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EDITED BY
Daniel Loic Pouliquen,
Inserm UMR 1307 (CRCI2NA), ICO., France

REVIEWED BY
Patrizia Diana,
University of Palermo, Italy
Tan Suet May Amelia,
University of Malaysia Terengganu, Malaysia

*CORRESPONDENCE
Hubing Shi
shihb@scu.edu.cn

†These authors have contributed equally to this work

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The therapeutic potential and application of marine alkaloids in treating breast cancer

Jing Yu†, Xinmin Wang†, Peixin Du and Hubing Shi*

Institute of Breast Health Medicine, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu, Sichuan, China

Breast cancer is a major threat to women's health worldwide. Although the 5-year survival rate is relatively high, treating recurrent and metastatic breast cancer remains challenging. Existing anticancer drugs are often accompanied by adverse reactions; thus, there is an urgent need to explore safer and more effective treatment options. Marine natural compounds, especially alkaloids, are considered to be a potential treasure trove of new anticancer drugs due to their unique chemical structure and wide range of biological activities. A variety of marine alkaloids against breast cancer, including ecteinascidins, halichondrins, manzamines, and trabectedins, have opened new avenues for breast cancer treatment by employing multiple mechanisms, such as inducing cell apoptosis and autophagy, blocking cell cycle, inhibiting angiogenesis, targeting oncogene pathways, and inhibiting metastasis and invasion. Currently, Yondelis (trabectedin) has completed phase II clinical trials in patients with breast cancer and has shown certain efficacy. However, the clinical application of marine alkaloids still needs further research and development. This article deeply explores the mechanism of action of marine alkaloids against breast cancer and anticipates their clinical application prospects. With the deepening of research and the advancement of development, marine alkaloids are expected to bring new breakthroughs in breast cancer treatment.

KEYWORDS

marine organisms, marine alkaloids, breast cancer, cancer therapy, antitumor mechanism

Introduction

More than 2.3 million cases of breast cancer occur annually, and breast cancer has surpassed lung cancer as the leading cause of cancer worldwide, accounting for 11.7% of all cancer cases (Sung et al., 2021). It is estimated that more than 680,000 people died from breast cancer in 2020, making it the primary cause of cancer deaths among women (Sung et al., 2021). Breast cancer mortality is markedly different due to differences in access to diagnosis, treatment, and palliative care. To eliminate inequalities in breast cancer outcomes, the World Health Organization launched a Global Breast Cancer Initiative

(GBCI) in 2021, aiming to reduce breast cancer by 2.5% per year through health promotion and early detection, timely diagnosis, and comprehensive breast cancer management (Trapani et al., 2022). Currently, the mainstay of treatment for breast cancer is surgical resection and chemotherapy. For patients with advanced metastatic breast cancer, radiotherapy and/or chemotherapy alone is usually used, with a 5-year survival rate of less than 30% (Burguin et al., 2021; Miller et al., 2022). However, chemotherapy drugs are usually highly toxic. At the same time, traditional drug preparations lack tumor-targeting activity, which results in only a few drugs being able to effectively target tumor tissues, leading to low drug utilization (Mayer, 2013). Therefore, there is an urgent need to discover and develop new safe and effective anticancer drugs.

Natural compounds have emerged as essential sources of novel pharmaceuticals. These compounds, derived from diverse natural resources, exhibit a remarkable chemical variety and thus demonstrate an astonishing diversity of pharmacological processes (Hussain et al., 2023). Oceans, which cover more than 70% of the Earth's surface and account for 95% of the entire biosphere, stand as a vast and invaluable natural treasure trove of compounds (Hussain et al., 2023). Over 30,000 marine natural products have been isolated from the aquatic world (Lyu et al., 2021). These organisms, along with their secondary metabolites, present attractive structures and a wide range of biological activities that may be useful for finding drugs with greater efficacy and specificity for treating many human diseases (Proksch et al., 2002). According to the US Food and Drug Administration (FDA) (https://www.fda.gov) and the Australian Therapeutic Goods Administration (TGA) (https://www.tga.gov.au), as of March 2024, the FDA or TGA has approved 15 marine-derived drugs, 10 of which are used in cancer treatments. Ara-C (cytarabine) isolated from Caribbean sponges *Cryptotheca crypta*, which is the first marine drug, received FDA approval in 1969 to treat leukemia (Glaser and Mayer, 2009). Eribulin mesylate is a synthetic analog of the marine natural product halichondrin B, which was approved by the FDA in 2010 for the treatment of metastatic breast cancer (Huyck et al., 2011). Trabectedin, a marine-derived alkylating agent from tunicates, underwent a phase II clinical trial in patients with progressive breast cancer and was approved for use in soft tissue sarcoma and ovarian cancer (Zelek et al., 2006; Barone et al., 2017; Gadducci and Cosio, 2022).

There are still many marine secondary metabolites undergoing preclinical studies, of which alkaloids are among the most diverse and studied compounds. Marine alkaloids are alkaline natural products with important biological activities, including amine nitrogen functional groups and complex carbon skeleton ring structures (Zhou et al., 2021). In the past decade of research, it has shown extraordinary pharmacological potential due to its anti-tumor ability, not only showing significant effects in the treatment of breast cancer, but also showing potential therapeutic value in other types of malignant tumors, such as pancreatic cancer and mesothelioma (Hoda et al., 2016; Li Petri et al., 2020; Fernandes et al., 2022; Carbone et al., 2023; Hussain et al., 2023). These alkaloids mainly act on different tumor cells through various mechanistic pathways, such as cytotoxicity, antiproliferation, apoptosis, cell cycle arrest, and autophagy, to inhibit tumor progression (Figure 1). Rehman et al. compiled a review of the anticancer bioactivity of marine-derived compounds and their potential mechanisms (Wali et al., 2019) and Bhubalan et al. reviewed the potential applications of natural products synthesized by sponge-associated microorganisms in medicine and other industries (Amelia et al., 2022). Both reviews describe the anti-breast cancer activity exhibited by marine derivatives. In 2011, Gali-Muhtasib et al. published a review on anticancer marine alkaloids, discussing extensively studied marine alkaloids and their mechanisms of action (Tohme et al., 2011). However, it did not specifically focus on treating breast cancer. Hussain et al. recently summarized the cytotoxic effects of various marine derivatives on breast cancer cells in their review (Hussain et al., 2023), but this review only included 24 marine alkaloids and did not provide a comprehensive description of marine alkaloids. In this review, we retrospectively summarize the marine alkaloids with cytotoxic effects on breast cancer cell lines, along with the clinical breast cancer therapeutic efficacy of some compounds, and discuss their potential targets and mechanisms of action.

Marine alkaloids: an overview

Marine alkaloids, a class of secondary metabolites of marine organisms with several nitrogenated structures, are among the most important natural products mainly derived from sponges, bacteria, fungi, cyanobacteria, algae, and tunicates. Nearly 40% of the 800 compounds extracted from cyanobacteria were alkaloids, which may be due to the remarkable nitrogen-fixing ability of cyanobacteria, which facilitates the production of alkaloids (Han et al., 2022). The presence of nitrogen electron-donor atoms in the structure of marine alkaloids significantly enhances their interaction with target proteins, enzymes, and receptors by making several types of interactions, such as hydrogen bonds, dipole–dipole interactions, hydrophobic interactions, van der Waals forces, and stacking interactions (Vitaku et al., 2014). This structural feature is crucial for the biological activity of these compounds and their potential as lead compounds in drug development. Marine alkaloids usually have complex and specific chemical structures and can be divided into approximately 20 different chemical classes, including acridine, β-carboline, bromotyrosine, brominated, dimeric aaptamine, guanidine, imidazole, indole, peptide, piperidine, pyrimidine, pyridine, pyrrole, pyrroloiminoquinone, quinoline and quinolizidine, tetrahydroisoquinoline, steroidal, terpenoidal, manzamine, and sesquiterpene quinone/hydroquinone alkaloids (Elissawy et al., 2021). Among marine alkaloids, approximately 25% are indole alkaloids, which are the most common and complex alkaloids (Kobayashi et al., 1990). Moreover, marine alkaloids exhibit a strong diversity of biological activities and are considered lead compounds for the development of potent antibacterial, antifungal, antiviral, antiprotozoal, antimalarial, antituberculosis, anti-inflammatory, antidiabetic, immunomodulatory, or neurological diseases control agents (Gul and Hamann, 2005; Arai et al., 2008; Souza et al., 2020; Willems et al., 2020; Ajebli et al., 2021; Tempone et al., 2021; Izumida et al., 2022; Montuori

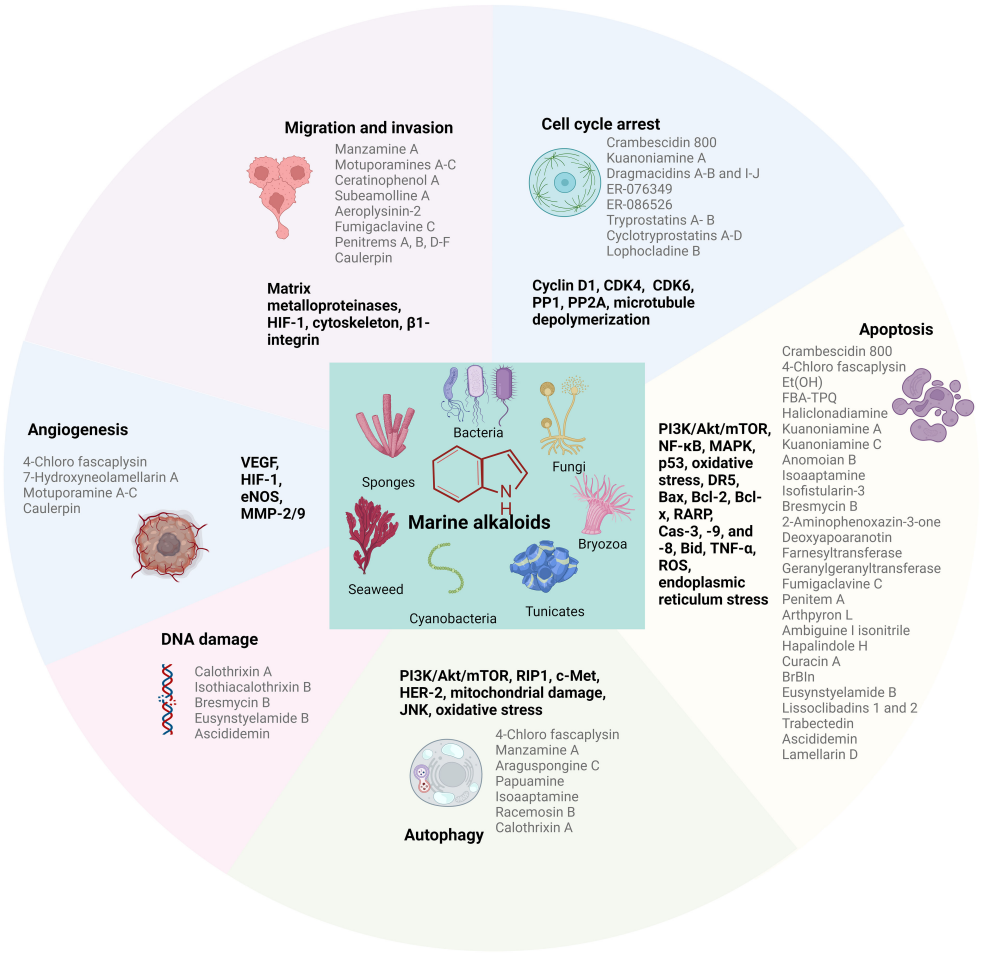

FIGURE 1
Major sources of marine alkaloids and their primary mechanisms of action as anticancer agents. The graphic is completed by using BioRender.com.

et al., 2022). At the same time, numerous studies have shown their significant cytotoxic effects on different types of cancer cells (Tohme et al., 2011; Imperatore et al., 2014).

Marine anti-breast cancer alkaloids

Marine sponge

Sponges are the most primitive invertebrates in the marine ecosystem, accounting for 30% of all marine natural products (Bian et al., 2020). The particularly porous structure of sponges provides raw materials, sites, and storage space and releases opportunities for the synthesis of secondary metabolites with special structures and functions (Table 1). Sponges generally obtain sufficient nutrients by filtering large amounts of water, and this filter-feeding behavior introduces bacteria and other microorganisms into the sponge's waterways, thus forming a sponge–microbe holobiont (Amelia et al., 2022). Studies have gradually shown that some sponge-derived metabolites may not originate from sponges but from sponge-associated bacteria (Amelia et al., 2022). It is worth noting that not all sponge-derived metabolites can be confirmed to originate from marine biological hosts or bacterial symbionts. Therefore, the sponge-derived alkaloids involved here may originate from sponge-associated microorganisms. The structures of some alkaloids from marine sponges are shown in Figure 2.

Crambescidin 800, a guanidine alkaloid isolated from the sponge *Monanchora viridis*, was found to exhibit cytotoxicity against various breast cancer cell lines, especially the triple-negative breast cancer cell lines T11 and SUM159PT, with IC_{50} values of 0.07 ± 0.01 and 0.59 ± 0.08 μM, respectively (Shrestha et al., 2018). The cytotoxic effect of crambescidin 800 occurs mainly through inhibiting the protein expression of cyclin D1, CDK4, and CDK6, which causes tumor cells to undergo cell cycle arrest in the G2/M phase. Furthermore, this inhibition is associated with decreased phosphorylation of the Akt/mTOR, NF-κB, and MAPK pathways, which, in turn, mediates tumor cell apoptosis (Shrestha et al., 2018). Alkaloids sourced from different species within the *Monanchora* genus are recognized for their diverse chemical structures and biological activities. Compounds such as monanchoradin A, crambescidin 814, monalidine A, monanchomycalin C, and ptilomycalin A exhibit antiproliferative effects on different cancer cells. Among them, crambescidin 814 is more cytotoxic, with an IC_{50} of approximately 0.05 μM for the

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TABLE 1 Alkaloids derived from marine sponges against breast cancer.

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Crambescidin 800	*Monanchora viridis*	SUM159PT	0.59 ± 0.08 μM	Cell cycle arrest; apoptosis; inhibit Akt, NF-κB, and MAPK pathways	(Shrestha et al., 2018)
		T11	0.07 ± 0.01 μM		
		MDA-MB-435	0.009/0.015 μM	Cytotoxicity	(El-Demerdash et al., 2016)
Monanchoradin A	*Monanchora n.* sp.	MDA-MB-435	11/9.3 μM	Cytotoxicity	(El-Demerdash et al., 2016)
		MDA-MB-231	GI_{50}: 0.068 μM		(Gogineni et al., 2020)
		MDA-MB-468	GI_{50}: 0.095 μM		
Crambescidin 814		MDA-MB-435	0.04/0.07 μM		(El-Demerdash et al., 2016)
Monalidine A			0.32/0.86 μM		
Monanchomycalin C	*Monanchora pulchra*	MDA-MB-231	8.2 μM	Cytotoxicity	(Tabakmakher et al., 2013)
Ptilomycalin A			4.3 μM		
Fascaplysin	*Thorectandra* sp.	MCF-7	0.03–0.38 mg/mL	Cytotoxicity	(Charan et al., 2004)
		T-47D	5 ± 0.2 μM		(Zhidkov et al., 2019)
4-Chloro fascaplysin	/	MDA-MB-231	0.3 μM	Apoptosis and autophagy; anti-angiogenesis; inhibit PI3K/Akt/mTOR pathway	(Sharma et al., 2017)
1-Deoxysecofascaplysin A	*Thorectandra* sp.	MCF-7	1.5 μg/mL	Cytotoxicity	(Charan et al., 2004)
3,10-Dibromofascaplysin		T-47D	>5 μM		(Zhidkov et al., 2019)
3-Bromofascaplysin					
14-Bromoreticulatate					
14-Bromoreticulatine					
Et(OH)	*Stylissa carteri*	MDA-MB-231, MDA-MB-468, SKBR3, HCC-1954	<15 μg/mL	Apoptosis; anti-migratory	(Bashari et al., 2019)
Debromohymenialdisine	*Stylissa flabeliformis*	MCF-7	25 mM	Cell cycle arrest	(Yang et al., 2015)
Manzamine A	*Acanthostrongylophora ingens*	MCF-7	2.86 ± 0.19 μM	Autophagy	(Wang et al., 2023)
		MDA-MB-231	7.87 ± 0.30 μM	/	
(+)-8-Hydroxymanzamine A		BT-549	0.75 ± 0.05 μg/mL	Cytotoxicity	(Samoylenko et al., 2009)
(+)-Manzamine A			1.1 ± 0.0 μg/mL		
Annomontine		MCF-7	1.21 μg/mL	Cytotoxicity	(Ibrahim and Mohamed, 2017)
Acanthomine A			2.81 μg/mL		
1,2,3,4-Tetrahydronorharman-1-one			8.27 μg/mL		
Ingenine E			3.50 μg/mL		
7-Hydroxyneolamellarin A	*Dendrilla nigra*	T47D	1.9 μM	Anti-angiogenesis	(Liu et al., 2007)
Araguspongine C	*Xestospongia* sp.	BT-474	15.2 ± 2.1 μM	Autophagy; inhibit PI3K/Akt/mTOR pathway	(Akl et al., 2015)

(Continued)

TABLE 1 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
		MCF-7	8.5 ± 1.6 μM	/	
		MDA-MB-231	10.1 ± 2.3 μM		
		SKBR3	18.3 ± 2.5 μM		
		T-47D	46.1 ± 4.8 μM		
Meso-araguspongine C		MCF-7	0.44 ± 0.05 μM	Cytotoxicity	(Dung et al., 2019)
Araguspongine N			7.36 ± 1.16 μM		
Araguspongine O			5.32 ± 0.67 μM		
Araguspongine P			5.68 ± 0.89 μM		
Araguspongine A			7.82 ± 0.53 μM		
Araguspongine E			24.85 ± 1.2 μM		
Araguspongine L			24.85 ± 0.91 μM		
Renieramycin M		MDA-MB-231	3.8 nM	Cytotoxicity	(Hussain et al., 2023)
		MDA-MB-435	6.3 ± 0.1nM	Downregulate the expression of PTPRK	(Charupant et al., 2009)
Motuporamines A-C	*Xestospongia exigua*	MDA-MB 231	/	Anti-invasive, anti-angiogenic	(Tohme et al., 2011)
Makaluvamines (4a–g, 7c–g)	/	MCF-7	1.0–13.2 μM	Inhibit the enzyme topoisomerase II	(Shinkre et al., 2007)
		MDA-MB-468	0.3–4.5 μM		
FBA-TPQ	*Zyzzya*	MCF-7	0.097 μmol/L	Apoptosis; activate JNK; mitochondrial damage	(Wang et al., 2009)
		MDA-MB-468	0.125 μmol/L		
PEA-TPQ		MCF-7	0.435 μmol/L		
		MDA-MB-468	0.101 μmol/L		
MPA-TPQ		MCF-7	0.709 μmol/L		
		MDA-MB-468	0.428 μmol/L		
DPA-TPQ		MCF-7	1.22 μmol/L		
		MDA-MB-468	0.277 μmol/L		
Panuramine	*Haliclona* sp.	MCF-7	20 μM (Inhibition: 98.7%)	Autophagy	(Kanno et al., 2013)
			1.39 μM	Apoptosis	(Yamazaki et al., 2013)
Haliclonadiamine			1.35 μM		
3-Dodecyl pyridine containing a terminal cyano group			48.4 μM	Cytotoxicity	(Zhang et al., 2016)
Haliclonacyclamine A			2.6 μg/mL		(Mani et al., 2011)
Kuanoniamine A	*Oceanapia sagittaria*	MCF-7	0.81 ± 0.11 μM	Cell cycle arrest; apoptosis	(Kijjoa et al., 2007)
		MDA-MB-231	10.23 ± 3.35 μM	Cytotoxicity	
Kuanoniamine C		MCF-7	0.12 ± 0.07 μM	Apoptosis	
		MDA-MB-231	0.73 ± 0.27 μM	Cytotoxicity	
Dragmacidin A	*Hexadella* sp.	MDA-MB-231	3.8 μM	Cell cycle arrest; antiproliferative; inhibit of PP1 and/or PP2A phosphatases	(Cruz et al., 2018)
Dragmacidin B			28 μM		

(Continued)

TABLE 1 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Dragmacidin I	*Dragmacidon* sp.		4.7 μM		
Dragmacidin J			7.5 μM		
Anomoian B	*Hexadella* sp.	MDA-MB-231	5.3 μM	Apoptosis	(Tarazona et al., 2017)
Aaptamine	*Aaptos aaptos*	MDA-MB-231	147.2 ± 3.9 μM	Apoptosis	(Dyshlovoy et al., 2014)
Demethyl(oxy)aaptamine			9.1 ± 1.4 μM		
		T-47D	33.02 ± 8.49 μM	Cytotoxicity	(Wu et al., 2018)
		MCF-7	23.11 ± 2.36 μM		
Isoaaptamine		MDA-MB-231	10.6 ± 2.8 μM	Apoptosis	(Dyshlovoy et al., 2014)
		T-47D	30.13 ± 3.07 μM	Induces apoptosis and autophagy via oxidative stress	(Wu et al., 2018)
		MCF-7	49.12 ± 12.28 μM	Cytotoxicity	
2,3-Dihydro-2,3-dioxoaaptamine		MCF-7	40.70 ± 2.65 μM	Cytotoxicity	(Trang et al., 2021)
Laulimalide	*Cacospongia*	MDA-MB-435	5.74 nM	Pro-apoptotic effect by inducing mitotic arrest and activation of the caspase pathways	(Mooberry et al., 1999)
Isofistularin-3	*Aplysina aerophoba*	MDA-MB-231	GI_{50}: 7.3 ± 7.0 μM	Cell cycle arrest; sensitization to TRAIL	(Florean et al., 2016)
ER-076349	*Halichondria okadai*	MDA-MB-435	0.14 ± 0.1 nM	G2/M cell cycle arrest; disruption of mitotic spindles	(Towle et al., 2001)
ER-086526			0.09 ± 0.01 nM		
Ceratinophenol A	*Pseudoceratina arabica*	MDA-MB-231	/	Anti-migratory	(Shaala et al., 2015b)
Ceratamines A, B	*Pseudoceratina* sp.	MCF-7	10 μg/mL	Anti-mitotic	(Manzo et al., 2003)
Subereamolline A	*Suberea mollis*	MDA-MB-231	400 nM (anti-migratory), 1.7 μM (anti-invasion)	Anti-migration, anti-invasion	(Shaala et al., 2012)
Aeroplysinin-2	*Suberea* sp.	MDA-MB-231	18 μM	Anti-migratory	(Shaala et al., 2015a)
Maedamine A		MCF-7	6.9 μM	Cytotoxicity	(Saha et al., 2013)
Maedamine B			10.5 μM		
Hemimycalin C	Hemimycale sp.	MDA-MB-231	28.5 ± 0.21 μM	Cytotoxicity	(Shaala and Youssef, 2021)
Hemimycalin D			31.7 ± 0.25 μM		
Hemimycalin E			21.5 ± 0.18 μM		
Netamine C	*Biemna laboutei*	MDA-MB-231	GI_{50}: 2.6 μM	Cytotoxicity	(Sorek et al., 2006)
Netamine D			GI_{50}: 6.3 μM		
Damirine A	*Damiria* sp.	MDA-MB-231	GI_{50}: 2.0 μM	Inhibit protein kinase C	(Tran et al., 2021)
3,3′-BIEA	*Gellius* sp.	MCF-7	3.4 μM	Cytotoxicity	(Chantana et al., 2021)
		MDA-MB-231	3.4 μM		
		VERO cells	3.8 μM		
Trachycladindole A	*Trachycladus laevispirulifer*	MDA-MB-231	GI_{50}: 1.2 μM	Cytotoxicity	(Capon et al., 2008)

(Continued)

TABLE 1 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Trachycladindole B			GI_{50}: 2.7 μM		
Trachycladindole C			GI_{50}: 12.2 μM		
Trachycladindole D			GI_{50}: 2.4 μM		
Trachycladindole E			GI_{50}: 1.1 μM		
Trachycladindole F			GI_{50}: 2.3 μM		
Neopetrosiamine A	*Neopterans proxima*	MCF-7	3.5 μM	Cytotoxicity	(Wei et al., 2010)
Psammaplysin Z	*Aplysinella* sp.	MDA-MB-231	19.4 ± 1.80 μM	Cytotoxicity	(Shaala and Youssef, 2019)
19-Hydroxypsammaplysin Z			13.2 ± 0.45 μM		
Psammaplysin A			3.90 ± 0.20 μM		
Psammaplysin E			0.29 ± 0.05 μM		
(−)-Calcaridine	*Leucetta chagosensis*	MCF-7	25.3 μM	Cytotoxicity	(Tang et al., 2019)
(2E, 9E)-Pyronaamidine-9-(N-methylimine)			24.2 μM		
Naamine J	*Leucandra* sp.	MCF-7	20.1 μM	Cytotoxicity	(Tang et al., 2017)
Aplyzanzine B	Jaspis *sp.* and Bubaris *sp.*	MDA-MB-231	7.8 μM	Apoptosis	(Tarazona et al., 2017)
Madangamine F	*Pachychalina alcaloidifera*	MDA-MB-435	16.2 μg/mL	Cytotoxicity	(de Oliveira et al., 2007)
Haliclonacyclamine F			1.0 μg/mL		
Arenosclerin D			1.2 μg/mL		
Arenosclerin E			3.1 μg/mL		
Ingenamine G	*Pachychalina* sp.	MCF-7	23.6 μM	Cytotoxicity	(de Oliveira et al., 2004)
1,5-Diazacyclohenicosane	*Mycale* sp.	MDA-MB-231	GI_{50}: 5.74 μM	Cytotoxicity	(Coello et al., 2009)
Oroidin	*Agelas oroides*	MCF-7	GI_{50}: 42 μM	Cytotoxicity	(Dyson et al., 2014)
19-Oxofasciospongine A	*Fasciospongia* sp.	MCF-7	13.4 μM	Cytotoxicity	(Yao et al., 2009)
Actinozine	*Streptomyces* sp.	MCF-7	88.8 μM	Cytotoxicity	(Shaala et al., 2019)
Makaluvamine G	*Histodermella* sp.	MCF-7	0.4 μg/mL	Cytotoxicity	(Carney et al., 1993)
3,5-Bis(3′-indolyl) pyrazole 9a	*Spongosorites ruetzleri*	MCF-7	GI_{50}: 3.95 μM	Cytotoxicity	(Diana et al., 2007)
		NCI/ADR-RES	GI_{50}: 27.6 μM		
		MDA-MB-231	GI_{50}: 8.06 μM		
		HS 578T	GI_{50}: 18.5 μM		
		BT-549	GI_{50}: 15.9 μM		
		T-47D	GI_{50}: 79.7 μM		
3,5-Bis(3′-indolyl) pyrazole 9d		MCF-7	GI_{50}: 2.64 μM		
		NCI/ADR-RES	GI_{50}: 2.25 μM		

(Continued)

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TABLE 1 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
		MDA-MB-231	GI_{50}: 2.95 μM		
		HS 578T	GI_{50}: 3.27 μM		
		MDA-MB-435	GI_{50}: 2.99 μM		
		BT-549	GI_{50}: 2.03 μM		
		T-47D	GI_{50}: 4.06 μM		

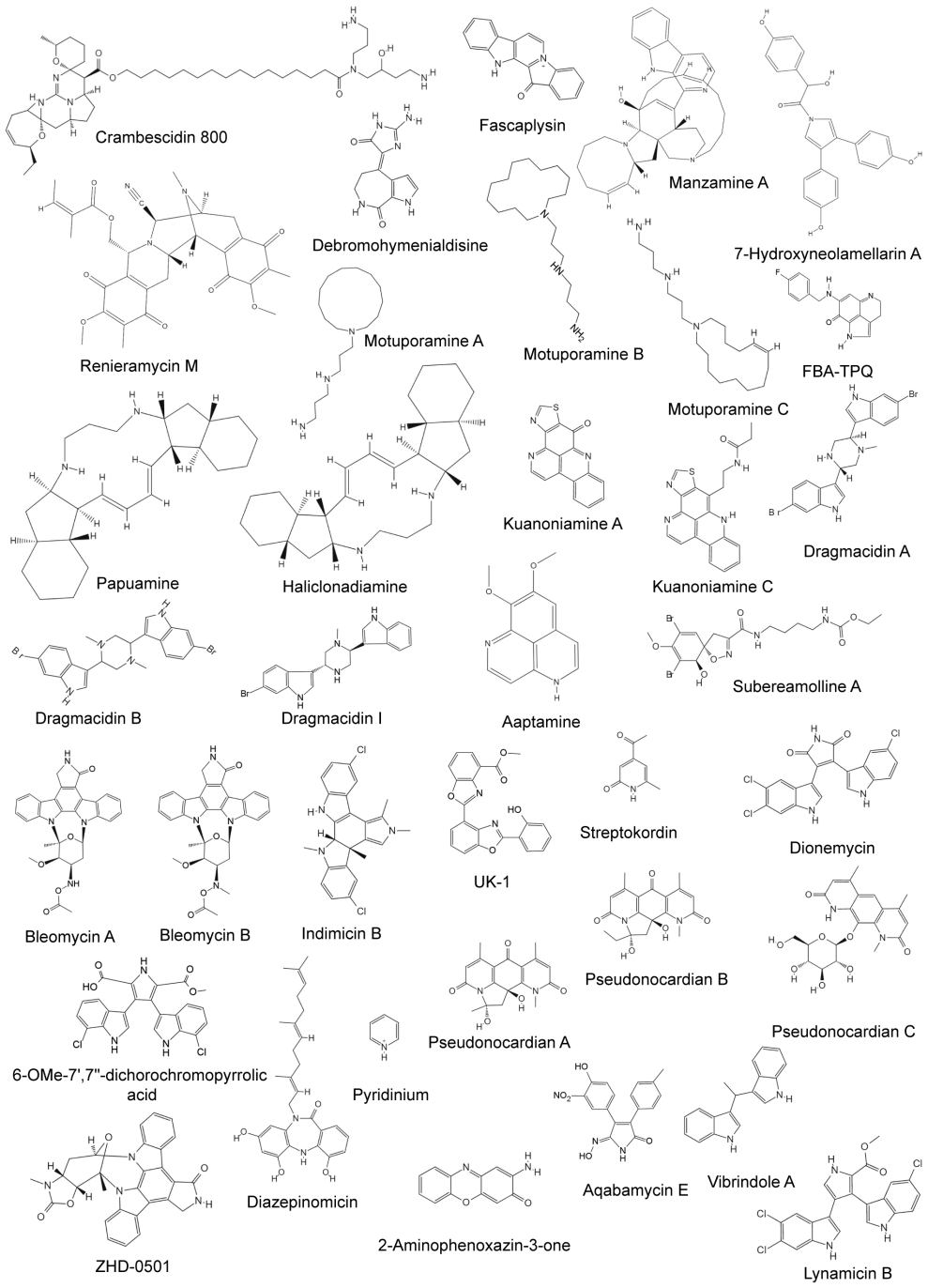

FIGURE 2
Chemical structures of anti-breast cancer alkaloids derived from marine sponge and bacteria.

MDA-MB-435 cell line (Tabakmakher et al., 2013; El-Demerdash et al., 2016; Gogineni et al., 2020).

Angiogenesis is a prominent characteristic of various types of cancer and is a critical process in tumor growth and progression. Fascaplysin is a beta-carboline alkaloid isolated from *Thorectandra* sp. sponge that exhibits significant cytotoxicity against MCF-7 and T-47D cells, with IC_{50} values of 0.03–0.38 mg/mL and 5 ± 0.2 μM, respectively (Charan et al., 2004; Zhidkov et al., 2019). 4-Chloro fascaplysin, an analog of fascaplysin, has been shown to inhibit VEGF-dependent angiogenesis by affecting key proangiogenic factors such as HIF-1α, eNOS, and MMP-2/9 (Sharma et al., 2017). It also inhibited survival in the MDA-MB-231 cell line by modulating the PI3K/Akt/mTOR signaling cascade, simultaneously inducing autophagy and apoptosis (IC_{50} = 0.3 μM). Notably, 4-chloro fascaplysin does not show significant toxicity in experimental tumor mice at therapeutic doses, indicating good safety (Sharma et al., 2017). In addition, other analogs of fascaplysin, 1-deoxysecofascaplysin A, 3-bromofascaplysin, and 3,10-dibromofascaplysin can also inhibit the proliferation of breast cancer cells (Charan et al., 2004; Zhidkov et al., 2019). 3-Bromofascaplysin and 3,10-dibromofascaplysin can be used to synthesize the alkaloids 14-bromoreticulatate and 14-bromoreticulatine, the latter of which is cytotoxic to a variety of cell lines (Zhidkov et al., 2019).

Et(OH), an extract obtained from the sponge *Stylissa carteri*, exhibited potential dose-dependent cytotoxic effects on different breast cancer cell lines, such as HCC-1954, MDA-MB-231, MDA-MB-468, and SKBR3 (with IC_{50} < 15 μg/mL) (Bashari et al., 2019). In the HCC-1954 cell line, it exerts cytotoxic effects by inhibiting growth and inducing apoptosis (Bashari et al., 2019). In the triple-negative breast cancer cell line MDA-MB-231, Et(OH) not only has anti-metastatic effects but also synergistically enhances cell death when combined with adriamycin or paclitaxel (Bashari et al., 2019). Debromohymenialdisine, also isolated from *Stylissa* species, is a pyrrole seven-membered ring lactam alkaloid (Yang et al., 2015). When combined with radiotherapy, it can increase the MCF-7 inhibition rate and exert a strong radiotherapy effect by downregulating the expression of pCHK1/2 while reducing the survival rate of breast cancer $CD44^+/CD24^-$ stem cells (Yang et al., 2015).

Manzamine A exhibited significant cytotoxicity in inhibiting the proliferation, migration, and invasion of both MDA-MB-231 and MCF-7 breast cancer cells, with IC_{50} values of 7.87 ± 0.30 and 2.86 ± 0.19 μM, respectively (Wang et al., 2023). Mechanistic studies have shown that manzamine A treatment reduces the expression level of RIP1, a key upstream regulator of autophagy, thereby mediating the autophagy process of tumor cells through the inhibition of the Akt/mTOR pathway (Wang et al., 2023). *Acanthostrongylophora ingens* can produce a variety of manzamine alkaloids. In addition to manzamine A, (+)-8-hydroxymanzamine A and (+)-manzamine A were also isolated, and both showed significant anti-breast cancer activity (Samoylenko et al., 2009). In addition to manzamine alkaloids, *A. ingens* is a rich source of pyrimidine β-carboline alkaloids. Among them, annomontine, acanthomine A, 1,2,3,4-tetrahydronorharman-1-one, and ingenine E can significantly inhibit the activity of various tumors, including breast cancer, colorectal cancer, and lung cancer (Ibrahim and Mohamed, 2017).

7-Hydroxyneolamellarin A, a laminin-like alkaloid derived from the sponge *Dendrilla nigra*, serves as an inhibitor of HIF-1 and VEGF. It exhibits cytotoxic effects by suppressing hypoxia-induced activation of HIF-1 (with an IC_{50} of 1.9 μM), subsequently reducing the activation of its downstream target gene, VEGF (Liu et al., 2007).

A variety of bis-1-oxaquinolizidine alkaloids can be isolated from the sponge *Xestospongia*, including araguspongines A, C, E, L, and N–P and meso-araguspongine C, all of which are capable of killing breast cancer cells (Dung et al., 2019). Among them, meso-araguspongine C has the most potent cytotoxicity (IC_{50} = 0.44 μM), and araguspongine C is cytotoxic to different breast cancer cell lines (Akl et al., 2015; Dung et al., 2019). In BT-474, which overexpress HER-2, araguspongine C significantly induces autophagy cell death, which is mainly achieved by inhibiting the activation of c-Met and the receptor tyrosine kinase HER-2 (Akl et al., 2015). Renieramycin M is also isolated from *Xestospongia* sp. and can effectively inhibit the growth of cancer cells. The IC_{50} values for breast cancer MDA-MB-231 and MDA-MB-435 cells reached nanomolar levels, which were 3.8 and 6.3 ± 0.1 nM, respectively (Charupant et al., 2009; Hussain et al., 2023). For the MDA-MB-435 cell line, renieramycin M treatment significantly downregulated the expression of PTPRK (Charupant et al., 2009). Motuporamines A–C are anti-angiogenic and anti-invasive alkaloids extracted from the marine sponge *Xestospongia exigua* that can inhibit the invasion of breast and prostate cancers into the basement membrane *in vitro* (Tohme et al., 2011). Among them, motuporamine C is the most effective. It hinders the migration and angiogenesis of tumor cells by changing the cytoskeleton and inhibiting the activation of β1-integrin, but it does not affect cell proliferation (Tohme et al., 2011).

Makaluvamines are marine alkaloids from a wide range of sources, including *Zyzzya* cf. *marsalis*, *Histodermella* species, *Zyzzya fuliginosa*, and *Smenospongia aurea* (Shinkre et al., 2007). Its multiple analogs exhibit *in vitro* cytotoxicity against breast cancer, providing a solid foundation for the development of new anticancer drugs (Shinkre et al., 2007; Wang et al., 2009). Among them, FBA-TPQ exhibited significant anticancer effects on the MDA-MB-231 and MCF-7 cell lines through the induction of apoptosis, with IC_{50} values of 0.125 μmol/L and 0.097 μmol/L, respectively (Wang et al., 2009). These effects are primarily mediated through the activation of p53, which then regulates the cell cycle, apoptosis, and DNA damage-related proteins (Wang et al., 2009). Encouragingly, these anticancer mechanisms were independent of the intracellular p53 status, suggesting that FBA-TPQ may have potential roles in different contexts (Wang et al., 2009).

Papuamine derived from the marine sponge *Haliclona* sp. has a significant cytotoxic effect on the MCF-7 cells, with an inhibition rate of 98.7% at 20 μM (Kanno et al., 2013). Papuamine initiates MCF-7 autophagy by inducing mitochondrial damage and JNK pathway activation, thereby reducing the cell survival rate (Kanno et al., 2013; Yamazaki et al., 2013). Haliclonadiamine, 3-dodecyl pyridine containing a terminal cyano group, and haliclonacyclamine A, also from *Haliclona* species, also have antiproliferative effects on MCF-7 cell lines (Mani et al., 2011; Yamazaki et al., 2013; Zhang et al., 2016). Haliclonadiamine can induce cancer cell apoptosis, but the

mechanisms of action of the remaining two compounds are still unknown and await further research (Yamazaki et al., 2013).

Kuanoniamines A and C are two pyridine acridine alkaloids isolated from *Oceanapia sagittaria*. Kuanoniamine A has a significant growth inhibitory effect on both ER^+ (MCF-7) and ER^- (MDA-MB-231) breast cancer cells (Kijjoa et al., 2007). However, kuanoniamine C can only decrease the viability of ER^+ breast cancer cell lines, and its antiproliferative effect may be related to estrogen receptors (Kijjoa et al., 2007). Both can cause an increase in the number of apoptotic MCF-7 cells, but kuanoniamine A treatment can cause G1 phase cell cycle arrest, while kuanoniamine C does not (Kijjoa et al., 2007).

Dragmacidins A–B and I–J were obtained from *Hexadella* sp. and *Dragmacidon* sp., respectively. This family of compounds can cause cell cycle arrest by inhibiting the phosphorylation activity of PP1 and/or PP2A, thereby affecting cell proliferation. Dragmacidins A, I, and J showed low micromolar cytotoxicity toward MDA-MB-231 cells (Cruz et al., 2018). Anomoian B also comes from *Hexadella* species, and it can mediate cytotoxicity against MDA-MB-231 cells by inducing apoptosis (Tarazona et al., 2017).

Aaptamine is a marine alkaloid isolated from *Aaptos* sp. Its various derivatives including demethyl(oxy)aaptamine, isoaaptamine, and 2,3-dihydro-2,3-dioxoaaptamine, all have specific anticancer effects (Dyshlovoy et al., 2014; Wu et al., 2018). Among them, isoaaptamine mainly exerts cytotoxic effects through apoptosis and autophagy induced by oxidative stress (Wu et al., 2018).

Isofistularin-3 is a DNA methyltransferase inhibitor derived from *Aplysina aerophoba* (Florean et al., 2016). It can not only induce G0/G1 phase cycle arrest but also induce the expression of TRAIL receptor death receptor 5 by triggering endoplasmic reticulum stress, thereby causing cell apoptosis and showing cytotoxicity to a variety of tumor cells (Florean et al., 2016).

Halichondrin B is a tubulin depolymer with significant *in vitro* and *in vivo* anticancer activity, and ER-076349 and ER-086526 (eribulin mesylate) are its two analogs (Towle et al., 2001). In the MDA-MB-435 cell line, ER-076349 and ER-086526 can exhibit nanomolar cytotoxicity by inducing G2/M phase cell cycle arrest and disrupting the mitotic spindle (Towle et al., 2001).

Ceratinophenol A, subeamolline A, and aeroplysinin-2 have all been shown to inhibit the migration of breast cancer cells, among which subeamolline A can also prevent invasion (Shaala et al., 2012, 2015a, b). In addition to the above-mentioned alkaloids, a large number of alkaloids of various structural types with anti-breast cancer activity have also been found in other sponges, but their specific anticancer mechanisms need to be further studied (Table 1).

Marine bacteria

Marine bacteria are an important source of bioactive secondary metabolites. The *Streptomyces* genus is known for its ability to produce novel structures and bioactive metabolites (Table 2), many of which are unique alkaloids (Toumatia et al., 2015). The structures of some alkaloids from marine bacteria are shown in Figure 2. Two indolocarbazole alkaloids, bresmycins A and B, are produced by *Streptomyces* sp. NBU3142 (Ding et al., 2023). Both have potential cytotoxicity, with bresmycin B exhibiting greater inhibitory effects on MCF-7 cells (IC_{50} = 2.01 ± 0.35 μM) than bresmycin A (IC_{50} = 5.01 ± 0.82 μM) (Ding et al., 2023). Furthermore, bresmycin B also had significant inhibitory effects on MCF/ADR cells (a doxorubicin-resistant MCF-7 cell line), with an inhibition rate exceeding 50% (IC_{50} = 4.47 μM). DNA damage and cell apoptosis may be the possible mechanisms underlying these effects (Ding et al., 2023). Indimicins A–E and spiroindimicins A–D, bisindole alkaloids, were isolated from *Streptomyces* sp. SCSIO 03032, a deep-sea actinomycete. However, only indimicin B exhibited moderate cytotoxicity (IC_{50} = 10.0 ± 0.3 μM) against the MCF-7 cell line (Zhang et al., 2012, 2014). Several other alkaloids from different *Streptomyces* species have been shown to have inhibitory effects on MCF-7 cells (Table 2). Notably, UK-1 (GI_{50} = 0.65 μM) exhibited even greater potency (Hohmann et al., 2009). Streptokordin, originating from *Streptomyces* sp. KORDI-3238, possesses potent cytotoxic activity against MDA-MB-231 cells with an IC_{50} value of 7.5 μg/mL (Jeong et al., 2006). Dionemycin and 6-OMe-7′,7″-dichorochromopyrrolic acid, both isolated from *Streptomyces* sp. SCSIO 11791, have significant cytotoxic effects on the MDA-MB-435 and MDA-MB-231 cell lines, exhibiting IC_{50} values ranging from 3.9 to 25 μM (Song et al., 2020).

HD-0501 is a dimeric indole alkaloid isolated from *Actinomadura* sp. 007 that can inhibit the proliferation of the thermosensitive mouse breast cancer cell line tsFT210 (Han et al., 2005). Iodinin, 1,6-phenazinediol, questiomycin A, chandrananimycins A–C, and phenoxazin-3-one are also from *Actinomadura* species, among which iodinin and 1,6-phenazinediol showed obvious cytotoxicity to the breast cancer cell line MAXF 401NL (IC_{50} < 4.0 μg/mL), while other compounds showed antitumor activity against MCF-7 (IC70 < 1.4 μg/mL) (Maskey et al., 2003).

Diazepinomicin and pyridinium were obtained from the actinomycetes *Micromonospora* DPJ12 and *Amycolatopsis alba* var. nov. DVR D4, respectively. The former has a cytotoxic effect on MDA-MB-231 cells (IC_{50} = 2.1 μM), while the latter can significantly inhibit the proliferation of MCF-7 cells (Gourdeau et al., 2008; Dasari et al., 2012). Pseudonocardians A–C are produced by *Pseudonocardia* sp. SCSIO 01299, which is also a member of marine actinomycetes. All three compounds showed effective cytotoxicity to MCF-7 cells, among which pseudonocardians A and B were more active, with IC_{50} values of 0.027 and 0.021 μM, respectively (Li et al., 2011).

2-Aminophenoxazin-3-one, 2-amino-6-hydroxyphenoxazin-3-one, and 2-amino-8-benzoyl-6-hydroxyphenoxazin-3-one were all derived from *Halomonas* sp. strain GWS-BW-H8hM. All of these compounds showed obvious cytotoxic effects on the MCF-7 cell line, with GI_{50} values of 0.13, 1.6, and 2.0 μg/mL, respectively (Bitzer et al., 2006). Among them, 2-aminophenoxazin-3-one can reduce the ratio of G0/G1 cells and induce the apoptosis of tumor cells (Bitzer et al., 2006). Aqabamycin E and vibrindole A are produced by certain *Vibrio* species and have certain cytotoxic effects on both the MDA-MB-231 and MCF-7 cell lines, with IC_{50} values between 20 and 50 μg/mL (Al-Zereini et al., 2010). Lynamicin B isolated from *Marinispora* sp. NPS12745 showed antitumor effects against MDA-MB-435 and MDA-MB-231, with IC_{50} values of 6.9 and 28.6 μM, respectively (Song et al., 2020).

TABLE 2 Alkaloids derived from marine bacteria against breast cancer.

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Bresmycin A	*Streptomyces* sp. NBU3142	MCF-7	5.01 ± 0.82 μM	Apoptosis	(Ding et al., 2023)
Bresmycin B			2.01 ± 0.35 μM		
Indimicin A	*Streptomyces* sp. SCSIO 03032	MCF-7	23.7 ± 0.3 μM	Cytotoxicity	(Zhang et al., 2014)
Indimicin B			10.0 ± 0.3 μM		
Indimicin C			21.8 ± 0.9 μM		
Indimicin E			36.4 ± 2.3 μM		
Spiroindimicin A			>100 μg/mL		(Zhang et al., 2012)
Spiroindimicin B					
Spiroindimicin C					
Spiroindimicin D					
UK-1	*Streptomyces* sp.	MCF-7	GI_{50}: 0.65 μM	Cytotoxicity	(Hohmann et al., 2009)
SSV	*Streptomyces* sp. KS1908	MCF-7	4.44 μg/mL	Antiproliferative	(Kadiri et al., 2013)
Caboxamycin	*Streptomyces* sp. NTK 937	MCF-7	GI_{50}: 7.3 μM	Antiproliferative	(Hohmann et al., 2009)
Anandin A	*Streptomyces anandii* H41–59	MCF-7	7.5 μg/mL	Cytotoxicity	(Zhang et al., 2017)
Anandin B			>50 μg/mL	/	
Cyclo(6-OH-d-Pro-l-Phe)	*Streptomyces* sp.	MCF-7	30 μM	Cytotoxicity	(Shaala et al., 2016)
Bacillusamide			27 μM		
Cyclo(l-Pro-l-Leu)			30 μM		
Cyclo(l-Pro-l-Ile)			27 μM		
Marmycin A	*Streptomyces* sp. CNH990	/	/	Cytotoxicity	(Martin et al., 2007)
Streptokordin	*Streptomyces* sp. KORDI-3238	MDA-MB-231	7.5 μg/mL	Cytotoxicity	(Jeong et al., 2006)
Dionemycin	*Streptomyces* sp. SCSIO 11791	MDA-MB-435	3.9 μM	Cytotoxicity	(Song et al., 2020)
		MDA-MB-231	19.4 μM		
6-OMe-7′,7″-dichorochromopyrrolic acid		MDA-MB-435	11.2 μM		
		MDA-MB-231	>25.0 μM		
ZHD-0501	*Actinomadura* sp. 007	tsFT210	Inhibition rate: 28.3%	antiproliferative	(Han et al., 2005)
Iodinin	*Actinomadura* sp. M048	MAXF 401NL	<4.0 μg/mL	Cytotoxicity	(Maskey et al., 2003)
1,6-Phenazinediol			<4.0 μg/mL		
Questiomycin A		MCF-7	IC_{70}: <1.4 μg/mL		
Chandrananimycin A			IC_{70}: <1.4 μg/mL		
Chandrananimycin B			IC_{70}: <1.4 μg/mL		
Chandrananimycin C			IC_{70}: <1.4 μg/mL		
Phenoxazin-3-one			IC_{70}: <1.4 μg/mL		
Diazepinomicin	*Micromonospora* DPJ12	MDA-MB-231	2.1 μM	Cytotoxicity	(Gourdeau et al., 2008)
Pyridinium	*Amycolatopsis alba* var. nov. DVR D4	MCF-7	Inhibition rate: 60.4%	Cytotoxicity	(Dasari et al., 2012)

(Continued)

TABLE 2 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Pseudonocardian A	*Pseudonocardia* sp. SCSIO 01299	MCF-7	0.027 μM	Cytotoxicity	(Li et al., 2011)
Pseudonocardian B			0.021 μM		
Pseudonocardian C			8.0 μM		
2-Aminophenoxazin-3-one	*Halomonas* sp.	MCF-7	GI_{50}: 0.13 μg/mL	Cell cycle arrest; apoptosis	(Bitzer et al., 2006)
2-Amino-6-hydroxyphenoxazin-3-one			GI_{50}: 1.6 μg/mL	Cytotoxicity	
2-Amino-8-benzoyl-6-hydroxyphenoxazin-3-one			GI_{50}: 2.0 μg/mL		
Aqabamycin E	*Vibrio* sp.	MDA-MB-231	25 μg/mL	Cytotoxicity	(Al-Zereini et al., 2010)
		MCF-7	20 μg/mL		
Vibrindole A		MDA-MB-231	30 μg/mL		
		MCF-7	50 μg/mL		
Lynamicin B	*Marinispora* sp. NPS12745	MDA-MB-435	6.9 μM	Cytotoxicity	(Song et al., 2020)
		MDA-MB-231	28.6 μM		

Marine fungi

Because of the extreme ecological environments faced by marine fungi (e.g., high salinity, UV exposure, low temperature, restricted growth substrates, and extreme hydrostatic pressure), they produce secondary metabolites with unique structures that exhibit diverse biological activities, including antimicrobial, antidiabetic, and anticancer properties (Debbab et al., 2010; Gonçalves et al., 2022). These metabolites have significant therapeutic potential (Table 3), making marine fungi an important fresh source of secondary metabolites for drug discovery purposes (Ding et al., 2018). The structures of some alkaloids from marine fungi are shown in Figure 3.

Deoxyapoaranotin, a diketopiperazine disulfide, is produced by *Aspergillus* sp. KMD 901 (Choi et al., 2011). Deoxyapoaranotin induces mitochondria-mediated tumor cell apoptosis by regulating Bax, Bcl-2, and Bcl-xl in a dose-dependent manner, and upregulates the cleavage of PARP, and Cas-3, -9, and -8 (Choi et al., 2011). Gliotoxin is also from a marine-derived *Aspergillus* species, is a dual inhibitor of farnesyltransferase and geranylgeranyltransferase I, has significant antitumor activity, and can mediate growth inhibition of various breast cancer cells by inhibiting prenyltransferase enzymes (IC_{50} range, 38–985 nM) (Vigushin et al., 2004). Farnesyltransferase and geranylgeranyltransferase play crucial roles in the posttranslational modification of Ras proteins that regulate cell proliferation, differentiation, and apoptosis (Klochkov et al., 2019).

Fumigaclavine C, tryprostatins A and B, and cyclotryprostatins A–D were all isolated from *Aspergillus fumigatus* (Cui et al., 1995, 1997; Li et al., 2013). Fumigaclavine C not only significantly inhibits the growth of MCF-7 cells (inhibition rate of 93% at 20 μM) but also significantly inhibits the migration and invasion of tumor cells by downregulating the expression of relevant matrix metalloproteinases (Li et al., 2013). It mainly achieves a cytotoxic effect by arresting the cell cycle at the G1 phase, inducing the expression of the proapoptotic proteins Bax and Bid, and promoting the protein hydrolysis activity of caspase-3, -8, and -9, thereby causing cell apoptosis (Li et al., 2013). Importantly, fumigaclavine C is also an effective and specific chemosensitizer that can completely reverse BCRP-mediated drug resistance *in vitro* (Rabindran et al., 2000), but it has severe neurotoxic effects (Allen et al., 2002). Its novel tetracyclic analogs Ko132, Ko134, and Ko143 all exhibited significant cytotoxicity against MCF-7 cells (Allen et al., 2002). Ko143 not only significantly increased the oral availability of topotecan in mice but also showed no signs of toxicity *in vitro* and *in vivo* (Allen et al., 2002). Thus, Ko143 is the first potent and specific BCRP inhibitor applicable *in vivo* (Allen et al., 2002). Tryprostatins A and B are indole alkaloids that cause G2/M cell cycle arrest in mammalian cells (Cui et al., 1995). Tryprostatin A not only significantly inhibited the growth of the thermosensitive tsFT210 mouse cell line but also exhibited an obvious cytotoxic effect on MCF-7 cells as a BCRP inhibitor (IC_{50} = 0.013 ± 0.006 μM) (Cui et al., 1995). Cyclotryprostatins A–D also inhibit the growth of tsFT210 cells by arresting cell cycle progression in the G2/M phase with IC_{50} values of 5.6 μM, 19.5 μM, 23.4 μM, and 25.3 μM, respectively (Cui et al., 1997). Preussin, isolated from the marine sponge-associated fungus *Aspergillus candidus*, has been shown to reduce cell viability, impair cell proliferation, and induce cell death in both 2D and 3D cell cultures in a dose-dependent manner (Seabra et al., 2023). It exhibits antiproliferative effects against the MDA-MB-231, MCF-7, and SKBR3 cell lines (Malhão et al., 2019).

The *Penicillium* genus is an important source of biologically active secondary metabolites. Indole diterpene alkaloids can be directly isolated from *Penicillium* species, including penitrems A, B, D, E, and F, and paspaline, emnidole SB, semisynthetic 6-bromopenitrems B and E, and 25-o-methylpenitrem A (Table 3) exhibited good antiproliferation, anti-migration, and anti-invasion properties against MDA-MB-231 and MCF-7 (Sallam et al., 2013a, 2013; Goda et al., 2018). Among them, penitrem A can reduce the

TABLE 3 Alkaloids derived from marine fungi against breast cancer.

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Deoxyapoaranotin	*Aspergillus* sp. KMD 901	MCF-7	31 ± 0.63 μM	Apoptosis	(Choi et al., 2011)
Gliotoxin	*Aspergillus* sp. strain YL-06	MCF-7	985 nM	Inhibit prenyltransferase enzyme	(Vigushin et al., 2004)
		T47D	365 nM		
		BT-474	102 nM		
		ZR75–1	158 nM		
		MDA-MB-231	38 nM		
		MDA-MB-435	87 nM		
Fumigaclavine C	*Aspergillus fumigatus*	MCF-7	20 μM (Inhibition: 93%)	Cell cycle arrest; apoptosis; inhibit NF-kappa-B cell survival pathway	(Li et al., 2013)
Ko132			15 μM	Inhibitor of BCRP	(Allen et al., 2002)
Ko134			15 μM		
Ko143			19 μM		
Tryprostatin A		tsFT210	50 μg/mL	G2/M cell cycle arrest	(Cui et al., 1995)
		MCF-7	0.013 ± 0.006 μM	Inhibitor of BCRP	(Woehlecke et al., 2003)
Tryprostatin B		tsFT210	12.5 μg/mL	G2/M cell cycle arrest	(Cui et al., 1995)
Cyclotryprostatin A	*Aspergillus fumigatus* BM939	tsFT210	5.6 μM	G2/M cell cycle arrest	(Cui et al., 1997)
Cyclotryprostatin B			19.5 μM		
Cyclotryprostatin C			23.4 μM		
Cyclotryprostatin D			25.3 μM		
Preussin	*Aspergillus ochraceus*	MDA-MB-231	30.06 μM	Cell cycle arrest	(Seabra et al., 2023)
		MCF-7	<50 μM	Cytotoxicity	(Malhão et al., 2019)
		SKBR3			
Painter A	*Penicillum commune* sp. GS20	SK-BR-3	15.1 μM	Target Maxi-K (BK) channel; induced G1 cell cycle arrest; reduced active forms of AKT and STAT3	(Goda et al., 2018)
		BT-474	10.3 μM		
		MCF-7	11.9 μM	Antiproliferation; anti-migration; anti-invasion	(Sallam et al., 2013b)
		MDA-MB-231	9.8 μM		
Penitrem B	*Penicillium* sp.	MCF-7	5.5 μM	Antiproliferation; anti-migration; anti-invasion	(Sallam et al., 2013b)
		MDA-MB-231	13.7 μM		
Penitrem D		MCF-7	8.3 μM		
		MDA-MB-231	29.7 μM		
Penitrem E		MCF-7	17.5 μM		
		MDA-MB-231	25.4 μM		
		SK-BR-3	36.7 μM		(Goda et al., 2018)

(Continued)

TABLE 3 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
		BT-474	31.8 μM		
Penitrem F		MCF-7	15 μM		
		MDA-MB-231	13.8 μM		
Paspaline		MCF-7	12.8 μM		
		MDA-MB-231	12.4 μM		
Emnidole SB		MCF-7	10.1 μM		(Sallam et al., 2013b)
		MDA-MB-231	21.3 μM		
6-Bromopenitrem B		MCF-7	19.3 μM		
		MDA-MB-231	18.8 μM		
6-Bromopenitrem E		MCF-7	16.7 μM		
		MDA-MB-231	8.5 μM		
25-O-methylpenitrem A		MDA-MB-231	37.8 μM		
		BT-474	22.4 μM	Cytotoxicity	(Goda et al., 2018)
		SK-BR-3	27.1 μM		
Brevicompanine G	*Penicillium* sp. TJ403–1	MDA-MB-231	>40 μM	Cytotoxicity	(Yang et al., 2018)
Penicillivinacine	*Penicillium vinaceum*	MDA-MB-231	18.4 μM	Anti-metastatic	(Asiri et al., 2015)
Penochalasin K	*Penicillium chrysogenum V11*	MDA-MB-435	4.65 ± 0.45 μM	Cytotoxicity	(Zhu et al., 2017)
Penochalasin I	*Penicillium chrysogenum*	MDA-MB-435	7.55 ± 0.71 μM	Cytotoxicity	(Huang et al., 2016)
Penochalasin J			36.68 ± 0.90 μM		
Chaetoglobosin A			37.56 ± 0.95 μM		
Chaetoglobosin C			19.97 ± 1.03 μM		
Chaetoglobosin F			37.77 ± 0.41 μM		
Chaetoglobosin G			38.77 ± 0.65 μM		
Cytoglobosin C			12.58 ± 0.90 μM		
Arthpyrone L	*Arthrinium* sp.	MCF-7	14.00 ± 0.44 μM	G0/G1 cell cycle arrest; apoptosis; inhibit PI3K/Akt signaling pathway	(Zhang et al., 2021)
		MDA-MB-231	21.34 ± 2.10 μM		
Terretrione A	*Aspergillus terreus*	MDA-MB-231	17.7 μM	Anti-metastatic	(Asiri et al., 2015)
Loonamycin A	*Nocardiopsis flavescens* NA01583	SUM1315	121.3 nM	Cytotoxicity	(Yang et al., 2020)
Isochromophilone X	*Diaporthe* sp.	MCF-7	14.9 μM	Cytotoxicity	(Zang et al., 2012)
Luteoalbusin A	*Acrostalagmus luteoalbus* SCSIO F457	MCF-7	0.23 ± 0.03 μM	Cytotoxicity	(Wang et al., 2012)
Luteoalbusin B			0.25 ± 0.00 μM		
T988A			5.60 ± 0.58 μM		
Gliocladine C			6.57 ± 0.81 μM		
Gliocladine D			17.78 ± 0.27 μM		
Avrainvillamide	*Avrainvillea* sp.	BT-549	34 nM	Antiproliferative	(Fenical et al., 2000)
		T-47D	72 nM		

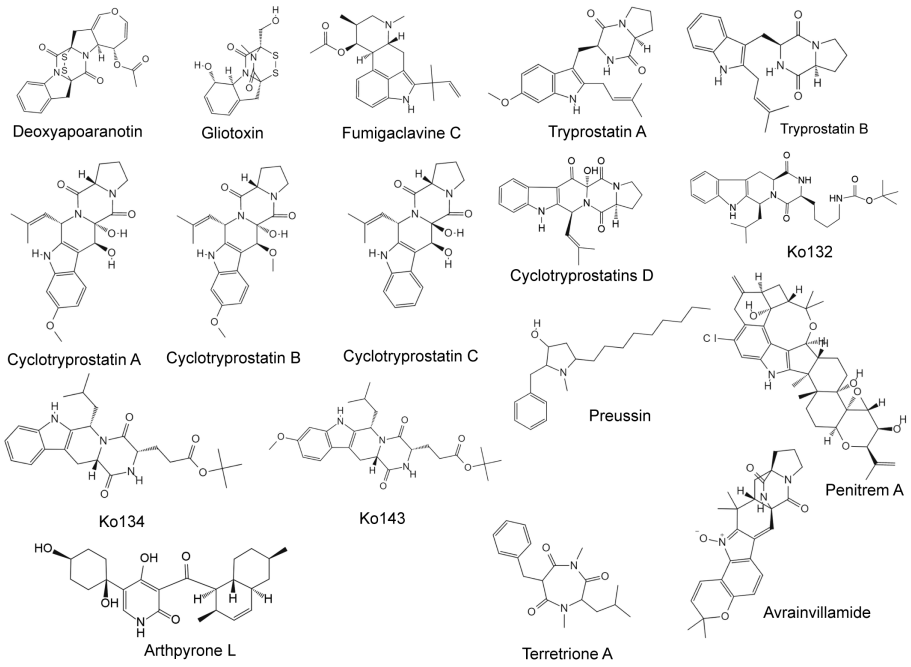

FIGURE 3
Chemical structures of anti-breast cancer alkaloids derived from marine fungi.

expression of high-conductance calcium-activated potassium channels and increase the expression of TNF-α while inducing G1 cell cycle arrest in breast cancer cells and upregulating the expression of the arrest protein p27 (Goda et al., 2018). In addition, penitrem A can produce synergistic antiproliferative effects with anti-HER drugs by reducing the active forms of AKT and STAT3 (Goda et al., 2018). Brevicompanine G; penicillivinacine; penochalasins K, I, and J; chaetoglobosins C, F, and G; and cytoglobosin C are also from the *Penicillium* species, while penochalasins K and I showed significant cytotoxicity to MDA-MB-435 cells (Table 3, IC_{50} < 10 μM) (Asiri et al., 2015; Huang et al., 2016; Zhu et al., 2017; Yang et al., 2018).

Arthpyrone L, a novel pyridone alkaloid isolated from *Arthrinium* species, exhibits significant antiproliferative effects on both MCF-7 and MDA-MB-231 cells. Arthpyron L induces G0/G1 cell cycle arrest and simultaneously inhibits tumor cell growth by activating the caspase-regulated apoptosis pathway and downregulating the PI3K/Akt pathway (Zhang et al., 2021). In addition, terretrione A, loonamycin A, and isochromophilone X were isolated from *Aspergillus terreus*, *Nocardiopsis flavescens*, and *Diaporthe* sp., respectively (Asiri et al., 2015; Yang et al., 2020), and also had certain cytotoxic effects on the MDA-MB-231 (IC_{50} = 17.7 μM), SUM1315 (IC_{50} = 121.3 nM), and MCF-7 (IC_{50} = 14.9 μM) cell lines. Luteoalbusins A and B, T988A, and gliocladines C and D were all isolated from *Acrostalagmus luteoalbus* in deep-sea sediments. These five compounds all showed significant cytotoxicity to the MCF-7 cell line, and the cytotoxicities of luteoalbusins A and B were significantly greater than those of the other compounds (Wang et al., 2012). Avrainvilamide, which is isolated from *Avrainvillea* species, binds to the proposed oncogenic nuclear chaperone nucleophosmin, which is overexpressed in many different human tumors. *In vitro* experiments have shown that avrainvillamide has a dose-dependent antiproliferative effect on the BT-549 and T-47D cell lines, with IC_{50} values of 34 and 72 nM, respectively (Fenical et al., 2000).

Marine seaweed

Seaweed is found in all oceans and is widely consumed as a food and medicinal herb, especially in some historical Asian countries such as China and Japan (El Gamal, 2010). In traditional Chinese medicine, seaweed is mainly used to treat diseases such as goiter, scrofula, testicular swelling, and edema, and is also used as a source of vitamin supplements, cholesterol-lowering agents, and blood sugar-lowering drugs (El Gamal, 2010). Recent studies have shown that the secondary metabolism of seaweed has various biological effects, such as antioxidant, anti-inflammatory, antidiabetic, antibacterial, and anticancer effects (Lee et al., 2013; Sharifuddin et al., 2015). The structures of some alkaloids from marine seaweed are shown in Figure 4.

Racemosin B is a marine alkaloid with an unusual indolo[3,2-a] carbazole skeleton that is isolated from the green alga *Caulerpa racemose*. MTT assays of racemosin B and several derivatives revealed that many of its derivatives could significantly inhibit the growth of MDA-MB-231 and MCF-7 cells (Table 4). Further studies revealed that compound 25, which was designed and synthesized based on racemosin B, showed stronger and more effective activities against MDA-MB-231 (IC_{50} = 1.06 μM), MCF-7 (IC_{50} = 2.00 μM), and 4T1 (IC_{50} = 2.77 μM) cells (Xiao et al., 2018). Compound 25 can induce G2/M cell cycle arrest and promote apoptosis by blocking autophagic flux in breast cancer

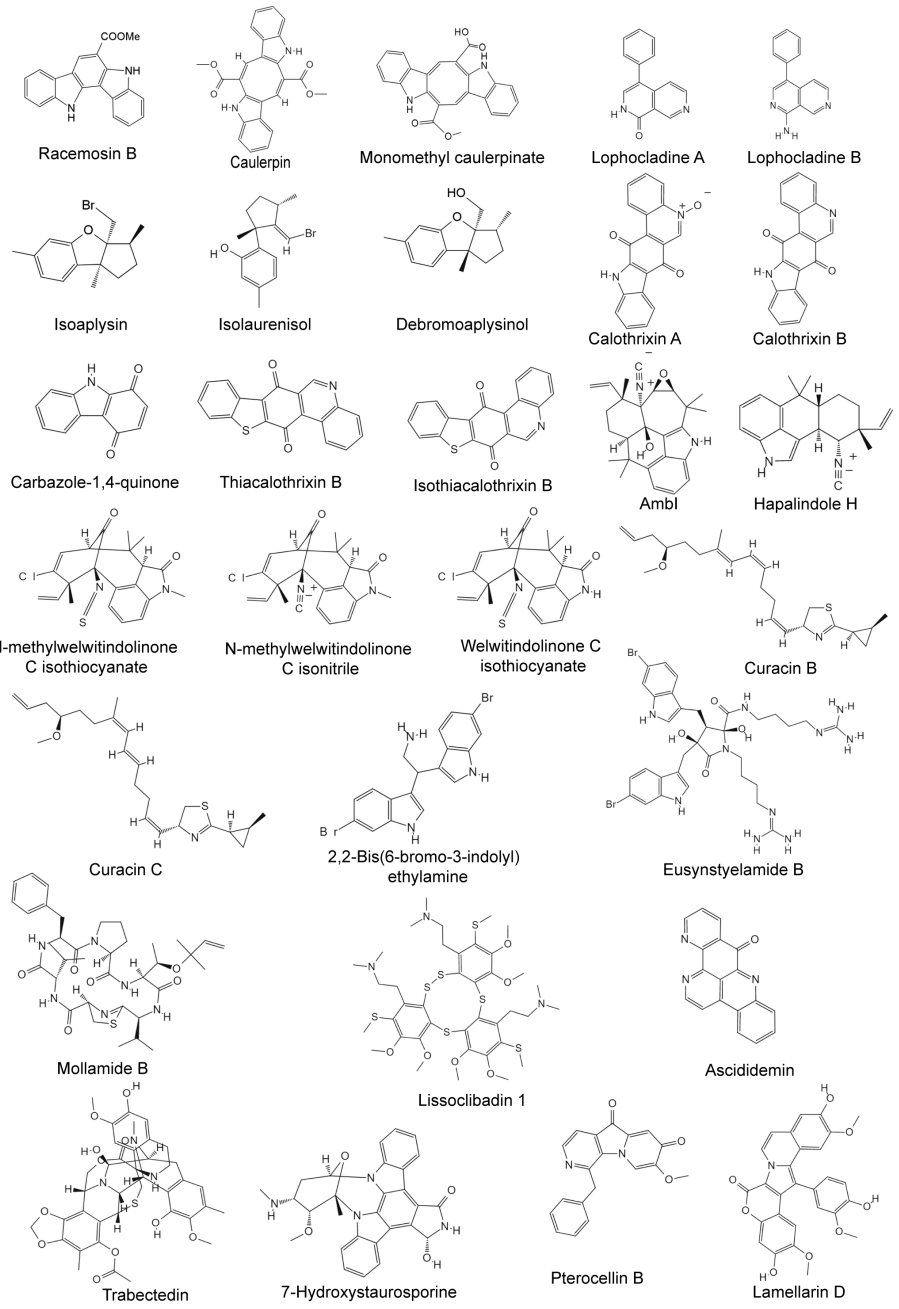

FIGURE 4
Chemical structures of anti-breast cancer alkaloids derived from marine seaweed, cyanobacteria, tunicate, and bryozoa.

cells, and the inhibition of autophagy is achieved by regulating the phosphorylation level of mTOR (Xiao et al., 2018).

Caulerpin was first isolated from the green algae genus *Caulerpa* and was also recently discovered in n-hexane extracts of the macroalgae *Halimeda cylindracea*. *In vitro* evaluation revealed that caulerpin can exhibit strong cytotoxic activity against SK-BR-3 cells, with an IC_{50} value of 3.71 μM (Dini et al., 2021). Moreover, caulerpin exhibited dose-dependent cytostatic effects on the T47D, MCF-7, and MDA-MB-231 cell lines (Table 4). Under hypoxic conditions, caulerpin inhibits hypoxia-induced HIF-1 gene activation, VEGF protein secretion, and tumor angiogenesis in T47D cells (Liu et al., 2009). In addition to inducing angiogenesis, HIF-1 is involved in regulating the expression of genes related to complex metastasis processes. In addition, caulerpin has been shown to have anti-metastatic activity in MDA-MB-231-based wound healing models. Monomethyl caulerpinate, also isolated from *Caulerpa cylindracea*, has strong cytotoxic effects on MCF-7 and MDA-MB-231 cells, with IC_{50} values of 16.82 ± 1.12 and 13.96 ± 0.52 μM, respectively (Erol et al., 2022).

Lophocladines A and B are two 2,7-naphthyridine alkaloids isolated from the marine red alga *Lophocladia*, among which lophocladine B can induce microtubule depolymerization and G2/

TABLE 4 Alkaloids derived from marine seaweed against breast cancer.

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Racemocin B C25	*Caulerpa racemose*	MDA-MB-231	1.06 μM	G2/M c ell cycle arrest, apoptosis	(Xiao et al., 2018)
		MCF-7	2 μM	Antiproliferation	
		4T1	2.77 μM		
Racemocin B C26		MDA-MB-231	1.82 ± 0.19 μM		
		MCF-7	1.30 ± 0.14 μM		
Caulerpin	*Halimeda cylindracea, Caulerpa cylindracea*	SK-BR-3	3.71 μM	Cytotoxicity;	(Dini et al., 2021)
		T-47D	\	Anti-angiogenesis	(Liu et al., 2009)
		MCF-7	15.68 ± 0.38 μM	Cytotoxicity; anti-metastatic	
		MDA-MB-231	11.85 ± 1.03 μM		
Monomethyl caulerpinate	*Caulerpa cylindracea*	MCF-7	16.82 ± 1.12 μM	Cytotoxicity	(Erol et al., 2022)
		MDA-MB-231	13.96 ± 0.52 μM		
Lophocladine A	*Lophocladia* sp.	MDA-MB-435	>450 μM	/	(Gross et al., 2006)
Lophocladine B			3.1 μM	G2/M cell cycle arrest; microtubule inhibition	
Isoaplysin	*Laurencia pacifica*	MCF-7	GI_{50}: 20 ± 1.3 μM	Cytotoxicity	(Zaleta-Pinet et al., 2014)
		MCF10A	GI_{50}: 46 ± 3.2 μM		
Isolaurenisol		MCF-7	GI_{50}: >50 μM		
		MCF10A	GI_{50}: >50 μM		
Debromoaplysinol		MCF-7	GI_{50}: 14 ± 1.7 μM		
		MCF10A	GI_{50}: 28 ± 1.0 μM		

M cell cycle arrest in MDA-MB-435 cells, resulting in significant cytotoxicity (IC_{50} = 3.1 μM). While lophocladine A lacks cytotoxicity to tumor cells, it was found to have an affinity for NMDA receptors and appears to be a delta-opioid receptor antagonist (Gross et al., 2006).

Isoaplysin, isolaurenisol, and debromoaplysinol are all isolated from the sesquiterpenes of *Laurencia pacifica*, where isoaplysin and debromoaplysinol (Table 4) showed promising cytostatic effects on MCF-7 cells and were two times more potent in MCF-7 cells than in nontumor-derived normal breast MCF10A cells (Zaleta-Pinet et al., 2014).

Marine cyanobacteria

Cyanobacteria, also known as blue-green algae, are ancient photosynthetic prokaryotes. They have extremely strong adaptability and are widely distributed in various environments around the world, from freshwater to oceans, soil, and extreme environments (such as glaciers and hot springs) (Demay et al., 2019). Cyanobacteria can produce toxins, which can lead to algae blooms, disrupt the ecological balance of water bodies, and have a negative impact on human and animal health (Demay et al., 2019). However, they also produce a variety of secondary metabolites with different biological activities, and these complexes exhibit enormous potential beneficial properties in various fields, including antibacterial, antifungal, anticancer, immunosuppressive, anti-inflammatory, and antituberculosis activities (Demay et al., 2019). The structures of some alkaloids from marine cyanobacteria are shown in Figure 4.

Calothrixins A and B are carbazole-1,4-quinone alkaloids isolated from *Calothrix* sp. These compounds, along with analogs such as 3-fluoro-calothrixin 15h and 4-fluoroquinocarbazole 21b, have been found to exhibit potent cytotoxicity against the MCF-7 and MDA-MB-231 cell lines (Table 5), with GI_{50} values in the range of 0.02–0.95 μM (Muthu Ramalingam et al., 2018). Calothrixins A and B both stabilize the cleavable complex of topo I-DNA, but calothrixin A induces extensive DNA damage. At low concentrations (0.1 μM), calothrixin A can induce G1 cell cycle arrest in tumor cells, and at high concentrations, calothrixin A can cause reversible G2/M arrest, thereby generating reactive oxygen species and inducing cell death through autophagy (Muthu

TABLE 5 Alkaloids derived from marine cyanobacteria against breast cancer.

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Calothrixin A	*Calothrix cyanobacteria*	MCF7	GI_{50}: 0.03 ± 0.0 μM	DNA cleavage, cell cycle arrest and apoptosis	(Muthu Ramalingam et al., 2018)
		MDA-MB-231	GI_{50}: 0.26 ± 0.01 μM		
Calothrixin B		MCF7	GI_{50}: 0.04 ± 0.01 μM	DNA damage	
		MDA-MB-231	GI_{50}: 0.16 ± 0.02 μM		
3-Fluoro-calothrixin B 15h		MCF7	GI_{50}: 0.85 ± 0.07 μM	DNA cleavage, cell cycle arrest, and apoptosis	
		MDA-MB-231	GI_{50}: 0.30 ± 0.12 μM		
4-Fluoro-quinocarbazole 21b		MCF7	GI_{50}: 0.02 ± 0.01 μM		
		MDA-MB-231	GI_{50}: 0.95 ± 0.07 μM		
Thiacalothrixin B		MCF7	GI_{50}: >4 μM	DNA strand breaks	(Dhatchana Moorthy et al., 2018) i
		MDA-MB-231			
Isothiacalothrixin B		MCF7	GI_{50}: 0.23± 0.04 μM	S and G2/M cell cycle arrest, apoptosis	
		MDA-MB-231	GI_{50}: 0.22 ± 0.06 μM		
3-Fluoro-isothiacalothrixin B		MCF7	GI_{50}: 1.6 ± 0.10 μM	DNA strand breaks	
		MDA-MB-231	GI_{50}: 0.70 ± 0.10 μM		
11-Fluoro-isothiacalothrixin B		MCF7	GI_{50}: 1.9 ± 0.24 μM		
		MDA-MB-231	GI_{50}: 0.30 ± 0.00 μM		
Ambiguine I isonitrile (AmbI)	*Fischerella ambigua*	MCF7	EC_{50}: 1.7 μM	Cell cycle arrest, apoptosis	(Acuña et al., 2015)
Hapalindole H	*Fischerella muscicola*	MCF-7	EC_{50}: 5.96 μM	Apoptosis; inhibit NF-κB; affect the intrinsic mitochondrial pathway	(Acuña et al., 2018)
			16.3 ± 3.3 μM	Cytotoxicity	(Kim et al., 2012)
Hapalindole X	*Westiellopsis* sp. and *Fischerella muscicola*	MCF-7	35.4 ± 2.8 μM	Cytotoxicity	
13-hydroxy dechlorofontonamide			>100 μM	/	
Hapalindole I					
Hapalindole J			43.7 ± 10.0 μM	Cytotoxicity	
Hapalindole A			30.7 ± 7.1 μM		
Hapalindole U			>100 μM	/	
Hapalindole C					
Anhydrohapaloxindole A			56.7 ± 10.5 μM	Cytotoxicity	
Fischerindole L			28.3 ± 8.1 μM		
N-methylwelwitindolinone C isothiocyanate	*Hapalosiphon welwitschii*	MCF7	3.03 μM	Cytotoxicity	(Smith et al., 1995)
N-methylwelwitindolinone C isonitrile			0.12 μM		

(Continued)

TABLE 5 Continued

Compound name	Species name	Cell lines	IC_{50}	Mechanism	References
Welwitindolinone C isothiocyanate			0.13 μM		
Curacin A	*Lyngbya majuscule*	MCF-7	0.038 μM	Anti-mitotic	(Verdier-Pinard et al., 1998)
Curacin B			0.32 μM		
Curacin C			3.6 ± 0.8 μM		

Ramalingam et al., 2018). In another study, the biological activity of analogs of calothrixin B in which the carbazole nitrogen (NH) was replaced with a sulfur atom was explored. Thiacalothrixin B was less cytotoxic than calothrixin B (Dhatchana Moorthy et al., 2018). However, isothiacalothrixin B and its fluorinated analogs (3-fluoro-isothiacalothrixin B and 11-fluoro-isothiacalothrixin B) produced after isomerization have excellent anticancer effects, and the GI_{50} values of MCF-7 and MDA-MB-231 cells range from 0.22 to 1.9 μM (Dhatchana Moorthy et al., 2018). The cytotoxicity of the sulfur analogs of calothrixin B is mediated in part by the induction of cellular DNA strand breaks and the arrest of cells. Among them, isothiacalothrixin B induces apoptosis by irreparable DNA damage (Dhatchana Moorthy et al., 2018).

The indole alkaloids ambiguine I isonitrile (AmbI) and hapalindole H (Hap H) are both obtained from *Fischerella ambigua* (Acuña et al., 2015, 2018). AmbI and Hap H are potent inhibitors of NF-κB, which prevents cancer cells from entering an apoptotic state and has been shown to contribute to the progression of certain tumors (Acuña et al., 2015, 2018). AmbI significantly inhibited MCF-7 cell proliferation (EC_{50} = 1.7 μM), and AmbI treatment caused mitochondrial dysfunction and increased ROS levels in MCF-7 cells, subsequently leading to caspase-independent cell death (Acuña et al., 2015). The antiproliferative effect of Hap H on MCF-7 is weaker than that of AmbI (EC_{50} = 5.96 μM), but its mechanism of inducing cell death is similar to that of AmbI. Hap H treatment causes damage to the mitochondrial outer membrane, which, in turn, mediates caspase-3-independent apoptosis (Acuña et al., 2018). In addition to Hap H, indole alkaloids such as hapalindoles A, C, I, J, and U; anhydrohapaloxindole A and fischerindole L; and two hapalindole-type alkaloids, hapalindole X and 13-hydroxy dechlorofontonamide, can also be isolated from *Westiellopsis* sp. and *Fischerella muscicola* (Table 5). Among them, fischerindole L and hapalindole A showed relatively more effective cytotoxic effects on MCF-7 cells (Kim et al., 2012).

N-Methylwelwitindolinone C isothiocyanate, N-methylwelwitindolinone C isonitrile, and welwitindolinone C isothiocyanate, which are members of the Welwitindolinones family, are isolated from the blue-green algae *Hapalosiphon welwitschii*, and they strongly inhibit the proliferation of the MCF-7 cells (Table 5), with IC_{50} values of 3.03, 0.12, and 0.13 μM, respectively (Smith et al., 1995). Moreover, the presence of N-methylwelwitindolinone C isothiocyanate has been shown to diminish the resistance of MCF-7/ADR cells to anticancer drugs such as vincristine, paclitaxel, doxorubicin, daunorubicin, and colchicine (Smith et al., 1995).

Curacins A, B, and C are all extracted from *Lyngbya majuscule* and have been proven to have anti-mitotic properties (Verdier-Pinard et al., 1998). Among them, curacin A is the most obvious and can significantly inhibit MCF-7 cell proliferation, with an IC_{50} of 0.038 μM (Verdier-Pinard et al., 1998). Further studies revealed that curacin A can inhibit microtubule assembly and induce cell cycle arrest and apoptosis (Wipf et al., 2004).

Marine tunicate

Because of their powerful immune defense systems and associated bioactive symbiotic microorganisms, tunicates have become a high-priority pharmaceutical resource in the ocean and are considered one of the most intensively studied organisms of the 21st century (Palanisamy et al., 2017; Ramesh et al., 2021). Statistics on the structures of secondary metabolites of 572 kinds of tunicates reported from 1994 to 2014 revealed that approximately 74% of the secondary metabolites were alkaloids (Palanisamy et al., 2017). The secondary metabolites of tunicates have a variety of biological activities, but anticancer drugs are the main type of marine natural product derived from tunicates (64%), followed by antimalarial drugs (6%). In addition, they can also be used for antibacterial, antidiabetic, anti-HIV, antiviral, anti-inflammatory, antifungal, and other applications (Palanisamy et al., 2017). The structures of some alkaloids from marine tunicate are shown in Figure 4.

2,2-Bis(6-bromo-3-indolyl)ethylamine (BrBIn) can be derived from the tunicate *Didemnum candidum* and can also be obtained from the sponge *Orina*. BrBIn has effective cytotoxicity against a variety of tumor cells (Supplementary Table 1), e.g., MCF-7 cells (IC_{50} = 10.0 μM). BrBIn can inhibit the expression of antiapoptotic factors (Bcl-2/Bcl-x) while enhancing the expression of proapoptotic factors (Bax), thereby inducing the release of cytochrome c from mitochondria, leading to the cleavage of caspase-9 and promoting the activation of caspase-3, which ultimately mediates tumor cell death through apoptosis (Salucci et al., 2018). Eusynstyelamide B, a bisindole alkaloid also identified from *Didemnum candidum*, can induce G2 cell cycle arrest in tumor cells, trigger apoptosis, and exhibit significant cytotoxicity in MDA-MB-231 cells (IC_{50} = 5 μM). In addition, eusynstyelamide B has also been shown to be a nonintercalative topoisomerase II toxic agent, leading to DNA double-strand breaks (Liberio et al., 2015). Granulatimide and isogranulatimide, which are extracted from *Didemnum granulatum*, are G2-specific cell cycle checkpoint

inhibitors. Both exhibit strong cytotoxicity against p53-deficient MCF-7 cells, with IC_{50} values in the range of 1–1.8 μM (Berlinck et al., 1998; Roberge et al., 1998). Mollamide B and fascaplysin A are also isolated from *Didemnum* species, both of which have obvious cytotoxic effects on breast cancer, and the fascaplysin A derivative 3-bromofascaplysin can inhibit the growth of a variety of breast cancer cells (Supplementary Table 1), including HS 578T, BT-549, and T-47D cells (Segraves et al., 2004; Donia et al., 2008).

Lissoclibadins 1, 2, 3, 8, and 14, as well as lissoclinotoxins E and F, are derived from *Lissoclinum* cf. *badium*, and two monomeric compounds of lissoclibadins [3,4-dimethoxy-6-(2′-N,N-dimethylaminoethyl)-5-(methylthio)benzotrithiane, N,N-dimethyl-5-(methylthio)varacin] have significant cytotoxic effects on a variety of breast cancer cell lines (Supplementary Table 1), including T-47D, MDA-MB-231, MDA-MB-468, and MCF-7 (Davis et al., 2003; Oda et al., 2007; Tatsuta et al., 2017). The antiproliferative effects of lissoclibadins 1 and 2 are more prominent, and lissoclibadin 1 inhibits tumor cell growth mainly by inducing intrinsic caspase-dependent apoptosis (Tatsuta et al., 2017).

Trabectedin, which is isolated from *Ecteinascidia turbinata*, has been approved in the European Union since 2009 for the treatment of platinum-sensitive recurrent ovarian cancer in combination with pegylated liposomal doxorubicin. Subsequently, in 2015, trabectedin was approved by the U.S. FDA for the treatment of unresectable or metastatic liposarcoma or leiomyosarcoma in patients who had previously received anthracycline-based chemotherapy (Gadducci and Cosio, 2022). Trabectedin also shows obvious cytotoxicity to breast cancer cells. For breast cancer cells of different genotypes, trabectedin can activate apoptosis mediated by exogenous and/or endogenous pathways, thereby causing the death of tumor cells (Atmaca et al., 2013).

Aplicayanins A–F are brominated derivatives isolated from *Aplidium cyaneum* (Supplementary Table 1), among which aplicayanins B and D–F have strong cytotoxic and antimitotic effects on MCF-7 cells (Reyes et al., 2008b). Botryllamides K and L and caelestines A–D were extracted from *Aplidium altarium* and *Aplidium caelestis* (Supplementary Table 1), respectively, but these six compounds showed poor cytotoxicity to MCF-7 cells, with IC_{50} values ranging from 39 to 91 μM (Yin et al., 2010a, b).

7-Hydroxystaurosporine (UCN-01) was isolated from *Eudistoma* sp. and was originally used as a protein kinase C inhibitor (Mizuno et al., 1995). It was later discovered that UCN-01 can eliminate S and G2 phase cell cycle arrest and enhance cisplatin cytotoxicity and apoptosis in breast cancer cells without itself being cytotoxic (Lee et al., 1999).

Ascididemin, which is isolated from *Cystodytes dellechiajei*, is also a topoisomerase II inhibitor. Ascididemin can induce DNA damage and the release of reactive oxygen species, followed by the activation of caspase-2, leading to oxidative stress-dependent apoptosis, which has potent antiproliferative effects on the MCF-7 cell line (Morvan, 2013). Two indolocarbazole alkaloids, 7-oxo-3,8,9-trihydroxystaurosporine and 7-oxo-8,9-dihydroxy-4′-N-demethylstaurosporine, were also extracted from *Cystodytes* species and showed strong cytotoxic effects on MDA-MB-231, with GI_{50} values of 28.4 and 32.1 nM, respectively (Reyes et al., 2008a). Arnoamines A and B are also extracted from the same genus and are pentacyclic pyridoacridine alkaloids. Both natural products have cytotoxic effects on MCF-7 cells, with IC_{50} values of 0.3 and 2–3 μg/mL, respectively (Plubrukarn and Davidson, 1998).

Botryllamides E–G are extracted from *Botryllus tyreus*, and they have been shown to have cytotoxic effects on breast cancer carcinoma, exhibiting IC_{50} values of 27, 41, and 6.9 μM, respectively (Palanisamy et al., 2017). 3,6-Dibromoindole, 6-bromo-3-chloroindole, and 6-bromo-2-oxindole are produced by *Distaplia skoogi*, but these three compounds do not have strong cytotoxic effects on MDA-MB-231 cells, with IC_{50} values of 117.72, 72.53, and 74.41 μM, respectively (Palanisamy et al., 2017). Tanjungides A and B are two dibrominated indoleamide alkaloids extracted from *Diazona* cf. *formosa*, and both have strong antitumor effects on MDA-MB-231 cells, with GI_{50} values of 0.23 and 1.63 μM, respectively (Murcia et al., 2014).

Marine bryozoa

Bryozoa are a type of aquatic suspension-feeding invertebrate that is abundant, diverse, and widely distributed, with more than 6,000 species (Figuerola and Avila, 2019). Bryozoa are extremely vulnerable to biological pollution, predator predation, and pathogen attack. To adapt to the harsh living environments, bryozoans have evolved a chemical defense strategy by producing potent secondary metabolites (Hanssen et al., 2021). The metabolites produced by bryozoans have a variety of biological activities, such as anticancer, antiviral, antiparasitic, anti-Alzheimer's disease, and anti-Parkinson's disease activities (Ciavatta et al., 2020). The structures of some alkaloids from marine bryozoa are shown in Figure 4.

Pterocellins A and B are two alkaloids with novel heterocyclic skeletons isolated from *Pterocella vesiculosa*. Both of these compounds showed significant cytotoxicity to a variety of breast cancer cell lines (Supplementary Table 2), among which the toxicity to MDA-MB-435 (GI_{50}: 0.2, 0.2 μM) and MDA-N (GI_{50}: 0.2, 0.2 μM) cell lines was the most significant (Yao et al., 2003; Pejin et al., 2014). Securidine A is a novel brominated alkaloid isolated from *Securiflustra securifrons* (Michael et al., 2017). *In vitro* MTS experiments revealed that securidine A did not have any significant anticancer activity against the A2058, HT29, and MCF7 cell lines at concentrations of 50 μM or 100 μM (Supplementary Table 2). Securamines C, E and H–J are also extracted from *S. securifrons*. Studies have shown that only Securamines H, I, C, and E can affect tumor cell proliferation. Among them, H, I, and E have stronger potent cytotoxic effects on MCF-7 cells, with IC_{50} values of 2.1, 2.4, and 8.3 μM, respectively (Hansen et al., 2017). Tambjamine K is a 2,20-bipyrrolic class of cytotoxic alkaloids obtained from Azorean nudibranch *Tambja ceutae*. This compound can inhibit the proliferation of MB-231 cells, with an IC_{50} value of 15.3 μM (Aldrich et al., 2010). In addition, analysis of the crude extract of the bryozoan *Cryptosula zavjalovensis* Kubanin revealed that the ethyl acetate fraction of *C. zavjalovensis* had excellent cytotoxic activity against the MCF-7 cell line (Supplementary Table 2).

Other marine sources of anti-breast cancer alkaloids

Lamellarin D is a hexacyclic pyrrole alkaloid extracted from the marine mollusk *Lamellaria* sp (Pla et al., 2006). It was originally identified as a topoisomerase I inhibitor that induces apoptosis by mediating the DNA damage response. Recently, studies have shown that lamellarin D can also mediate cell death by activating the intrinsic, mitochondria-dependent apoptotic pathway in cancer cells (Ballot et al., 2009). Lamellarin D is highly cytotoxic to the MDA-MB-231 cell line with a GI_{50} of 0.25 μM (Pla et al., 2006).

Marine alkaloids combat breast cancer: *in vivo* study

In vitro models are very important for evaluating the mechanism of action and complex assessment of candidate compounds. Owing to the large differences between *in vitro* and *in vivo* environments, *in vivo* models are often required to further evaluate the safety, efficacy, and delivery of candidate drugs (Table 6).

4-Chloro fascapysin exhibits obvious pharmacological activity through oral or intraperitoneal administration and can significantly hinder HIF-1α/VEGF-mediated microvessel sprouting and angiogenesis in C57/BL6J mice infected with MDAMB-231 cells and inhibit Ehrlich ascites carcinoma growth (Sharma et al., 2017). At the doses tested, 4-chloro fascapysin treatment did not have any toxic effects, such as weight loss or mortality (Sharma et al., 2017).

Halichondrin B is a highly potent antimitotic drug, and ER-076349 and ER-086526 are two macrocyclic ketone analogs that retain the significant efficacy of the parent compound. In the MDA-MB-435 xenograft model, both ER-076349 and ER-086526 can significantly inhibit tumor growth after an intravenous injection of 0.25–1.0 mg/kg (Towle et al., 2001). However, the efficacy of ER-086526 is even more powerful, achieving 95% tumor regression after 14 days of treatment and showing a fourfold therapeutic window (Towle et al., 2001).Two phase I clinical studies have shown that

TABLE 6 The effects of marine-derived alkaloids on breast cancer were studied *in vivo*.

Compound name	Cell lines	Mode of tumor formation	Mode of delivery	Doses	Tumor suppressor	References
4-Chloro fascapysin	MDA-MB-231	Injected subcutaneously into the ventral area of C57/BL6J female mice	Oral gavage	Daily for 5 days; 1, 3 and 5 mg/kg/day	Inhibited microvessels and blood vessel formation	(Sharma et al., 2017)
ER-076349	MDA-MB-435	Female BALB/c nude mice received subcutaneous injection with 1×10^6 cells	Intravenous injection	Mice received injections with 200 mL of test compound in saline on Monday/Wednesday/Friday i.v. schedules, beginning on day 13 for four weekly cycles	Treatment with 0.25–1.0 mg/kg ER-076349 led to 60%–70% inhibition at day 42	(Towle et al., 2001)
ER-086526	MDA-MB-435	Female BALB/c nude mice received injections s.c. with 1×10^6 cells	Intravenous injection	Mice received injections with 200 mL of test compound in saline on Monday/Wednesday/Friday i.v. schedules, beginning on day 13 for four weekly cycles	Treatment with 0.25–1.0 mg/kg ER-086526 led to >95% inhibition at day 14	(Towle et al., 2001)
FBA-TPQ	MCF-7	5×10^6 cells (total volume 0.2 mL) was subcutaneously injected into the left inguinal area of the female nude mice	Intraperitoneal injection	Doses of 5 mg/kg/d, 3 days/week for 3 weeks, 10 mg/kg/d, 3 days/week for 2 weeks, or 20 mg/kg/d, 3 days/week for 1 week	A dose of 5 mg/kg given 3 d/week led to nearly 40% tumor growth inhibition	(Wang et al., 2009)
Gliotoxin	Induced with N-methyl-N-nitrosourea	Inbred virgin female (Ludwig/Wistar/Olac) rats bearing tumors induced with N-methyl-N-nitrosourea (NMU)	Subcutaneous injection	10 mg/kg in 0.2 mL DMSO, weekly for 4 week	All five gliotoxin-treated rats completing the study responded to treatment, three of which had >50% tumor regression (partial response) and two others with stable disease (<50% tumor regression)	(Vigushin et al., 2004)
Trabectedin	MX-1	Athymic nude mice bearing the *nu/nu* gene	Intravenous injection	20 mg/kg, once every 3 days	The average tumor volume was reduced by 98.5%	(Takahashi et al., 2002)
UCN-01	MCF-7, Br-10	Female nude mice with a BALB/c nu/nu genetic background. The tumor was inoculated into the subcutaneous tissue of the bilateral dorsum	Intraperitoneal injection	5 mg/kg, five consecutive days a week for 2 weeks	Marginal antitumor effect	(Koh et al., 2003)

eribulin mesylate has therapeutic activity in patients with advanced breast cancer (Synold et al., 2005; Goel et al., 2009). Three phase II studies showed that the objective response rate and clinical benefit rate of ER-086526 treatment in patients with metastatic breast cancer who were previously treated with anthracyclines and taxanes were 9.3%–21.3% and 17.1%–27.5 (Table 7), respectively (Vahdat et al., 2009; Cortes et al., 2010; Aogi et al., 2012). Encouraged by these results, two open-label, randomized, controlled, parallel-group phase III studies were subsequently conducted, and eribulin showed a significant and clinically meaningful improvement in overall survival compared with treatment of physician's choice in women with heavily pretreated metastatic breast cancer, but was not shown to be superior to capecitabine concerning OS or PFS (Cortes et al., 2011; Kaufman et al., 2015). Eribulin was approved in the USA (2010) and Europe (2011) for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease (Huyck et al., 2011; Orditura et al., 2017). Since then, many phase I/II clinical studies have been conducted to evaluate the efficacy and safety of eribulin in patients with breast cancer with different molecular subtypes (Table 7) as first- or second-line chemotherapy, and in combination with cisplatin S-1, trastuzumab, pembrolizumab, and gemcitabine (Aogi et al., 2012; Koczywas et al., 2014; Wilks et al., 2014; Inoue et al., 2016; Takashima et al., 2016; Orditura et al., 2017; Hayashida et al., 2018; Sakaguchi et al., 2018; Iwasa et al., 2019; Tolaney et al., 2019; Pellegrino et al., 2021; Hasler-Strub et al., 2023).

FBA-TPQ is a synthetic derivative of makaluvamine. The results of *in vivo* experiments by Wang et al. showed that this compound could significantly inhibit breast cancer MCF-7 xenograft tumor growth at three tested concentrations (5, 10, and 20 mg/kg), with inhibition rates ranging from 36.2% to 71.6% (Wang et al., 2009). However, experiments have also shown that high doses (10 and 20 mg/kg) can cause weight loss in mice (Wang et al., 2009).

In the N-methyl-N-nitrosourea rat mammary carcinoma model, gliotoxin showed significant antitumor activity, and all rats that completed gliotoxin treatment experienced a certain degree of tumor regression (Vigushin et al., 2004). However, gliotoxin treatment can cause local toxicity at the injection site such as itching, alopecia, induration, and occasional ulceration. Fortunately, these reactions are transient, and systemic toxicity does not occur (Vigushin et al., 2004).

Trabectedin was approved by the US FDA in 2015 for the treatment of unresectable or metastatic liposarcoma and leiomyosarcoma and is approved in multiple countries for the treatment of patients with recurrent platinum-sensitive ovarian

TABLE 7 Clinical trials of marine-derived alkaloids against breast cancer.

Compound name	Clinical phase	Patients	Cases (*n*)	Doses	Results	References
Eribulin mesylate (ER-086526)	Phase I	Advanced solid malignancies	32 (2 breast cancer)	Eribulin mesylate (1-h i.v. infusion) on days 1, 8, and 15 of a 28-day cycle	One breast cancer patient reported stable disease	(Goel et al., 2009)
Eribulin mesylate (ER-086526)	Phase I	Advanced or refractory solid tumors	40 (4 breast cancer)	Eribulin mesylate was administered as a weekly bolus 3 weeks out of 4, starting at 0.125 mg/m^2/week	One breast cancer patient reported MR	(Synold et al., 2005)
Eribulin mesylate (ER-086526)	Phase I	Advanced solid tumors	36 (4 breast cancer)	Patients received eribulin mesylate 0.7–1.4 mg m^{-2} and cisplatin 60–75 mg m^{-2}. Eribulin mesylate was administered on days 1, 8, and 15 in combination with cisplatin day 1 every 28-day cycle	One breast cancer patient had unconfirmed partial responses	(Koczywas et al., 2014)
Eribulin mesylate (ER-086526)	Phase II	Patients with locally advanced breast cancer or metastatic breast cancer who had previously been treated with an anthracycline and a taxane	80	Patients received 1.4 mg/m^2 eribulin mesylate (2- to 5-min i.v. infusion on days 1 and 8 of a 21-day cycle)	Objective response rate was 21.3%; the clinical benefit rate was 27.5%	(Aogi et al., 2012)
Eribulin mesylate (ER-086526)	Phase II	Patients with metastatic breast cancer	103	Eribulin mesylate (1.4 mg/m^2) as a 2- to 5-min intravenous infusion on days 1, 8, and 15 of a 28-day cycle. Because of neutropenia (at day 15), an alternative regimen of eribulin on days 1 and 8 of a 21-day cycle was administered	Eribulin achieved an independently reviewed objective response rate of 11.5% and a clinical benefit rate of 17.2%	(Vahdat et al., 2009)
Eribulin mesylate (ER-086526)	Phase II	Patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, taxane, and capecitabine	299	Eribulin mesylate (1.4 mg/m^2) administered as a 2- to 5-min intravenous infusion on days 1 and 8 of a 21-day cycle	Objective response rate by independent review was 9.3% and clinical benefit rate was 17.1%	(Cortes et al., 2010)

(Continued)

TABLE 7 Continued

Compound name	Clinical phase	Patients	Cases (*n*)	Doses	Results	References
Eribulin mesylate (ER-086526)	Phase II	Patients with recurrent or metastatic HER2+ breast cancer	52	Patients received eribulin mesylate at 1.4 mg/m^2 intravenously (i.v.) on days 1 and 8 of each 21-day cycle with an initial trastuzumab dose of 8 mg/kg i.v. on day 1, followed by 6 mg/kg of trastuzumab on day 1 of each subsequent cycle	The ORR was 71.2%	(Wilks et al., 2014)
Eribulin mesylate (ER-086526)	Phase II	Patients with metastatic breast cancer who had well-defined taxane resistance	51	Patients received eribulin mesylate 1.4 mg/m^2 [equivalent to eribulin 1.23 mg/m^2 (expressed as free base)] as a 2- to 5-min intravenous infusion on days 1 and 8 of each 21-day cycle	The clinical benefit rate was 39.2%, and the rate of progressive disease was 49.0%	(Inoue et al., 2016)
Eribulin mesylate (ER-086526)	Phase II	HER2-negative locally advanced or metastatic breast cancer patients	35	Received intravenous eribulin (1.4 mg/m^2 on days 1 and 8 of each 21-day cycle)	Overall response rate and clinical benefit rate were 54.3% and 62.9%, respectively	(Takashima et al., 2016)
Eribulin mesylate (ER-086526)	Phase II	Patients with metastatic breast cancer	32	Patients were scheduled to receive eribulin mesylate 1.4 mg/m^{2}intravenously on days 1 and 8 of a 21-day cycle	The overall response rate was 43.8% and clinical benefit and tumor control rates were 56.3%	(Hayashida et al., 2018)
Eribulin mesylate (ER-086526)	Phase II	Untreated advanced or metastatic HER2-positive breast cancer	28	Patients received eribulin (1.4 mg/m^{2}intravenously; i.v.) on days 1 and 8 of each 21-day cycle, an initial trastuzumab dose (8 mg/kg i.v.) on day 1, and 6 mg/kg of trastuzumab on day 1 of each subsequent cycle	The response rate was 53.6%, and clinical benefit rate was 64.0%	(Sakaguchi et al., 2018)
Eribulin mesylate (ER-086526)	Phase II	Patients with advanced breast cancer	33	Patients receive a combination therapy of eribulin (1.4 mg/m^2 on days 1 and 8, every 21 days) and S-1 (65 mg/m^2, on days 1 to 14, every 21 days)	Confirmed objective response rate was 33.3%	(Iwasa et al., 2019)
Eribulin mesylate (ER-086526)	Phase II	Hormone receptor-positive (HR+) metastatic breast cancer	88	Pts were randomized 1:1 to mesylate 1.4 mg/m^2 intravenously (i.v.) on d1 and d8 with pembrolizumab 200 mg/m^2 i.v. on d1 of a 21-day cycle (Arm A) or mesylate alone (Arm B)	Median progression-free survival and objective response rate were not different between Arms A and B	(Tolaney et al., 2019)
Eribulin mesylate (ER-086526)	Phase II	Locally advanced or metastatic TNBC	83	Eribulin (0.88 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 of a 21-day cycle	An overall response rate was 37.3%, and the clinical benefit rate was 48.8%	(Pellegrino et al., 2021)
Eribulin mesylate (ER-086526)	Phase II	Patients with metastatic breast cancer aged ≥70 years	77	1 mg/m^2 d1 + 8 q3 weeks	The DCR was 40%, and overall response rate was 22%	(Hasler-Strub et al., 2023)
Eribulin mesylate (ER-086526)	Phase III	Patients with locally recurrent or metastatic breast cancer	762	Patients were randomly allocated (2:1) to eribulin mesylate (1·4 mg/m^2 administered intravenously during 2–5 min on days 1 and 8 of a 21-day cycle) or treatment of physician's choice	Median overall survival were 13.1 months for eribulin and 10.6 months for treatment of physician's choice	(Cortes et al., 2011)
Eribulin mesylate (ER-086526)	Phase III	Patients with locally advanced or metastatic breast cancer who had received prior anthracycline- and taxane-based therapy	1,102	Patients were randomly assigned (1:1) using a central interactive voice-response system to receive eribulin mesylate 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2) intravenously over 2 to 5 min on days 1 and 8, or capecitabine 1.25 g/m^2 orally twice per day on days 1 to 14, both in 21-day cycles	Objective response rates were 11.0% for eribulin and 11.5% for capecitabine	(Kaufman et al., 2015)

(Continued)

TABLE 7 Continued

Compound name	Clinical phase	Patients	Cases (*n*)	Doses	Results	References
Yondelis (trabectedin, ET-743)	Phase I	Patients with treatment-refractory solid tumors	52 (8 breast cancer)	Patients received a total of 158 cycles of ET-743 at one of nine dose levels (DLs) ranging from 50 to 1,800 μg/m^2	One patient with breast cancer has partial responses	(Taamma et al., 2001)
Yondelis (trabectedin, ET-743)	Phase II	Patients with progressive advanced breast cancer previously treated with anthracyclines and/or taxanes	21	Dose of 1.5 mg/m^2; 24-h i.v. continuous infusion; every 3 weeks (other chemotherapies were used)	Three confirmed partial responses, one unconfirmed partial response and two minor responses were observed	(Zelek et al., 2006)

cancer (Barone et al., 2017). Previous preclinical studies have shown that sequential treatment with paclitaxel and trabectedin improves the antitumor effects in nude mice with MX-1 xenografts (Takahashi et al., 2002). Moreover, a phase II study (Table 7) showed that trabectedin can induce response and tumor control in previously treated patients with advanced breast cancer with controllable toxicity (Zelek et al., 2006).

In vitro, both UCN-01 and tamoxifen can individually inhibit the proliferation of MCF-7 cells in a concentration-dependent manner, and their combined use exhibits superior synergistic antitumor effects at different concentrations (Koh et al., 2003). However, for Br-10 and MCF-7 xenograft tumors, UCN-01 and tamoxifen can only exert marginal antitumor effects when used alone and can have positive antitumor effects when combined (Koh et al., 2003). A phase I clinical trial by Fracasso et al. showed that the combination of UCN-01 and irinotecan induced responses in patients with advanced breast cancer (Fracasso et al., 2011). However, the results from further phase II clinical trials showed that the overall response rate of patients with metastatic triple-negative breast cancer to irinotecan combined with UCN-01 was only 4% (Ma et al., 2013).

Conclusion

Breast cancer is the most common cancer worldwide, affecting an estimated 12.9% of women in their lifetime (Delgado et al., 2021). For early-stage breast cancer, complete or breast-conserving surgical resection is the cornerstone of oncologic treatment. Usually, local treatment (radiotherapy) or systemic treatment (chemotherapy and targeted therapy) is supplemented before surgery (neoadjuvant) or after surgery (adjuvant) to prevent tumor recurrence (Harbeck et al., 2019). Unfortunately, approximately 30% of early-stage breast cancers will experience recurrence and metastasis (Pisani et al., 2002). Currently, effective treatments for advanced and recurrent breast cancer are lacking. Chemotherapy and systemic treatment can only be used to control tumor spread, improve quality of life, and extend life expectancy (Harbeck et al., 2019). Therefore, there is an urgent need to develop new effective drugs to treat cancer through the application of new technologies, new ideas, and new methods.

Marine resources account for 80% of the Earth's biological resources, and the special living environments (such as high pressure, low temperature, high salt, and lack of light and oxygen) of marine organisms have resulted in the metabolism and accumulation of numerous natural compounds with unique chemical structures and various biological activities, providing new tools for tumor treatment. Marine alkaloids, which are mainly derived from sponges, fungi with symbiotic relationships, bacteria, cyanobacteria with nitrogen-fixing capabilities, and tunicates, are important natural compounds in marine organisms. In recent years, with the advancement of modern technology, significant progress has been made in the field of marine chemistry, especially important breakthroughs in the separation and purification of natural marine compounds. The improvement of separation and purification technology has made it increasingly possible to extract different alkaloids from marine organisms. However, there are still some challenges. For example, most marine alkaloids still face problems such as small extraction volumes and low efficiency (Zhou et al., 2021). In addition, protecting and preserving natural marine habitats has become urgently important. To overcome these challenges, methods such as rational drug design, structural modification of lead compounds, and chemical synthesis can be used (Ballot et al., 2010).

Encouragingly, numerous studies have shown that marine alkaloids can exhibit significant antitumor activity by inducing apoptosis and autophagy, inhibiting mitophagy, migration, invasion, angiogenesis, and oncogene pathways (such as the PI3K/Akt/mTOR signaling cascade), and causing DNA damage. These findings not only provide a valuable resource for the development of new anticancer drugs, but also are closely linked to the goal of the GBCI, which is to reduce breast cancer mortality through innovation and global collaboration. Although most studies on marine alkaloids have been conducted *in vitro*, and only a small proportion of compounds have undergone *in vivo* studies and clinical trials, these preliminary results have pointed the way for the development of marine drugs for the treatment of breast cancer.

Therefore, it is crucial to further explore the anticancer mechanism of marine alkaloids, which will not only help to fully understand their potential as anticancer drugs but also contribute to the realization of the goals of GBCI. Some of the substances summarized in this review may provide researchers with a useful blueprint for selecting candidate anticancer drugs and inspire medicinal chemists in this field to actively explore and develop

new marine drugs for breast cancer. As these studies progress, we can expect to see more marine alkaloids developed into effective anticancer drugs, thus playing a key role in the global fight against breast cancer, bringing new hope to patients with breast cancer and directly contributing to reducing breast cancer mortality, which is in line with GBCI's ambitious goals.

Author contributions

HS: Funding acquisition, Project administration, Writing – original draft, Writing – review & editing, Supervision. JY: Writing – original draft, Writing – review & editing. XW: Writing – original draft, Writing – review & editing. PD: Writing – original draft, Writing – review & editing, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmars.2024.1440928/full#supplementary-material

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