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SHORT COMMUNICATION KISA ARAŞTIRMA

Anticancer secondary metabolites from marine sponges

Deniz süngerlerinden antikanser metabolitler

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Abstract: The oceans cover 70% of the Earth's surface. The marine environment is an important source of secondary metabolites with high biodiversity. Besides other marine species, sponges with a wide range of secondary metabolites are an important potential for drug discovery. Cancer is one of the leading causes of death with high morbidity and mortality. It is very important to discover new therapeutic agents in the treatment of cancer. In recent years, studies on exploring new anticancer compounds are focused on the marine source. In this review, our target is collecting the studies about marine sponges secondary metabolites which have an anticancer effect. Among most of the isolated compounds from sponges and their semisynthetic derivatives, there are three FDA (US Food and Drug Administration) approved compounds and three compounds in clinical phase. Moreover, more than 40 compounds isolated from marine sponges have been tested for anticancer activity in recent 10 years. In conclusion marine sponges secondary metabolites are a promising and important source of the anticancer compounds.

Keywords: Natural products, marine sponges, secondary metabolites, cancer treatment

Öz: Okyanuslar dünya yüzeyinin 70%'ini kaplamaktadır. Deniz ortamı, yüksek biyolojik çeşitlilik sunan, önemli bir sekonder metabolit kaynağıdır. Diğer deniz türlerinin yanı sıra, çok çeşitli sekonder metabolitlere sahip olan süngerler, ilaç keşfi için önemli bir potansiyel taşımaktadır. Kanser, yüksek morbidite ve mortalite ile önde gelen ölüm nedenlerinden biridir. Kanser tedavisinde yeni terapötik ajanların bulunması çok önemlidir. Son yıllarda, yeni antikanser bileşiklerini keşfetmeye yönelik çalışmalar deniz kaynaklarına odaklanmıştır. Bu derlemede hedefimiz antikanser etkisi olan, deniz süngerinden izole edilen sekonder metabolitler ile ilgili çalışmaları toplamaktır. Süngerlerden elde edilen bileşikler ve bu bileşiklerin yarısentetik türevleri arasından 3 adet bileşik FDA (Amerika Gıda ve İlaç Dairesi) tarafından onaylanmış ve 3 bileşik klinik faz çalışmalarındadır. Ayrıca, deniz süngerlerinden izole edilmiş 40'tan fazla bileşik, son 10 yılda antikanser aktivitesi açısından test edilmiştir. Sonuç olarak deniz süngerlerinden elde edilen sekonder metabolitler önemli ve gelecek vaat eden bir antikanser bileşik kaynağıdır.

Anahtar kelimeler: Doğal ürünler, deniz süngerleri, sekonder metabolitler, kanser tedavisi

INTRODUCTION

Cancer is a major global health problem responsible for 13 million deaths worldwide, and death rate is expected to rise to 13.1 million by 2030. Despite the progress in the field of cancer research, there is still a need to discover and develop anticancer therapeutic agents (Torre et al., 2015).

Natural products from plants, animals, and marine sources have been used for the treatment of different diseases and are becoming an important research area for drug discovery. Generally, they are used by the producing organisms to compete for vital resources, defend against predators and communicate interspecies (Dias et al., 2012; Mann, 1994). These products have been extensively studied and have shown some bio-activities such as antimicrobial, anti-inflammatory, antiprotozoal activity and anticancer activity. The natural source based drug discovery resulted mainly in the development of anticancer agents from plants (vincristine, vinblastine, etoposide, paclitaxel, camptothecin, topotecan and irinotecan), marine organisms (citarabine, aplidine and dolastatin) and micro-organisms (dactinomycin, bleomycin and doxorubicin (Thomas et al., 2010; L. Wang et al., 2012).

In the last decades, marine organisms are accepted as a new source of novel molecules for new drug discovery and drug development. The large diversity of the marine habitats led the marine invertebrates to produce wide range of bioactive compounds such as acids, alkaloids, esters, fatty acids, glycosides, lipids, peptides, terpenes, terpenoids, with therapeutic effect (Malve, 2016). Besides, the marine ecological environment has unique characteristics like, low level oxygen and light, high salt, extreme temperatures and high pressure. Due to these difficulties, enzyme reaction system and metabolic pathways of marine organisms are remarkably different from terrestrial counterparts (Schumacher et al., 2011).

Marine natural products provide a rich source of chemically diverse compounds which have significant potential to develop novel types of anticancer agents. The biodiversity of marine life and the accompanying chemical diversity enable the marine environment to possess infinite

bioactive secondary metabolites (Pihlanto-Leppälä, 2000). Bioactive secondary metabolites are isolated from such sources as corals, sponges, marine plants, animals and microorganisms (Rasmussen and Morrissey, 2007). These isolated bioactive secondary metabolites have been found to be effective as antifungal, neuroprotective, anti-tumor, photoprotective, antibiotic, and anti-infective bioactivities (Bérdy, 2005; Mishra and Tiwari, 2011; Molinski et al., 2009; Pettit et al., 1982; Sudek et al., 2007).

Owing to their various and significant bioactivities, marine natural products have become important for pharmaceutical and cosmetic industries. There are eight drugs from marine source on the market with FDA or EMEA (European Medicines Agency) approval (Figure 1) (Martins et al., 2014). Among these drugs, Halaven was obtained from sponges.

Number of new terpenoids from invertebrates is increasing, contrasting with the decreasing trend in the discovery of new alkaloids and aliphatic molecules (Leal et al., 2012). These secondary metabolites are important in the development of compounds to treat cancer. There are three compounds already approved by FDA for cancer treatment isolated from sponges (Table 1) and two secondary metabolites are in clinical trials at various stages (Table 2).

Besides the other marine organisms, sponges have ability to produce important quantity of secondary metabolites possessing unique structures with certain activities. Due to the lack of a protective shell, immune system and mobility, sponges have developed an ability to synthesize different compounds to survive. For this reason, sponges are considered as the focus of natural product studies for a long time (Livett et al., 2004). Up to date approximately, 8000 sponge species were identified, and almost two times not identified. Due to the fact that many natural resources have been investigated, attention moved to marine environment and specifically to marine microorganisms like cyanobacteria, sponge, fungi and several other groups of marine bacteria because of their wide diversity (Bhatnagar and Kim, 2010).

Figure 1. Eight drugs with FDA or EMEA approval from marine source on the market for different diseases (Martins et al., 2014)

Table 1. FDA Approved anticancer aompounds isolated from sponges

Compound	Source of Metabolite	Chemical Class	Clinical Status	Reference
Eribulin Mesylate (Halaven)	*Lissodendoryx* sp.	Macrolide	FDA Approved	(Menis and Twelves, 2011)
Cytarabine (Ara-C)	*Cryptotheca crypta*	Nucleoside	FDA Approved	(Krauss et al., 2018)
Gemcitabine	*Tectitethya crypta*	Nucleoside	FDA Approved	(Gesto et al., 2012)

Table 2. Currently in Clinical Pipeline Anticancer Compounds Isolated from Sponges

Compound	Source of Metabolite	Chemical Class	Clinical Status	Reference
Plocabulin (PM060184)	*Lithoplocamia lithistoides*	Polyketide	Phase II	(Pantazopoulou et al., 2018)
MORAb-202 (antibody–drug conjugate)	*Halichondria okadai*	Macrolide	Phase I	(Cheng et al., 2018)

RESULTS AND DISCUSSION

Marine sponges are still a virgin area. Studies should be concentrated in this area, especially since living organisms in the marine environment are important for the discovery of new metabolites. In the light of the given data it can be seen that many secondary metabolites are obtained from marine sponges. When these compounds are tested for cancer treatment, some of the compounds showed significant activity. Potential of these compounds are evaluating by clinical stages to product new drugs (Table 3).

It is hoped that the secondary metabolites, which have shown considerable success in preclinical experiments, can be used in the treatment of cancer by feeding the clinical experiment process.

Table 3. List of secondary metabolites which tested for anti cancer activity in last 10 years

Secondary Metabolite	Source of Metabolite	Cell Line	Concentration Range	Reference
Isoaaptamine	*Aaptos* sp.	THP-1	10-25 µM	(Dyshlovoy et al., 2014)
Aaptamine	*Aaptos aaptos*	THP-1	50-200 µM	(Dyshlovoy et al., 2014)
Microsclerodermin A	*Amphibleptula* sp.	AsPC-1	2.4 µM	(Guzman et al., 2015)
		BxPC-3	2.4 µM	
Isofistularin-3	*Aplysina aerophoba*	U937	50 µM	(Florean et al., 2016)
		Raji	50 µM	
Crambescidin 800	*Crambe crambe*	HepG2	0.5–2.5 µM	(Roel et al., 2016)
Salarin C	*Fascaplysinopsis* sp.	K562	0.01–0.2 µM	(Ben-Califa et al., 2012)
Fascaplysin	*Fascaplysinopsis Bergquist* sp.	A549	0.63 µM	(Rath et al., 2018)
		OVCAR3	0.52 µM	
		S457	0.2 µM	
Ilimaquinone	*Hippospongia metachromia*	HCT116	2.5–10 µM	(Lee et al., 2015)
Heteronemin	*Hyrtios* sp.	K562	1.4–5.6 µM	(Schumacher et al., 2010)
		DU145	0.01–1 µg/mL	
		PC-3	0.01–1 µg/mL	(Wu et al., 2016)
		LNCaP	0.01 µg/mL	
		T24	0.1–0.8 µg/mL	(Huang et al., 2016)
		A498	0.5–3 µM	
Stellettin B	*Jaspis stellifera*	K562	0.012–0.054 µM	(Chen et al., 2017)
		A549	0.02-1 µM	(Wang et al., 2016)
		SF295	0.04-1 µM	(Tang et al., 2014)
Leiodermatolide	*Leiodermatium* sp.	AsPC-1	0.01 µM	(Guzman et al., 2016)
Monanchocidin A	*Monanchora pulchra*	HeLa	1.39 µM	(Dyshlovoy et al., 2016a)
Monanchocidin B	*Monanchora pulchra*	HeLa	0.58 µM	
Rhizocalinin	*Rhizochalina incrustata*	HL-60	10-25 µM	(Jin et al., 2009)
		HT-29	1-6 µM	(Khanal et al., 2011)
		THP-1	1-10 µM	(Fedorov et al., 2009)
		PC-3	0.5-4 µM	(Dyshlovoy et al., 2016b)
		DU-145	0.5-4 µM	
		22Rv1	0.5-4 µM	
		VCaP	0.5-4 µM	
Sipholenol A	*Siphonochalina* sp.	HepG2	17.18 µM	(Abdel-Lateff et al., 2016)
		HCT-116	14.8 µM	(Sobahi et al., 2017)
Sipholenol L	*Siphonochalina* sp.	HepG2	24 µM	
		HCT-116	19.8 µM	
Spongiatriol	*Australian spongia* sp.	AsPC-1	6.8 µM	(Guzman et al., 2013)
		PANC-1	6.8 µM	
		MIA PaCa-2	6.8 µM	
		BxPC-3	6.8 µM	
Scalaradial	*Cacospongia scalaris*	HeLa	10 µg/mL	(De Stefano et al., 2012)
		T47D	10 µg/mL	
Callyspongidiol	*Callyspongia* sp.	HL-60	31.0–77.5 µM	(Umeyama et al., 2010)
Lasonolide A	*Forcepia* sp.	CA46	0.1 µM	(Zhang et al., 2012)
		MCF-7	0.1 µM	
		HCT-116	0.1 µM	
Geoditin A	*Geodia japonica*	HL-60	1.6 to 25 µg/mL	(Liu et al., 2005)
		HT-29	5-30 µM	(Cheung et al., 2010)
Spongistatin 1	*Hyrtios erecta*	MCF-7	0.0002–0.0005 µM	(Schneiders et al., 2009)
		L3.6pl	0.00001–0.01 µM	(Rothmeier et al., 2010)
Irciniastatin A	*Ircinia ramose*	Jurkat	0.01 µM	(Chinen et al., 2010)
	Psammocinia sp.			
Jaspine B	*Jaspis* sp.	B16	5 µM	(Salma et al., 2009)
		HaCaT	5 µg/mL	(Yoo et al., 2012)
Petrosterol-3,6-dione	*Lanthella* sp.	HL-60	19.9 µM	(Nguyen et al., 2009)
5,6-epoxy-petrosterol	*Lanthella* sp.	HL-60	21.3 µM	
Petrosterol	*Lanthella* sp.	HL-60	21.5 µM	
Latrunculin A	*Negombata magnifica*	NUGC-4	0.01–10 µM	(Konishi et al., 2009)
Psammaplysene A	*Psammaplysilla* sp.	ECC1	1 µM	(Berry et al., 2009)
		Ishikawa	1 µM	
Smenamides A and B	*Smenospongia aurea*	Calu-1	0.05–0.1 µM	(Teta et al., 2013)
Renieramycin M	*Xestospongia* sp.	H460	5-40 µM	(Halim et al., 2011)
Isobatzelline E	*Batzella* sp.	AsPC-1	5 or 25 µg/mL	(Guzman et al., 2009)
Calyculin A	*Discodermia calyx*	MDA-MB-468	0.01 µM	(Edelson and Brautigan, 2011)
		MCF-7	0.01 µM	
		MDA-MB-231	0.01 µM	
(19Z)-Halichondramide	*Chondrosia corticata*	A549	0.025–0.1 µM	(Bae et al., 2013)
Leiodermatolide	*Leiodermatium* sp.	A549	0.01–1 µM	(Paterson et al., 2011)
		U2OS	0.018–0.23 µM	(Mailhol et al., 2014)
Peloruside A	*Mycale hentscheli*	MCF-7	0.025–0.1 µM	(Chan et al., 2011)
FBA-TPQ	*Zyzzya* sp.	MCF-7	2.297 mumol/L	(W. Wang et al., 2009)
Manzamine A	*Haliclona* sp.	AsPC-1		(Radwan et al., 2012)
10-Acetylirciformonin B	*Ircinia* sp.	HL-60	2.5 g/mL	(Su et al., 2012)
Smenospongine	*Spongia pertusa Esper*	MCF-7-Nanog	6.06 µM	(Kong et al., 2008)
Candidaspongiolide A/B	*Candidaspongia* sp.	MCF-7	2.0 nM	(Whitson et al., 2011)
Jaspamide	*Jaspis johnstoni*	L5178Y	0.1 µg/mL	(Ebada et al., 2009)

CONCLUSION

Sponges are one of the most interesting taxa of marine organisms with respect to the discovery of active compounds for the pharmaceutical application. In conclusion, it has been seen that marine sponge secondary metabolites are important as the source of useful anticancer compounds. Among most of the isolated compounds from sponges and their semisynthetic derivatives, there are six compounds either approved or in clinical phase. Moreover, more than 40 compounds have been tested for anticancer activity in the last 10 years.

The future contribution of marine natural products to cancer treatment seems promising, with a significant improvement of more products from marine sponge secondary metaboites in the clinical and preclinical stages.

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