Volume 07, Issue 04 (July-August 2024), PP 165-184 www.ijmsdr.org
ISSN: 2581-902X

International Journal of Medical Science and Dental Research

Marine-Derived Compounds for the Prevention and Treatment of Colorectal Cancer-A Review

M V Dharani Priya[1], R Swetha Harini[1], Thumma Sweta Tejaswi[1], D Ramya Madhuri[1], K Alekhya[1], P.Suvarnalatha Devi[1]*

[1]*Department of Applied Microbiology, Sri Padmavati Mahila Visvavidyalayam, Tirupati-517502, Andhra Pradesh.*

Abstract:
Marine microorganisms, animals, and plants are the best sources to find bioactive compounds with an assortment of pharmacological characteristics, encompassing the capacity to absorb free radicals and have antitumor, antimicrobial, analgesic, neuroprotective, and immunomodulatory effects. The need for affordable, safe, and effective medications is increasing due to the world's population growth, and marine drugs offer a substitute supply. A widespread type of cancer to be diagnosed globally is colon cancer where a common pharmacological treatment is chemotherapy which may not be suitable for individuals due to its adverse consequences.Natural marine compounds are plentiful and have special chemical structures, which make them widely used in anticancer treatments. This review lists the secondary metabolites such as alkaloids, peptides, terpenes, etc extracted from marine actinomycetes and fungi as cutting-edge substitutes for cytotoxic substances directed opposing the malignancy cell lines from colon cancer Caco-2, RKO, HCT15, HT29, and HCT116. The in-vitro research provided an overview of the many compounds from marine origins and their pharmacological actions. According to tumor inhibition, hepatotoxicity, and nephrotoxicity, the in vivo studies assessed the anticancer properties of marine substances on mice modeled by colorectal cancer. The primary chemical categories and methods of operation of the clinical medications that possess received full and clinical clearance for their anti-cancer properties in marine environments were compiled from the clinical studies.

Keywords: *Actinomycetes, apoptosis, colorectal cancer, marine fungi, secondary metabolites, tumor.*

I. INTRODUCTION

Cancer incidence is expected to rise, making it one of the world's leading causes of death to roughly 68% by 2030[1]. Tumor formation activation, damage to DNA and abnormal DNA repair processes, destroyed suppressor of tumorsactivity, and cancer progresses due to factors such as angiogenesis and improved cell survival through metastasis[2], [3].Worldwide morbidity and mortality are primarily caused by cancer, with an approximate annual number of 18.1 million new cases[4]. Men are most likely to develop Lung, stomach, liver,

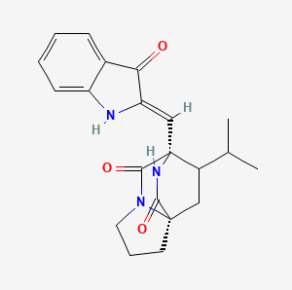
colon, and prostate cancers. In contrast, cervical, thyroid, breast, lung, and colorectal cancers are more common in women, while children are more likely to develop blood cancer. [5], [6]. Clinical surgery and chemotherapy: drug toxicity and resistance have resulted in a poor prognosis for colon cancer, a cancerous growth that has a significant fatality rate. Therefore, it is crucial and necessary to find safer and more effective drugs for clinical studies [7]. Throughout the globe, colorectal cancer (CRC) ranks second regarding mortality but third in incidence. An estimated colorectal cancer (CRC) statistic for 2020 showed 1.9 million new cases (including anus) and deaths of 935,000.; these figures represent roughly one in ten cases and deaths of cancer [8]. Most patients with stage I and II colon cancer (84%), however, get a colectomy without chemotherapy, while roughly two-thirds of patients with stage III colon cancer (and a small number of patients with stage II illness) have adjuvant chemotherapy to lower their chance of recurrence. Periodic or persistent diarrhea, along with intestinal dysfunction such as increased frequency of stools, radiation proctitis, perianal discomfort, and incontinence, are frequently associated with these treatments [9].Since 1960, pharmacology has utilized natural marine products as study subjects due to their unique biofunctional characteristics and extensive chemical diversity. These compounds are extracted from a variety of intertidal plants and microorganisms, including mangroves, algae (green, brown, and red), tunicates, echinoderms, sponges, cnidarians, bryozoans, and mollusks. The last five years have seen a steady rise in research on marine fungi and a decline in reports of novel chemicals from bacteria, cnidarians, and sponges[10]. Carotenoids, terpenoids, peptides, polysaccharides, and alkaloids that are separated from marine species are the primary sources of anticancer compounds. The FDA, which is based in the United States, has authorized eleven anticancer medications as of April 2022, highlighting the marine environment's enormous potential as a natural gold mine for substances having anticancer properties [11]. The third most deadly disease overall and the fourth most prevalent form diagnosed globally is colorectal cancer (CRC). In 2018, there were over a million new cases of colorectal cancer diagnosed, including around 704,000 new cases of rectal cancer and over a million new cases of colon cancer [12]. The most popular kind of medical care for patients with CRC is chemotherapy. Even with the improvements in CRC therapies, there are still two major problems with this medication: the resistance to cancer chemotherapy and the need for special CRC pharmacotherapy for the elderly, who are the most susceptible subgroup[13].Resistance to chemotherapy in colorectal cancer may arise due to variations in the way that related proteins genes. As an illustration, there is a strong correlation between the presence of the enzyme thymidylate synthase and fluorouracil's effectiveness (5-FU) in targeting it. The efficiency of 5-FU is also dependent on certain proteins' metabolism and breakdown, including dihydropyrimidine dehydrogenase, uridine phosphorylase, thymidine phosphorylase, and orotate phosphoribosyl transferase [14]. The adenocarcinoma form of colon cancer is characterized by an overexpression of the Rac1b gene. It has been demonstrated that Rac1b overexpression promotes chemoresistance against 5-FU or oxaliplatin treatment via NF-kB signaling[15]. Furthermore, the most susceptible subgroup of the population for CRC is the elderly, with a high incidence rate among those over 70. Given that every single one of them possesses a unique health condition, it is important to discuss CRC pharmacotherapy. Additionally, their medical interventions should become more targeted and take into account the side effects of radiation, surgery, or chemotherapy in terms of their weakness, state of cognition, and functionality, and any associated comorbidities[16]. It has been shown that marine organisms may provide novel compounds with anti-CRC properties. Furthermore, a brown seaweed sulfated polysaccharide in HCT-116 and HT-29 cells called fucoidan showed activity of apoptosis. [17]. Additionally, fucoidan has demonstrated strong anti-CRC activity in clinical trials with comparatively low adverse effects in people [18].The investigation of newly developed anticancer drugs originating from marine microbiology against colorectal cancers (CRCs) has garnered significant attention recently. 98 percent of the biomass in the oceans of the world is made up of marine microorganisms like bacteria, fungi, algae, and plankton [19]. The ability to extract bioactive compounds from marine microorganisms with great potency was revealed in several papers with the development of marine biotechnological methods. Of them, research on the synthesis of novel bioactive metabolites is primarily focused on bacteria and fungi [20].This review contains information about the anti-colon cancer compounds derived from marine microbes.

II. ANTI-COLORECTAL CANCER COMPOUNDS DERIVED FROM MARINE MICROORGANISMS

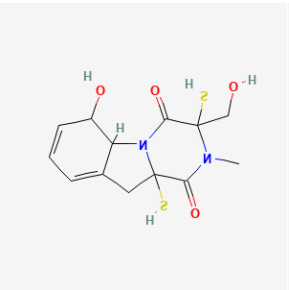
There are many compounds derived from marine microbes that constitute anti-cancer properties, these microbes include various species of fungi, actinomycetes, and a few bacteria and algae. Many of these derived compounds contain different anti-cancer properties one of which is anti-colon cancer. The derived compounds constitute various alkaloids, terpenes, peptides, carotenoids, polysaccharides, heterocyclic aromatics, amides, different benzene derivatives, polyether, and polyhydroxy compounds, etc.which were tested on different anti-colon cancer cell lines such as Caco-2, RKO, HCT15, HT29, and HCT116.

2.1 ALKALOIDS DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

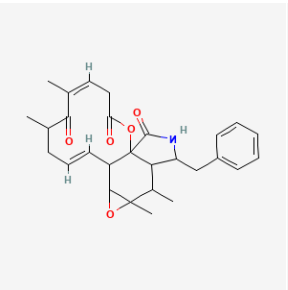
	Compound	Species	Mechanism	Reference
Fungi				
	Brevianamide C	*Penicillium brevicompactum*	Anti-proliferation	[21]
	Reduced-gliotoxin	*Neosartoryapseudofischeri*	Apoptosis, anti-proliferation, and anoikis	[22]
	GQQ-792	*Tilachlidium sp*.	Anti-proliferation	[23]
	Rosellichalasin	*Aspergillus sp. nov. F1*	Moderate Cytotoxicity	[24]
	Cytochalasin E	*Aspergillus sp. nov. F1*	Week Cytotoxicity	[24]
	19,20- dihydrophomacin C	*W. dispersa XL602*	Week Cytotoxicity	[25]
	19-methoxy-19,20-dihydrophomacin C	*W. dispersa XL602*	Week Cytotoxicity	[25]
	19-hydroxyl-19,20-dihydrophomacin C	*W. dispersa XL602*	Week Cytotoxicity	[25]
	Gymnastatin Z	*W. dispersa XL602*	Week Cytotoxicity	[25]
	Pityriacitrin	*D. cejpii F31-1*	Moderate Cytotoxicity	[26]
	epi-Fiscalin C	*N. siamensis KUFA 0017*	Week Cytotoxicity	[27]
Actinomycetes				
	6-OMe-70 ,7”-dichorochromopyrrolic acid	*Streptomyces strain SCSIO 11791*	Strong Cytotoxicity	[28]
	Lynamicin B	*Streptomyces strain SCSIO 11791*	Very Strong Cytotoxicity	[28]
	Spiroindimicin B	*Streptomyces strain SCSIO 11791*	Very Strong Cytotoxicity	[28]
Green Algae				
	Caulerpin	*Caulerpa cylindracea*		[29]



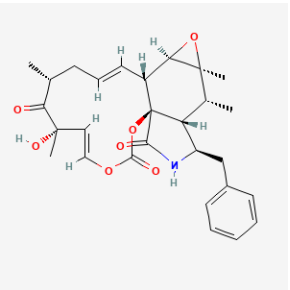
Brevianamide C



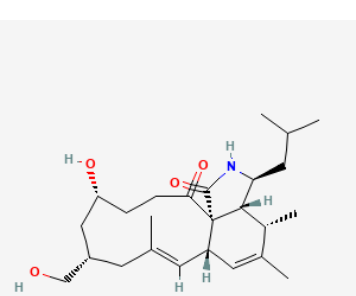
Reduced-gliotoxin



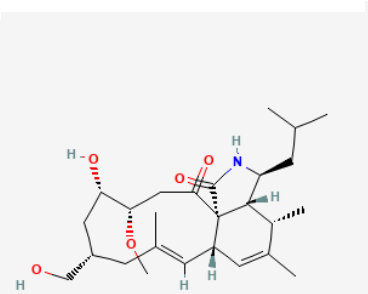
Rosellichalasin



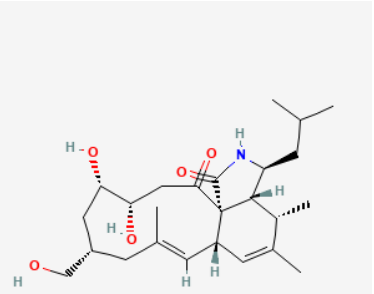
Cytochalasin E



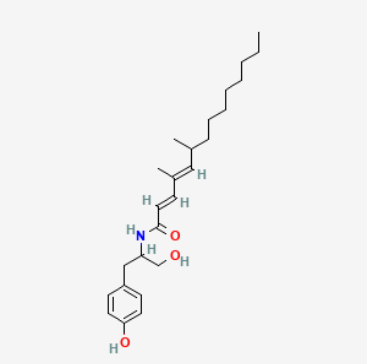
19,20- dihydrophomacin-C



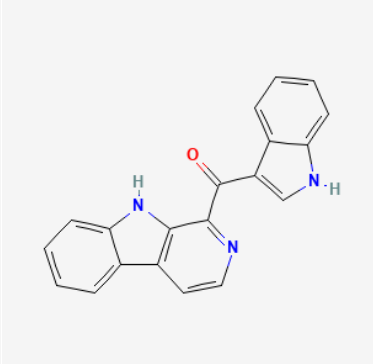
19-methoxy-19,20-dihydrophomacin-C



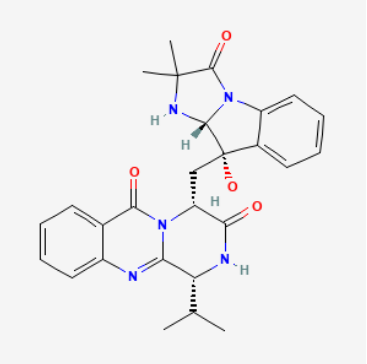
19-hydroxyl-19,20-dihydrophomacin-C



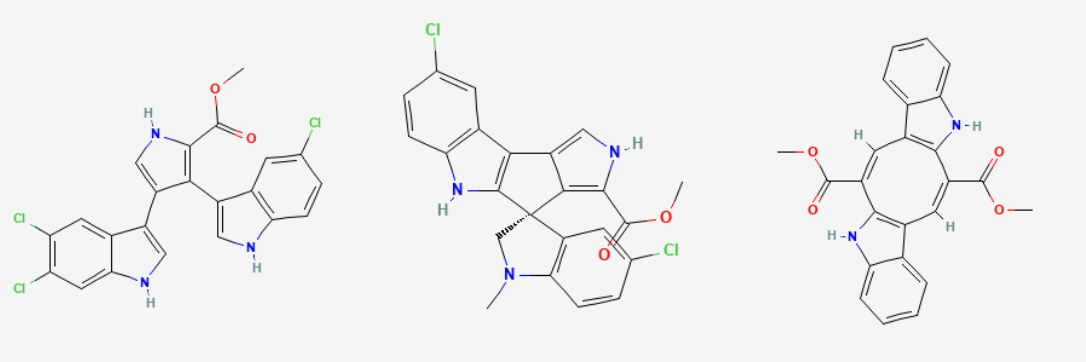
Gymnastatin-Z



Pityriacitrin



epi-Fiscalin C



6-OMe-70 ,7”- dichorochromo -pyrrolic acid

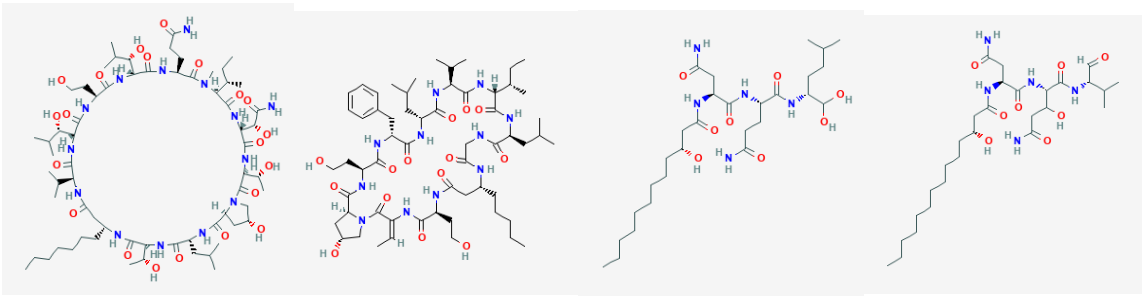
Spiroindimicin B

Caulerpin

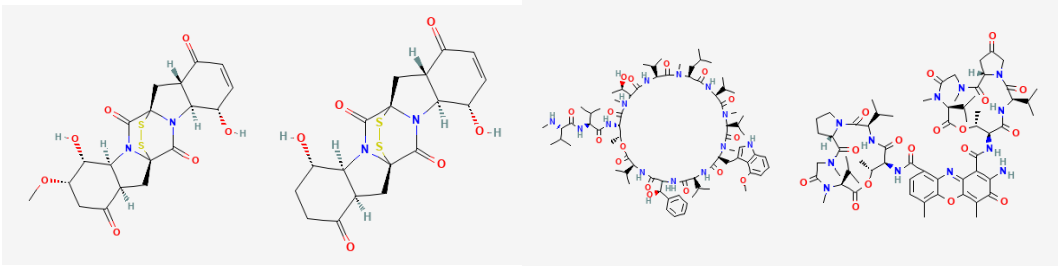
2.2 PEPTIDES DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

	Compound	Species	Mechanism	Reference
Bacteria				
	L-Glutaminase	*Halomonas meridian*	Anti-proliferation; apoptosis	[30]
Cyanobacteria				
	Laxaphycin B4	*Hormothamnionen teromorphoides*	Anti-proliferation	[31]
	Laxaphycin A2	*Hormothamnionen teromorphoides*	Anti-proliferation	[31]
Fungi				
	Fellutamide F	*A. versicolor PF10M*	Strong Cytotoxicity	[32]
	Fellutamide C	*A. versicolor PF10M*	Strong Cytotoxicity	[32]
	Brocazine A	*P. brocae MA-231*	Strong Cytotoxicity	[33]
	Brocazine B	*P. brocae MA-231*	Strong Cytotoxicity	[33]
Actinomycetes				
	Ohmyungsamycin A	*Streptomyces strain SNJ042*	G0/G1 cell cycle arrest, apoptosis, and anti-proliferation	[34],[39]
	Actinomycin-V	*Streptomyces sp.*	PI3K/AKT pathway, apoptosis, and anti-proliferation	[35]
	Androsamide	*Nocardiopsis sp.*	Anti-proliferation; block EMT	[36]
	Cyclo-(Pro-Ala)	*S. nigra sp. nov. 452*	Moderate	[37]

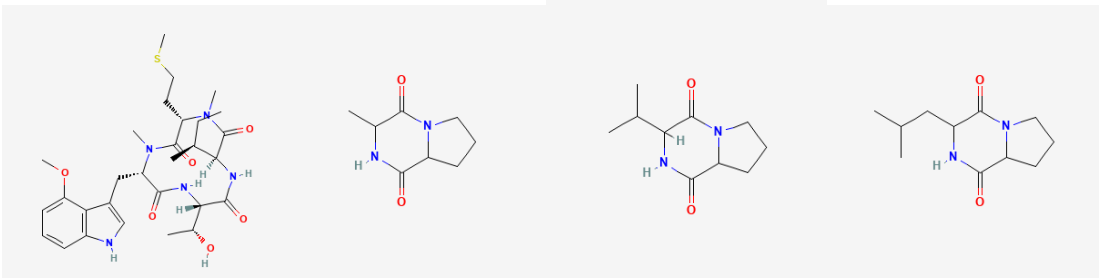
			Cytotoxicity	
	Cyclo-(Pro-Val)	*S. nigra sp. nov. 452*	Moderate Cytotoxicity	[37]
	Cyclo-(Pro-Leu)	*S. nigra sp. nov. 452*	Moderate Cytotoxicity	[37]
	Cyclo-(Pro-Phe)	*S. nigra sp. nov. 452*	Moderate Cytotoxicity	[37]
	Neo-actinomycin A	*Streptomyces sp. IMB094*	Strong Cytotoxicity	[38]
	Neo-actinomycin B	*Streptomyces sp. IMB094*	Strong Cytotoxicity	[38]
	Actinomycin D	*Streptomyces sp. IMB094*	Strong Cytotoxicity	[38]



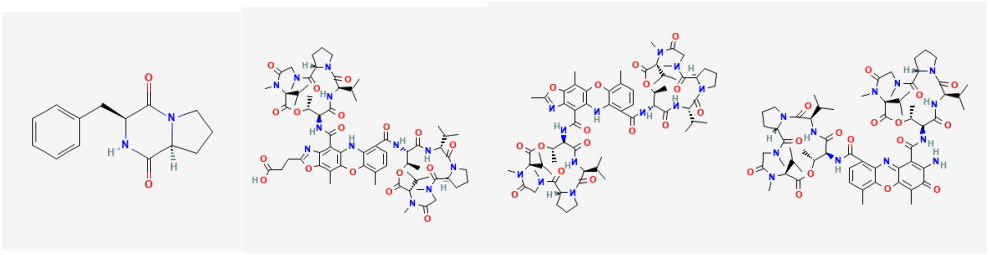
Laxaphycin B4 Laxaphycin A2 Fellutamide F Fellutamide C



Brocazine ABrocazine B Ohmyungsamycin A Actinomycin V



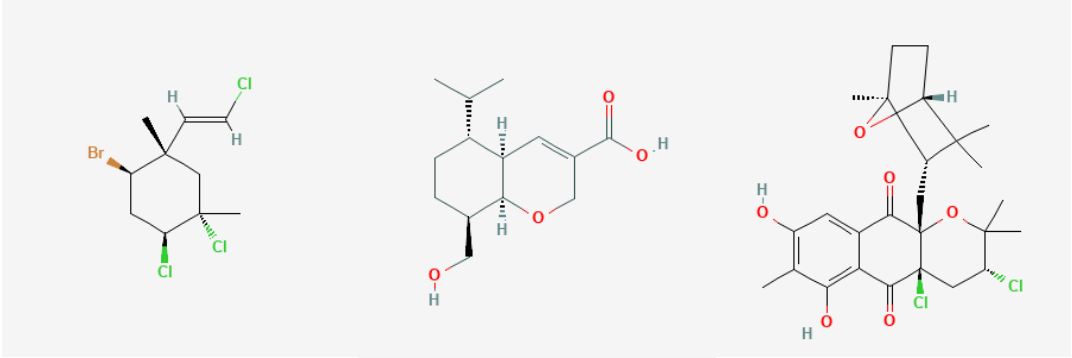
Androsamide Cyclo-(Pro-Ala) Cyclo-(Pro-Val) Cyclo-(Pro-Leu)



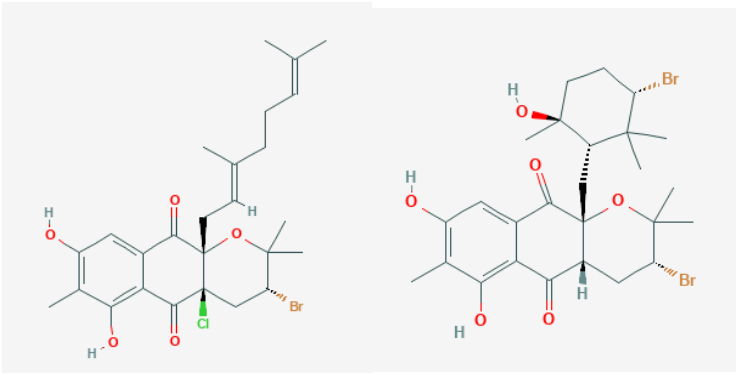
Cyclo-(Pro-Phe) Neo-actinomycin-A Neo-actinomycin-B Actinomycin-D

2.3 TERPENES DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

	Compound	Species	Mechanism	Reference
Red Alage				
	Mertensene	*Pterocladiellacapillacea*	Apoptosis, G2/M cell cycle arrest, anti-proliferation, ERK-1/-2, AKT, and NF-κB activation	[40]
Fungi				
	Trichodermaloids A	*Trichoderma sp.andDysidea sp.*	Anti-proliferation	[41]
	Trichodermaloids B	*Trichoderma sp.andDysidea sp.*	Anti-proliferation	[41]
	Trichodermaloids C	*Dysidea sp. and Trichoderma sp.*	Anti-proliferation	[41]
	Rhinomilisin E	*Trichoderma sp.andDysidea sp.*	Anti-proliferation	[41]
Actinomycetes				
	Napyradiomycin CNQ525.510B	*Streptomyces sp. CNQ525*	Strong Cytotoxicity	[42]
	Napyradiomycin CNQ525.538	*Streptomyces sp. CNQ525*	Very Strong Cytotoxicity	[42]
	Napyradiomycin CNQ525.600	*Streptomyces sp. CNQ525*	Moderate Cttotoxicity	[42]



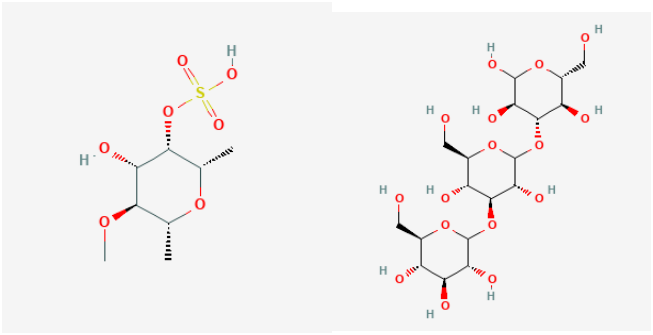
Mertensene Rhinomilisin E Napyradiomycin-CNQ525.510B



Napyradiomycin-CNQ525.538 Napyradiomycin-CNQ525.600

2.4 POLYSACCHARIDES DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

	Compound	Species	Mechanism	Reference
Brown Algae				
	Fucoidan	-	Apoptosis G_1 Phase Cell Cycle arrest	[43]
	Laminaran	-	Apoptosis	[44]

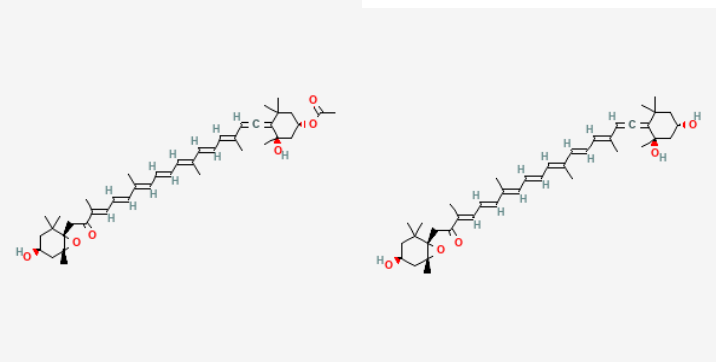


Fucoidan Laminaran

2.5 CAROTENOIDS DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

	Compound	Species	Mechanism	Reference
Brown Algae				
	Fucoxanthin	-	G_o/G_1 Cell cycle arrest Apoptosis	[45]

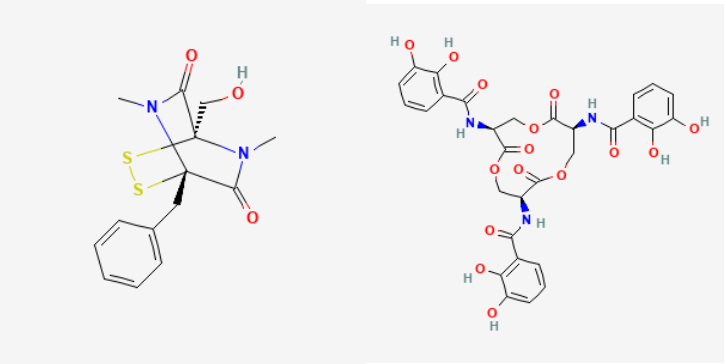
	Fucoxanthinol	-	Apoptosis	[46]



Fucoxanthin Fucoxanthinol

2.6 HETEROCYCLIC AROMATIC COMPOUNDS DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

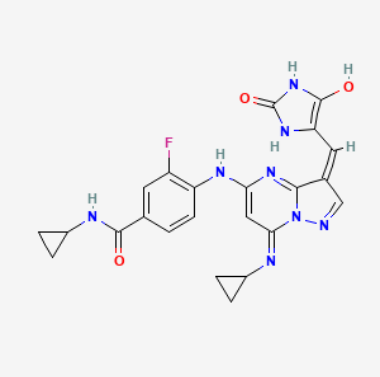
	Compound	**Species**	**Mechanism**	**Reference**
Fungi				
	Hyalodendrin	*P.salinaPC 362H*	Very Strong Ctotoxicity	[47]
Actinomycetes				
	2,3-Dihydroxybenzamide	Streptomyces sp. SBT348	Strong Ctotoxicity	[48]



Hyalodendrin 2,3- Dihydroxybenzamide

2.7 POLYETHER COMPOUNDS DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

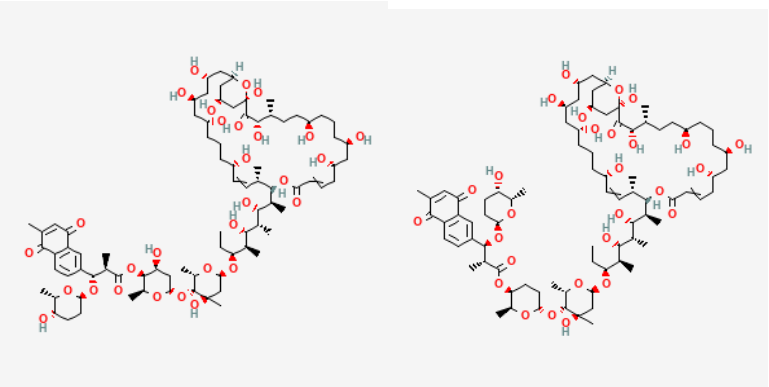
	Compound	**Species**	**Mechanism**	**Reference**
Actinomycetes				
	K41 A	*S.cacaoi 14CM034*	Very Strong Ctotoxicity	[49]



K41 A

2.8 POLYHYDROXYL COMPOUNDS DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

	Compound	Species	Mechanism	Reference
Actinomycetes				
	PM100117	*S. caniferus GUA-06-05-006A*	Very Strong Ctotoxicity	[50]
	PM100118	*S. caniferus GUA-06-05-006A*	Very Strong Ctotoxicity	[50]



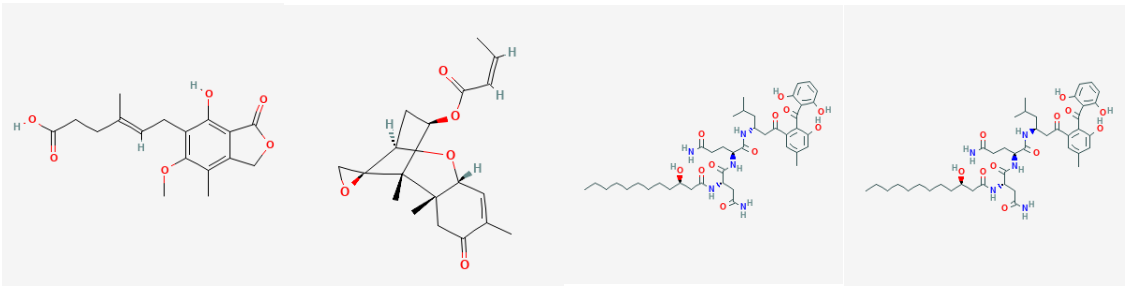
PM100117 PM100118

2.9 COMPOUNDS DERIVED FROM MARINE MICROBES AND THEIR ROLE IN ANTI-COLON CANCER (In-Vitro)

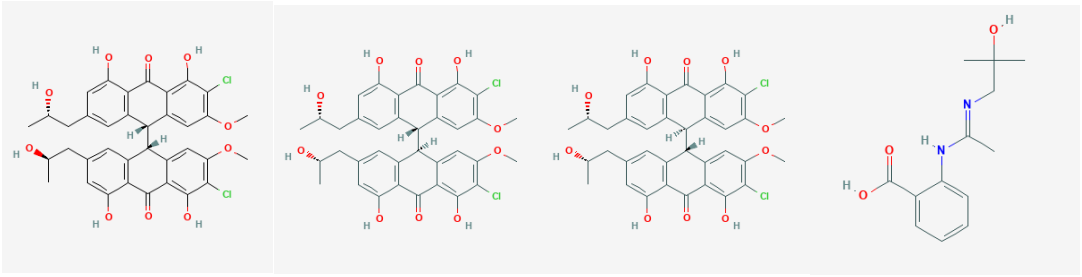
	Compound	Species	Mechanism	Reference
Bacteria				
	AVSC4 extract	*Bacillus flexus*	Cytotoxicity	[51]
Brown Algae				
	Methanol extract	*Halopteris scoparia L. Sauvageau*	Cytotoxicity; apoptosis; AKT	[52]

			pathway	
Fungi				
	Mycophenolic acid	*Penicillium brevicompactum*	Cytotoxicity	[53]
	Ganodermasides A	*Pseudogymnoascus sp. HSX2#-11*	Cytotoxicity	[54]
	Ganodermasides B	*Pseudogymnoascus sp. HSX2#-11*	Cytotoxicity	[55]
	Compound 1	*Aspergillus flocculosus 01NT-1.1.5*	Cytotoxicity	[56]
	Compound 9	*Aspergillus flocculosus 01NT-1.1.5*	Cytotoxicity	[56]
	Compound 10	*Aspergillus flocculosus 01NT-1.1.5*	Cytotoxicity	[56]
	Trichothecin	*Alternaria sp. TZP-11*	STAT3 pathway blockage, apoptosis, G0/G1 cell cycle arrest, and anti-proliferation	[57]
	Asperphenin A	*Aspergillus sp.*	Apoptosis; arrest of the G2/M cell cycle	[58]
	Asperphenin B	*Aspergillus sp.*	Cytotoxicity	[58]
	Allianthrone A	*A. alliaceus (new strain, G4)*	Cytotoxicity	[59]
	Allianthrone B	*A. alliaceu-new strain, G4*	Cytotoxicity	[59]
	Allianthrone C	*A. alliaceus-new strain, G4*	Cytotoxicity	[59]
	Penipacid A	*P. paneum SD-44*	Powerful Cytotoxicity	[60]
	Penipacid E	*P. paneum SD-44*	Powerfu-Cytotoxicity	[60]
Actinomycetes				
	Shellmycin A	*Streptomyces sp. Shell-016*	Cytotoxicity	[61]
	Shellmycin B	*Streptomyces sp. Shell-016*	Cytotoxicity	[61]
	Shellmycin C	*Streptomyces sp. Shell-016*	Cytotoxicity	[61]
	Shellmycin D	*Streptomyces sp. Shell-016*	Cytotoxicity	[61]
	Neaumycin B	*Micromonospora*	Cytotoxicity	[62]
	PM100117	*Streptomyces caniferus GUA-06-05-006A*	Cytotoxicity	[63]

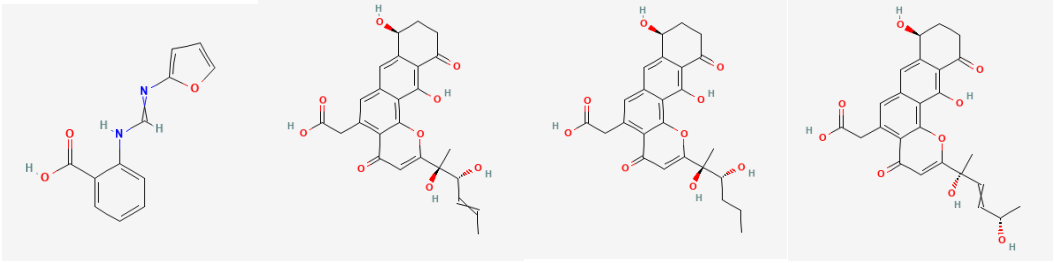
	PM100118	*Streptomyces caniferus GUA-06-05-006A*	Cytotoxicity	[63]
	Compound 2	*Streptomyces cacaoi*	Inhibit autophagy; induce apoptosis	[64]



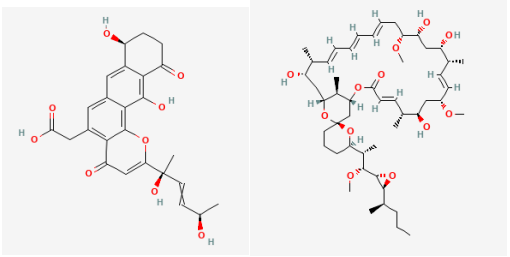
Mycophenolic acid TrichothecinAsperphenin AAsperphenin B



Allianthrone A Allianthrone BA llianthrone C Penipacid A



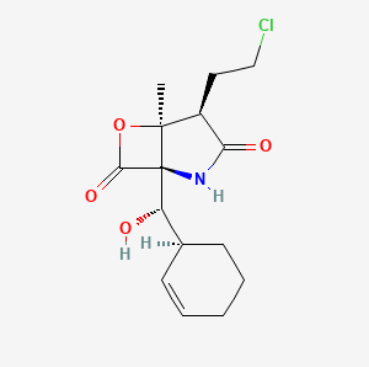
Penipacid E Shellmycin-A Shellmycin-B Shellmycin-C



Shellmycin-D Neaumycin B

A number of substances derived from marine sources have demonstrated encouraging anticancer properties, either by eliminating cancer cells directly or by altering pathways that contribute to the spread of cancer. These compounds' unique chemical structures frequently allow them to interact with biological targets in ways that compounds derived from the earth cannot, providing new avenues for the fight against cancer cells [65,66].

Salinosporamide A is a potent proteasome inhibitor isolated from the marine bacterium *Salinispora tropica*, which blocks the 20S proteasome complex, which breaks down ubiquitinated proteins, permanently. It causes the buildup of misfolded proteins, which causes cell cycle arrest and apoptosis in cancer cells by blocking proteasome activity. This mechanism works especially well in cancer cells, which mainly depend on the activity of proteasomes to survive. It causes CRC cells to undergo apoptosis and increases the potency of other chemotherapeutic drugs [67,68]. The process of programmed cell death known as apoptosis is frequently misregulated in cancerous cells. Through the restoration of CRC cells' capacity for apoptosis, these substances have the ability to successfully inhibit tumor growth and avert metastasis. The development of new blood vessels, or angiogenesis, is essential for the spread and growth of tumors. It has been demonstrated that substances derived from the sea inhibit angiogenesis by interfering with signaling pathways that encourage the formation of blood vessels. By depriving the tumor of vital nutrients and oxygen, this slows down the tumor's growth and hinders its ability to spread. Cancer cells spread from the original tumor to other parts of the body through a process called metastasis. Cell adhesion, migration, and invasion processes—all essential for metastasis—have been demonstrated to be disrupted by marine-derived substances such as salinosporamide A. These substances can aid in stopping the spread of CRC to other organs by focusing on these pathways [69-71].



Salinosporamide A

III. MARINE-MICROBES DERIVED COMPOUNDS –IN-VIVO STUDY OF ANTI-COLORECTAL CANCER

	Compound	Species	Cancer Cell lines	Tumor formation in mice(mode)	Compound delivery	Dosage	Suppression rate of tumor	Reference
Fungi								
	Asperpheni n A	*Aspergillus sp*	RKO	Subcutaneously injected into mice flanks	Injected Intraperitonially	100mg/kg (3 times/week0	Tumor Inhibition rate 52.1%	[57]
Actinomycetes								

	Ohmyungsamycin A	*Streptomyces sp.*	HCT-116	Subcutaneously injected into mice flanks	Oral	30mg/kg (alternative days)	Inhibition of tumor growth	[34]
Green alage								
	Caulerpin	*Caulerpa cylindracea*	SW480	Subcutaneously injected into mice right flanks	Injected Intraperitonially	8mg/kg (3 times/week)	Tumor Inhibition rate 68.7 ± 17.1%	[29]
	SPS-CF	*Capsosiphonfulvescens*	HT-29	Subcutaneously injected into mice back	Injected Intraperitonially	400mg/kg/day	Tumor Inhibition rate 20%	[72]
Brown algae								
	Fucoxanthin	-	HT-29	Subcutaneously injected into mice right femoral region	oral	2.5mg/kg (every 2/3 days)	Inhibition of tumor growth	[73]

Sustainable and ethical marine organism sourcing is one of the main obstacles to the development of drugs derived from marine organisms. A lot of marine species are endangered or hard to grow, which makes it hard to get enough bioactive compounds for developing new drugs. Technological developments in aquaculture, synthetic biology, and biotechnology are making it possible to produce marine-derived compounds sustainably, which is one way in which these challenges are being addressed. The synthesis and modification of marine natural products face significant challenges due to their structural complexity. Because of their complexity, it may be challenging to maximize the pharmacological qualities of these compounds or to produce them in large quantities. However, by making it possible to produce marine-derived compounds and their analogs efficiently, developments in synthetic chemistry and biosynthetic engineering are helping to overcome these difficulties [74,75].

Treatment effectiveness for colorectal cancer (CRC) is severely hampered by drug resistance. Marine-derived compounds, because of their distinct chemical makeup, present a promising solution to this problem. biological processes and structures. Novel bioactive substances found in marine environments include polysaccharides, terpenoids, alkaloids, and peptides that have shown strong anti-cancer effects. These substances have the ability to alter several signaling pathways, including Wnt/β-catenin, MAPK, and PI3K/AKT, which are linked to the development of cancer and drug resistance. For example, substances derived from marine organisms like trabectedin and halichondrin B have demonstrated effectiveness in preventing tumor growth and disabling cancer cell resistance mechanisms. Furthermore, it has been discovered that marine polysaccharides like fucoidan, which induce apoptosis and inhibit metastasis, improve the efficacy of chemotherapy medications. combining substances derived from marine [76-78].

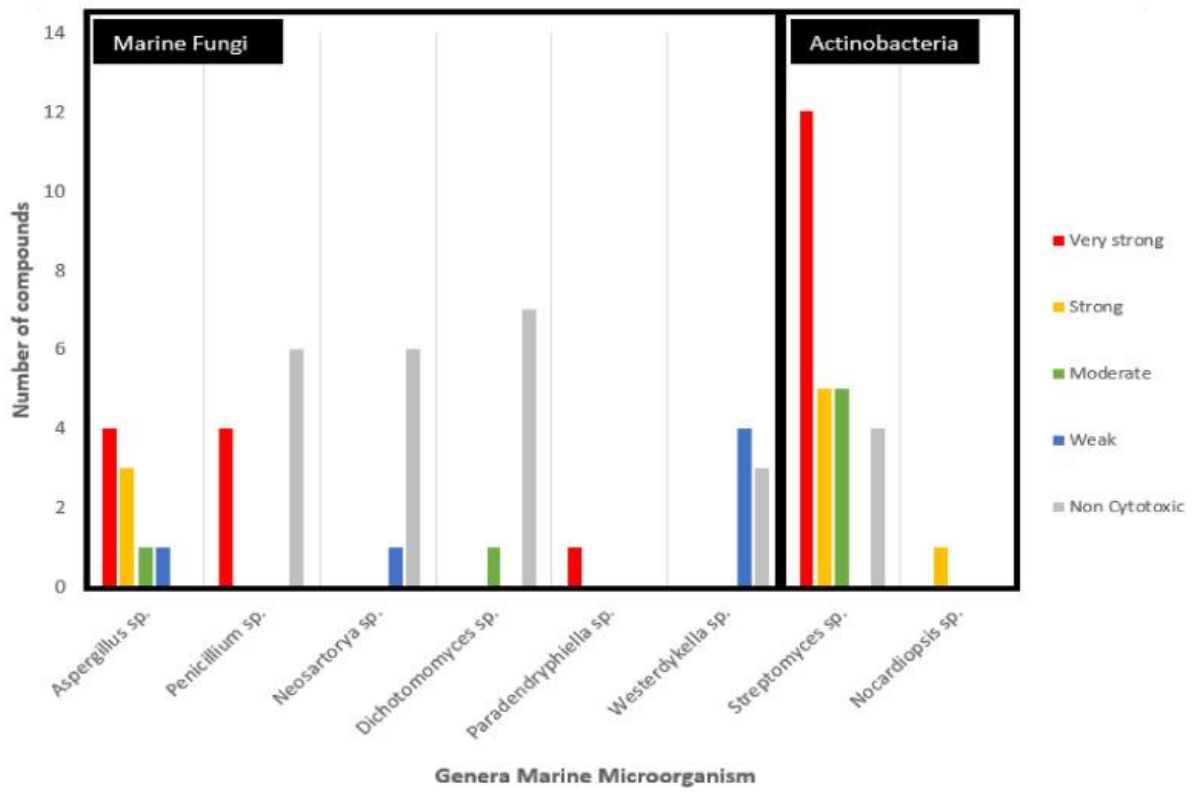


Fig.Anti-colorectal cancer compounds from different sps of marine fungi and actinobacteria[13].

IV. CONCLUSION

Secondary metabolites from marine microorganisms which include alkaloids, peptides, terpenes, etc, specifically those derived from the actinobacteria *Streptomyces sp.* and fungi *Penicillium sp., Aspergillus sp., Paradendryphiella sp.*, are potentially cytotoxic agents on colorectal cancer. The majority of the compounds are identified as diketopiperazines and indole alkaloids [13].According to their molecular compositions, marine compounds such as terpenoids, polysaccharides, carotenoids, peptides, and alkaloids have been shown in vitro studies to have anti-colorectal cancer effects. Additionally, we have clarified the primary marine compounds' pharmacological mechanisms against colorectal cancer (CRC). These mechanisms involve preventing intracellular signal transduction, preventing angiogenesis, deactivating DNA polymerase, and activating caspase protein, cancer cell invasion and metastasis [7]. These secondary metabolites can act as novel substitutes for cytotoxic substances directed in opposition to the cell lines for colorectal cancer Caco-2, RKO, HT29, HCT15, and HCT116. The in vitro research provided an overview of the many compounds' marine origins and pharmacological actions, such as their promotion of tumor apoptosis, properties that inhibit migration, invasion, angiogenesis, and proliferation. According to tumor inhibition, hepatotoxicity, and nephrotoxicity, the in vivo research assessed the marine compounds' antitumor effects on mice/ratsmodeled by colorectal cancer. The primary chemical categories and mechanisms of the clinical drugs' actions that have received full and clinical endorsement for their anticancer properties in marine environments were compiled from the clinical studies. In this review various secondary metabolites like alkaloids, peptides, terpenes, polysaccharides, carotenoids, heterocyclic aromatic, polyether, polyhydroxyl compounds derived from marine algae,fungi actinomycetes and bacteria with their invitro anti-colorectal cancer activity were listed and as well as the compounds that are studied in in-vivo were listed which can be used in further studies for their mechanism of action and can be replaced instead of chemotherapy, radiation, and surgery.

REFERENCES

[1] D.M. Pereira et al.Marine natural pigments: chemistry, distribution and analysis. Dyes and PigmentsVolume 111, 2014, Pages 124-134
[2] M.J. O'ConnorTargeting the DNA damage response in cancer.Mol. Cell,2015,60(4):547-60.
[3] M.E. Abd El-Hack et al.Microalgae in modern cancer therapy: current knowledge.Biomed. Pharmacother,2019,Volume 111, Pages 42-50
[4] G.A. Van NormanDrugs, devices, and the FDA: part 1: an overview of approval processes for drugs.JACC Basic to Transl. Sci,2016,1(3):170-179.
[5] R. Pangestuti et al.Biological activities and health benefit effects of natural pigments derived from marine algae.J. Funct. Foods, 2011,Volume 3, Issue 4, Pages 255-266
[6] L. Dufossé et al.Filamentous fungi are large-scale producers of pigments and colorants for the food industry.Curr. Opin. Biotechnol,2014,26:56-61.
[7] Ningning Han et al.Natural Marine Products: Anti-Colorectal Cancer In Vitro and In Vivo.Mar. Drugs 2022, 20, 349.
[8] Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca-A Cancer J. Clin. 2021, 71, 209–249.
[9] Miller, K.D.; Nogueira, L.; Mariotto, A.B.; Rowland, J.H.; Yabroff, K.R.; Alfano, C.M.; Jemal, A.; Kramer, J.L.; Siegel, R.L. Cancer treatment and survivorship statistics, 2019. Ca-A Cancer J. Clin. 2019, 69, 363–385.
[10] Carroll, A.R.; Copp, B.R.; Davis, R.A.; Keyzers, R.A.; Prinsep, M.R. Marine natural products. Nat. Prod. Rep. 2021, 38, 362–413.
[11] Clinical Pipeline Marine Pharmacology. Available online: https://www.marinepharmacology.org/ (accessed on 11 April 2022).
[12] Rawla, P.; Sunkara, T.; Barsouk, A. Epidemiology of Colorectal Cancer: Incidence, Mortality, Survival, and Risk Factors. Prz. Gastroenterol. 2019, 14, 89–103.
[13] Elin Julianti et al. Secondary Metabolites from Marine-Derived Fungi and Actinobacteria as Potential Sources of Novel Colorectal Cancer Drugs. Mar. Drugs 2022, 20, 67. https://doi.org/10.3390/md20010067.
[14] Van der Jeught, K.; Xu, H.C.; Li, Y.J.; Lu, X.B.; Ji, G. Drug Resistance and New Therapies in Colorectal Cancer. World J. Gastroenterol. 2018, 24, 3834–3848.
[15] Goka, E.T.; Chaturvedi, P.; Lopez, D.T.M.; Garza, A.D.L.; Lippman, M.E. RAC1b Overexpression Confers Resistance to Chemotherapy Treatment in Colorectal Cancer. Mol. Cancer Ther. 2019, 18, 957–968.
[16] Guren, M.G. The Global Challenge of Colorectal Cancer. Lancet Gastroenterol. Hepatol. 2019, 4, 894–895.
[17] Kim, E.J.; Park, S.Y.; Lee, J.Y.; Park, J.H.Y. Fucoidan Present in Brown Algae Induces Apoptosis of Human Colon Cancer Cells. BMC Gastroenterol. 2010, 10, 1–11.
[18] Tsai, H.L.; Tai, C.J.; Huang, C.W.; Chang, F.R.; Wang, J.Y. Efficacy of Low-Molecular-Weight Fucoidan as a Supplemental Therapy in Metastatic Colorectal Cancer Patients: A Double-Blind Randomized Controlled Trial. Mar. Drugs 2017, 15, 122.
[19] Science, A.I. of M. Australian Institute of Marine Science: Marine Microbes. Available online: https://www.aims.gov.au/docs/ research/marine-microbes/microbes/microbes.html (accessed on 16 February 2021).
[20] Salazar, G.; Sunagawa, S. Marine Microbial Diversity. Curr. Biol. 2017, 27, R489–R494.
[21] Xu, X.Y.; Zhang, X.Y.; Nong, X.H.; Wang, J.; Qi, S.H. Brevianamides and Mycophenolic Acid Derivatives from the Deep-SeaDerived Fungus Penicillium brevicompactum DFFSCS025. Mar. Drugs 2017, 15, 43.
[22] Chen, J.; Lou, Q.; He, L.; Wen, C.; Lin, M.; Zhu, Z.; Wang, F.; Huang, L.; Lan, W.; Iwamoto, A.; et al. Reduced-gliotoxin induces ROS-mediated anoikis in human colorectal cancer cells. Int. J. Oncol. 2018, 52, 1023–1032.

[23] Wang, Y.; Sun, L.; Yu, G.; Qi, X.; Zhang, A.; Lu, Z.; Li, D.; Li, J. Identification of a novel non-ATP-competitive protein kinase inhibitor of PGK1 from marine nature products. Biochem. Pharmacol. 2021, 183, 114343.
[24] Xiao, L.; Liu, H.; Wu, N.; Liu, M.; Wei, J.; Zhang, Y.; Lin, X. Characterization of the High Cytochalasin E and Rosellichalasin Producing-Aspergillus Sp. Nov. F1 Isolated from Marine Solar Saltern in China. World J. Microbiol. Biotechnol. 2013, 29, 11–17.
[25] Xu, D.; Luo, M.; Liu, F.; Wang, D.; Pang, X.; Zhao, T.; Xu, L.; Wu, X.; Xia, M.; Yang, X. Cytochalasan and Tyrosine-Derived Alkaloids from the Marine Sediment-Derived Fungus WesterdykellaDispersa and Their Bioactivities. Sci. Rep. 2017, 7, 1–9.
[26] Chen, Y.X.; Xu, M.Y.; Li, H.J.; Zeng, K.J.; Ma, W.Z.; Tian, G.B.; Xu, J.; Yang, D.P.; Lan, W.J. Diverse Secondary Metabolites from the Marine-Derived Fungus DichotomomycesCejpii F31-1. Mar. Drugs 2017, 15, 339.
[27] Ramos, A.A.; Buttachon, S.; Marques, P.; Dethoup, T.; Kijjoa, A.; Rocha, E. Cytotoxic Activity of Secondary Metabolites from Marine-Derived Fungus NeosartoryaSiamensis in Human Cancer Cells. Phyther. Res. 2016, 30, 1862–1871.
[28] Song, Y.; Yang, J.; Yu, J.; Li, J.; Yuan, J.; Wong, N.K.; Ju, J. Chlorinated Bis-Indole Alkaloids from Deep-Sea Derived Streptomyces Sp. SCSIO 11791 with Antibacterial and Cytotoxic Activities. J. Antibiot. 2020, 73, 542–547.
[29] Yu, H.; Zhang, H.; Dong, M.; Wu, Z.; Shen, Z.; Xie, Y.; Kong, Z.; Dai, X.; Xu, B. Metabolic reprogramming and AMPKα1 pathway activation by caulerpin in colorectal cancer cells. Int. J. Oncol. 2017, 50, 161–172.
[30] Mostafa, Y.S.; Alamri, S.A.; Alfaifi, M.Y.; Alrumman, S.A.; Elbehairi, S.E.I.; Taha, T.H.; Hashem, M. L-Glutaminase Synthesis by Marine Halomonasmeridiana Isolated from the Red Sea and Its Efficiency against Colorectal Cancer Cell Lines. Molecules 2021, 26, 1963.
[31] Cai, W.; Matthew, S.; Chen, Q.-Y.; Paul, V.J.; Luesch, H. Discovery of new A- and B-type laxaphycins with synergistic anticancer activity. Bioorg. Med. Chem. 2018, 26, 2310–2319.
[32] Lee, Y.M.; Dang, H.T.; Li, J.; Zhang, P.; Hong, J.; Lee, C.O.; Jung, J.H. A Cytotoxic Fellutamide Analogue from the Sponge-Derived Fungus Aspergillus versicolor. Bull. Korean Chem. Soc. 2011, 32, 3817–3820.
[33] Meng, L.H.; Li, X.M.; Lv, C.T.; Huang, C.G.; Wang, B.G. Brocazines A-F, Cytotoxic Bisthiodiketopiperazine Derivatives from Penicillium Brocae MA-231, an Endophytic Fungus Derived from the Marine Mangrove Plant Avicennia Marina. J. Nat. Prod. 2014, 77, 1921–1927.
[34] Byun, W.S.; Kim, S.; Shin, Y.-H.; Kim, W.K.; Oh, D.-C.; Lee, S.K. Antitumor Activity of Ohmyungsamycin A through the Regulation of the Skp2-p27 Axis and MCM4 in Human Colorectal Cancer Cells. J. Nat. Prod. 2020, 83, 118–126.
[35] Jiang, S.; Zhang, E.; Ruan, H.; Ma, J.; Zhao, X.; Zhu, Y.; Xie, X.; Han, N.; Li, J.; Zhang, H.; et al. Actinomycin V Induces Apoptosis Associated with Mitochondrial and PI3K/AKT Pathways in Human CRC Cells. Mar. Drugs 2021, 19, 599.
[36] Lee, J.; Gamage, C.D.B.; Kim, G.J.; Hillman, P.F.; Lee, C.; Lee, E.Y.; Choi, H.; Kim, H.; Nam, S.-J.; Fenical, W. Androsamide, a Cyclic Tetrapeptide from a Marine Nocardiopsis sp., Suppresses Motility of Colorectal Cancer Cells. J. Nat. Prod. 2020, 83, 3166–3172.
[37] Chen, C.; Ye, Y.; Wang, R.; Zhang, Y.; Wu, C.; Debnath, S.C.; Ma, Z.; Wang, J.; Wu, M. Streptomyces Nigra Sp. Nov. Is a Novel Actinobacterium Isolated from Mangrove Soil and Exerts a Potent Antitumor Activity in vitro. Front. Microbiol. 2018, 9, 1587.
[38] Wang, Q.; Zhang, Y.; Wang, M.; Tan, Y.; Hu, X.; He, H.; Xiao, C.; You, X.; Wang, Y.; Gan, M. Neo-Actinomycins A and B, Natural Actinomycins Bearing the 5H-Oxazolo[4,5-b]Phenoxazine Chromophore, from the Marine-Derived Streptomyces Sp. IMB094. Sci. Rep. 2017, 7, 3591.
[39] Byun, W.S.; Kim, S.; Shin, Y.H.; Kim, W.K.; Oh, D.C.; Lee, S.K. Antitumor Activity of Ohmyungsamycin A through the Regulation of the Skp2-P27 Axis and MCM4 in Human Colorectal Cancer Cells. J. Nat. Prod. 2020, 83, 118–126.

[40] Tarhouni-Jabberi, S.; Zakraoui, O.; Ioannou, E.; Riahi-Chebbi, I.; Haoues, M.; Roussis, V.; Kharrat, R.; Essafi-Benkhadir, K. Mertensene, a halogenated monoterpene, induces G2/M cell cycle arrest and caspase dependent apoptosis of human colon adenocarcinoma HT29 cell line through the modulation of ERK-1/-2, AKT and NF-κBsignaling. Mar. Drugs 2017, 15, 221.
[41] Cui, J.; Shang, R.-Y.; Sun, M.; Li, Y.-X.; Liu, H.-Y.; Lin, H.-W.; Jiao, W.-H. Trichodermaloids A-C, Cadinane Sesquiterpenes from a Marine Sponge Symbiotic Trichoderma sp. SM16 Fungus. Chem. Biodivers. 2020, 17, e2000036.
[42] Farnaes, L.; Coufal, N.G.; Kauffman, C.A.; Rheingold, A.L.; Dipasquale, A.G.; Jensen, P.R.; Fenical, W. Napyradiomycin Derivatives, Produced by a Marine-Derived Actinomycete, Illustrate Cytotoxicity by Induction of Apoptosis. J. Nat. Prod. 2014, 77, 15–21.
[43] Park, H.Y.; Park, S.-H.; Jeong, J.-W.; Yoon, D.; Han, M.H.; Lee, D.-S.; Choi, G.; Yim, M.-J.; Lee, J.M.; Kim, D.-H.; et al. Induction of p53-Independent Apoptosis and G1 Cell Cycle Arrest by Fucoidan in HCT116 Human Colorectal Carcinoma Cells. Mar. Drugs 2017, 15, 154.
[44] Malyarenko, O.S.; Malyarenko, T.V.; Usoltseva, R.V.; Surits, V.V.; Kicha, A.A.; Ivanchina, N.V.; Ermakova, S.P. Combined Anticancer Effect of SulfatedLaminaran from the Brown Alga Alaria angusta and Polyhydroxysteroid Glycosides from the Starfish Protoreasterlincki on 3D Colorectal Carcinoma HCT 116 Cell Line. Mar. Drugs 2021, 19, 540.
[45] Das, S.K.; Hashimoto, T.; Shimizu, K.; Yoshida, T.; Sakai, T.; Sowa, Y.; Komoto, A.; Kanazawa, K. Fucoxanthin induces cell cycle arrest at G(0)/G(1) phase in human colon carcinoma cells through up-regulation of p21(WAF1/Cip1). Biochim. Biophys. Acta-Gen. Subj. 2005, 1726, 328–335.
[46] Tamura, S.; Narita, T.; Fujii, G.; Miyamoto, S.; Hamoya, T.; Kurokawa, Y.; Takahashi, M.; Miki, K.; Matsuzawa, Y.; Komiya, M.; et al. Inhibition of NF-kappaB transcriptional activity enhances fucoxanthinol-induced apoptosis in colorectal cancer cells. Genes Environ. 2019, 41, 1.
[47] Dezaire, A.; Marchand, C.H.; Vallet, M.; Ferrand, N.; Chaouch, S.; Mouray, E.; Larsen, A.K.; Sabbah, M.; Lemaire, S.D.; Prado, S.; et al. Secondary Metabolites from the Culture of the Marine-Derived Fungus Paradendryphiella Salina PC 362H and Evaluation of the Anticancer Activity of Its Metabolite Hyalodendrin. Mar. Drugs 2020, 18, 191.
[48] Cheng, C.; Othman, E.M.; Stopper, H.; Edrada-Ebel, R.A.; Hentschel, U.; Abdelmohsen, U.R. Isolation of Petrocidin a, a New Cytotoxic Cyclic Dipeptide from the Marine Sponge-Derived Bacterium Streptomyces sp. SBT348. Mar. Drugs 2017, 15, 383.
[49] Khan, N.; Yılmaz, S.; Aksoy, S.; Uzel, A.; Tosun, Ç.; Kirmizibayrak, P.B.; Bedir, E. Polyethers Isolated from the Marine Actinobacterium Streptomyces Cacaoi Inhibit Autophagy and Induce Apoptosis in Cancer Cells. Chem. Biol. Interact. 2019, 307, 167–178.
[50] Pérez, M.; Schleissner, C.; Fernández, R.; Rodríguez, P.; Reyes, F.; Zuñiga, P.; De La Calle, F.; Cuevas, C. PM100117 and PM100118, New Antitumor Macrolides Produced by a Marine Streptomyces Caniferus GUA-06-05-006A. J. Antibiot. 2016, 69, 388–394.
[51] Syed, C.S.; Sairam, M.; Audipudi, A.V. Exploration of antibacterial and antiproliferative secondary metabolites from marine bacillus. J. Microbiol. Biotechnol. Food Sci. 2019, 9, 628–633.
[52] Guner, A.; Nalbantsoy, A.; Sukatar, A.; Yavasoglu, N.U.K. Apoptosis-inducing activities of Halopteris scopariaL. Sauvageau (Brown algae) on cancer cells and its biosafety and antioxidant properties. Cytotechnology 2019, 71, 687–704.
[53] Chen, L.; Zhu, T.; Zhu, G.; Liu, Y.; Wang, C.; Piyachaturawat, P.; Chairoungdua, A.; Zhu, W. Bioactive Natural Products from the Marine-Derived Penicillium brevicompactum OUCMDZ-4920. Chin. J. Org. Chem. 2017, 37, 2752–2762.
[54] Shi, T.; Li, X.Q.; Zheng, L.; Zhang, Y.H.; Dai, J.J.; Shang, E.L.; Yu, Y.Y.; Zhang, Y.T.; Hu, W.P.; Shi, D.Y. Sesquiterpenoids From the Antarctic Fungus Pseudogymnoascus sp. HSX2#-11. Front. Microbiol. 2021, 12, 1388.
[55] Qi, X.; Liu, B.; Jiang, Z. A new cytotoxic phenalenone derivative from Penicillium oxalicum. Nat. Prod. Res. 2021, 1–4.

[56] Cao Van, A.; Kang, J.S.; Choi, B.-K.; Lee, H.-S.; Heo, C.-S.; Shin, H.J. Polyketides and Meroterpenes from the Marine-Derived Fungi Aspergillus unguis 158SC-067 and A. flocculosus 01NT-1.1.5 and Their Cytotoxic and Antioxidant Activities. Mar. Drugs 2021, 19, 415.
[57] Qi, X.; Li, M.; Zhang, X.M.; Dai, X.F.; Cui, J.; Li, D.H.; Gu, Q.Q.; Lv, Z.H.; Li, J. Trichothecin Inhibits Cancer-Related Features in Colorectal Cancer Development by Targeting STAT3. Molecules 2020, 25, 2306.
[58] Bae, S.Y.; Liao, L.; Park, S.H.; Kim, W.K.; Shin, J.; Lee, S.K. Antitumor Activity of Asperphenin A, a Lipopeptidyl Benzophenone from Marine-Derived Aspergillus sp. Fungus, by Inhibiting Tubulin Polymerization in Colon Cancer Cells. Mar. Drugs 2020, 18, 110.
[59] Mandelare, P.E.; Adpressa, D.A.; Kaweesa, E.N.; Zakharov, L.N.; Loesgen, S. Coculture of Two Developmental Stages of a Marine-Derived Aspergillus alliaceus Results in the Production of the Cytotoxic BianthroneAllianthrone A. J. Nat. Prod. 2018, 81, 1014–1022.
[60] Li, C.-S.; Li, X.-M.; Gao, S.-S.; Lu, Y.-H.; Wang, B.-G. Cytotoxic Anthranilic Acid Derivatives from Deep Sea Sediment-Derived Fungus Penicillium Paneum SD-44. Mar. Drugs 2013, 11, 3068–3076.
[61] Han, Y.; Wang, Y.; Yang, Y.; Chen, H. Shellmycin A-D, Novel Bioactive Tetrahydroanthra-gamma-Pyrone Antibiotics from Marine Streptomyces sp. Shell-016. Mar. Drugs 2020, 18, 58.
[62] Kim, M.C.; Machado, H.; Jang, K.H.; Trzoss, L.; Jensen, P.R.; Fenical, W. Integration of Genomic Data with NMR Analysis Enables Assignment of the Full Stereostructure of Neaumycin B, a Potent Inhibitor of Glioblastoma from a Marine-Derived Micromonospora.J. Am. Chem. Soc. 2018, 140, 10775–10784.
[63] Garcia Salcedo, R.; Olano, C.; Fernandez, R.; Brana, A.F.; Mendez, C.; de la Calle, F.; Salas, J.A. Elucidation of the glycosylation steps during biosynthesis of antitumor macrolides PM100117 and PM100118 and engineering for novel derivatives. Microb. Cell Factories 2016, 15, 187.
[64] . Khan, N.; Yilmaz, S.; Aksoy, S.; Uzel, A.; Tosun, C.; Kirmizibayrak, P.B.; Bedir, E. Polyethers isolated from the marine actinobacterium Streptomyces cacaoi inhibit autophagy and induce apoptosis in cancer cells. Chem.-Biol. Interact. 2019, 307, 167–178.
[65] Blunt, J. W., Copp, B. R., Keyzers, R. A., Munro, M. H., & Prinsep, M. R. Marine naturalproducts. Natural Product Reports,2018, 35(1), 8-53.
[66] Hu, G.-P., Yuan, J., Sun, L., She, Z.-G., Wu, J.-H., Lan, X.-J., ... & Lin, Y.-C. Statisticalresearch on marine natural products based on data obtained between 1985 and 2008. Marine Drugs,2011, 9(4), 514-525.
[67] Feling, R. H., Buchanan, G. O., Mincer, T. J., Kauffman, C. A., Jensen, P. R., & Fenical, W.Salinosporamide A: A highly cytotoxic proteasome inhibitor from a novel microbial source,Salinispora tropica. AngewandteChemie International Edition,2003, 42(3), 355-357.
[68] Chauhan, D., Li, G., Auclair, D., Hideshima, T., Podar, K., Shringarpure, R., ... & Anderson, K. C. A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from Bortezomib. Cancer Cell, 2005,8(5), 407-419.
[69] Proksch, P., Edrada, R. A., & Ebel, R. Drugs from the sea—Current status andmicrobiological implications. Applied Microbiology and Biotechnology,2002, 59(2-3), 125-134.
[70] Molinski, T. F., Dalisay, D. S., Lievens, S. L., & Saludes, J. P. Drug development frommarine natural products. Nature Reviews Drug Discovery,2009, 8(1), 69-85
[71] Newman, D. J., & Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014.Journal of Natural Products, 79(3), 629-661.
[72] Halberg, R.B.; Katzung, D.S.; Hoff, P.D.; Moser, A.R.; Cole, C.E.; Lubet, R.A.; Donehower, L.A.; Jacoby, R.F.; Dove, W.F. Tumorigenesis in the multiple intestinal neoplasia mouse: Redundancy of negative regulators and specificity of modifiers. Proc. Natl. Acad. Sci. USA 2000, 97, 3461–3466.
[73] Terasaki, M.; Matsumoto, N.; Hashimoto, R.; Endo, T.; Maeda, H.; Hamada, J.; Osada, K.; Miyashita, K.; Mutoh, M. Fucoxanthin administration delays occurrence of tumors in xenograft mice by colonospheres, with an anti-tumor predictor of glycine. J. Clin. Biochem. Nutr. 2019, 64, 52–58.
[74] Leal, M. C., Puga, J., Serôdio, J., Gomes, N. C., & Calado, R. Trends in the discovery of newmarine natural products from invertebrates over the last two decades–Where and what are webioprospecting, PLoS One, 2012, 7(1), e30580.

[75] Skropeta, D., & Wei, L. Recent advances in deep-sea natural products. Natural ProductReports, 2014, 31(7), 999-1025.
[76] Blunt, J. W., et al. Marine Natural Products. Natural Product Reports,2023, 40(5), 854-903.
[77] Pereira, D. M., et al. Marine Natural Products in Anti-Cancer Therapy. Marine Drugs,2021, 19(6),306.
[78] Thomas, T. R. A., et al. Marine-Derived Compounds in Cancer Therapy. Molecular Cancer Therapeutics, 19(8), 2020, 1706-1718.