved in the development of cancer. Wang et al. reported that it is constitutively activated in PC cells but not in normal cells [38]. Nakanishi and Toi found that the constitutive activation of NFκB induces anti-apoptotic genes and inhibits apoptosis [39]. The cytoplasmic factor IkappaB (IκB) binds to NFkB and inhibits its translocation to the nucleus. After translocation to the nucleus, NFkB binds to a specific promotor and regulates the transcription of many genes associated with oncogenesis and tumor progression. Several studies have shown that the inhibition of NFκB results in the induction of apoptosis in cancer cells [40][41][42]. Therefore, the inhibition of NFκB antagonizes the survival of cancer cells and induces apoptosis [39].

While NFκB is known to inhibit apoptosis, the transcription factor p53, a tumor suppressor gene, is an inducer of apoptosis. p53 plays a regulation or progression role in the cell cycle, apoptosis, and genomic stability through multiple mechanisms, including cell cycle arrest, the activation of DNA repair proteins, and induction of apoptosis [43]. p53 limits cell proliferation by the induction of transient G1 cell cycle arrest or apoptosis. The molecular explanation for the p53 mediated growth arrest response is based on its ability to act as a sequence-specific DNA binding transcription factor. p53 has several downstream target genes, such as p21, Mouse Double Minute 2 homolog (MDM2), Growth Arrest and DNA Damage Inducible Alpha (GADD45), cyclin G, and Bax, whose expression products act as regulators of various aspects of cell growth [44][45]. The activation of p53 negatively regulates the expression and NFκB activity of the RelA (p65) subunit [43].

### 3.6. Increased Intracellular ROS Accumulation and Induction of Apoptosis

Oxygen molecules are a diradicals and are not reactive compared to other molecules. However, incomplete oxygen reduction leads to the formation of more chemically reactive oxygen species (ROS), which include superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), and hydroxyl radical (radical OH). Due to their strong chemical reactivity, ROS have traditionally been thought to mediate only oxygen toxicity. ROS have been implicated in oxidative stress mediated pathology, as they are considered disruptive agents that can structurally and functionally affect macromolecules such as nucleic acids, proteins, and lipids [46]. Several studies found that the accumulation of ROS decreases mitochondrial membrane potential (MMP) and mitochondria depolarization. The presence of ROS leads to cell cycle arrest at the G2/M phase, followed by the accumulation of DNA damage and induction of apoptosis [47][48]. Other researchers reported that marine extracts from nudibranchs, brown algae, and Arctic fungi trigger the intracellular accumulation of ROS in cancer cells originated from human CRC and PC, leading to apoptosis [28][49][50]. LH, a pimarane diterpenoid isolated from the Arctic marine fungus *Eutypella* sp. D-1, has effective cytotoxicity against a range of cancer cells and induces ROS accumulation. Further, Zhang et al. showed that LH exerts anti-proliferative activity against four PC cell lines in a dose-dependent manner, with IC50 values of 3.21, 0.67, 2.78, and 5.53 µM in PANC-1, SW1990, AsPC-1, and BxPC-3, respectively, after 48 h of treatment. In contrast, the IC50 value of LH for a normal pancreatic cell lines (HPDE6-C7) is 10.86 µM [28]. The clear difference between the IC50 value of LH between cancer cells and normal cells highlights LH as a potential drug lead.

## 4. Conclusions

MNPs have great potential as new compounds that can assist in the prevention and treatment of cancer, but extensive exploration is needed. Over the past 50 years, many MNPs with beneficial effects on the prevention and treatment of various types of cancer have been reported. For example, cytarabine, eribulin mesylate, brentuximab vedotin, and trabectidine are marine-based drugs used against leukemia, metastatic breast cancer, soft tissue sarcoma, and ovarian cancer [51][52]. MNPs compounds have different activities including the inhibition of the transformation of normal cells into tumor cells, halting tumor cell growth and microtumors development, and inducing apoptosis. A higher consumption of sea food is suggested as a promising strategy to prevent cancer [53][54]. Many marine edible organisms contain lipids enriched by polyunsaturated fatty acids (PUFAs), such as ω-3 fatty acids that have been shown in many experimental studies to suppress most forms of tumor development, including breast, colon, prostate, liver, and pancreatic tumors [55][56][57].

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