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Angiosuppressive properties of marine-derived compounds—a mini review

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Abstract Angiogenesis, formation of new blood vessels from preexisting one, is a critical step of tumorgenesis of solid tumors. Therefore, antiangiogenic therapy is one of the promising approaches to control tumor growth. In the past 20 years, a lot of compounds have been tested for their antiangiogenic properties. Bevacizumab, Avastin®, the first antiangiogenic drug approved by the US FDA, has been widely used in clinic for treating cancer. Indeed, many synthetic compounds are highly toxic and exert side effects even though they are effective in inhibiting neovessel formation and cancer cell growth. Using natural compounds or their derivatives is one of the ways to solve these problems. Sinomenine and ginsenosides are common antiangiogenic and anticancer compounds that are extracted from herbal medicines. Recent findings suggested that marine algae-derived natural pigments also possess similar activities. It has been reported that fucoxanthin from *Undaria pinnatifida*, Siphonaxanthin from *Codium fragile*, can inhibit angiogenesis and cancer growth effectively. In conclusion, natural compounds derived from marine algae could provide a novel and safe source for new drug development in anticancer and antiangiogenic properties in the future.

Keywords Angiogenesis · Marine-derived compound · Angiosuppression

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Introduction

The ocean covers approximately 70 % of Earth's surface. It contains around 97 % of Earth's water, and comprises about 50 % of total global biodiversity. Regarding to uniqueness of marine environment, marine organisms have developed a series of specific biochemical and physiological systems, so as to survive in this dynamic and competitive habitat. Thus, marine flora and fauna are rich sources of diverse compounds with different biological activities and potential health benefits. Increasing evidences indicate that these bioactive materials function as antimicrobial, antioxidative, antihypertensive, anticoagulant, or anticancer ingredient in the functional foods, nutraceuticals, or even pharmaceuticals with regard to their nutritional value and therapeutic potential in the disease prevention or treatment (Kim et al. 2008; Kim and Wijesekara 2010; Pomponi 1999). However, there is only a very limited portion, about 5 %, of the ocean has been explored (www.water.usgs.gov); indeed, a huge amount of valuable biological and chemical resources are undescribed.

In the past decade, natural compounds have been claimed for their valuable nutritional values. Moreover, many of them are pharmacologically active and used for medical purposes. According to WHO, cancer has become much more popular and the global cancer rates could further increase by 50 % to 15 million new cases by 2020 (www.who.inf). Data showed that lung cancer is the most common cancer found in both sex worldwide (www.wcrf.org; www.cancer.gov), while

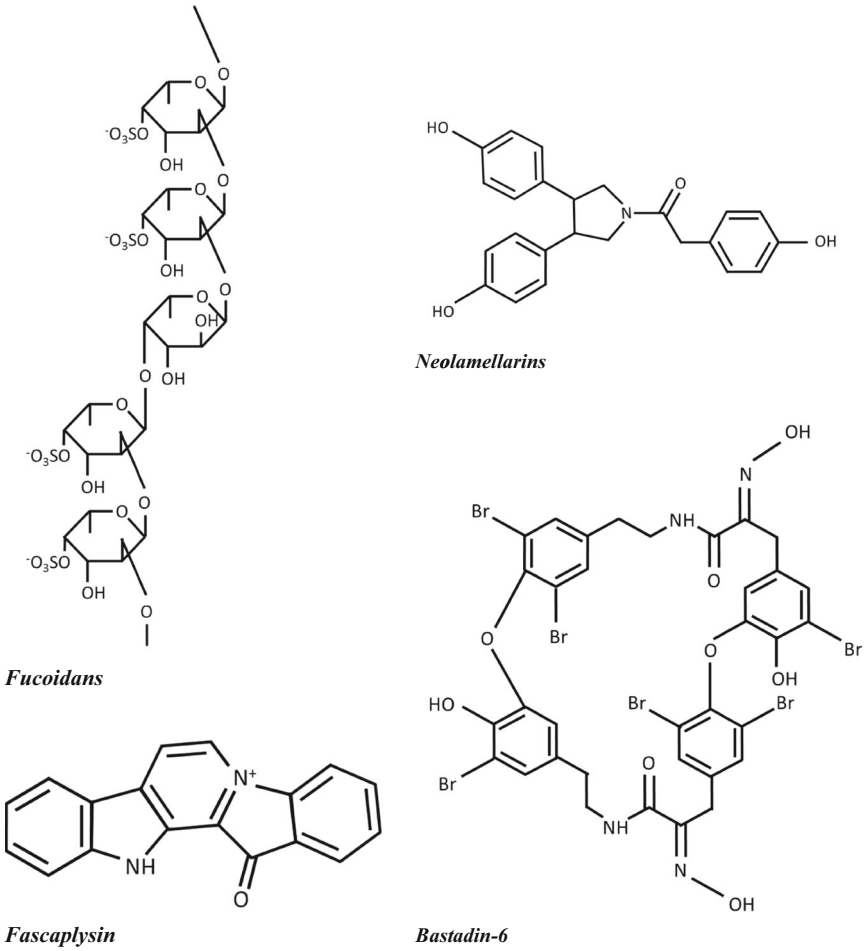


Fig. 1 Chemical structures of angiosuppressive marine-derived compounds

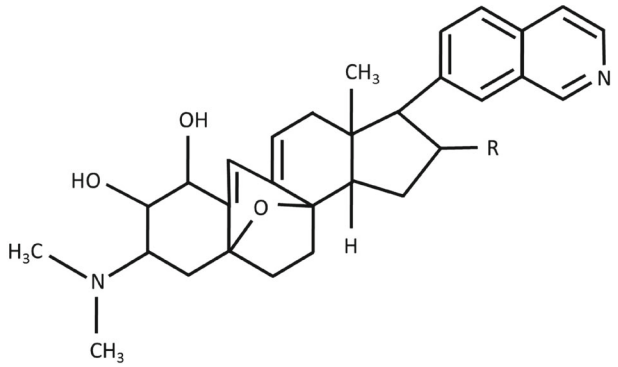
colorectal cancer is in the top-ranked position in some areas such as Hong Kong (www.cancer.fund.org; www.iarc.fr). One of the ways in cancer treatment is applying conventional cytotoxic anticancer drugs such as cisplatin, which can kill cancer cells directly. In fact, some potent anticancer drugs or potential drug candidates such as Taxol®, camptothecin, and combretastatin are natural in origin. Besides, many drug compounds are originated from marine organisms including marine sponge and algae.

Since Dr. Folkman proposed antiangiogenic strategy for cancer treatment in 1970, many compounds have been screened for any angiosuppressive properties. Eventually, the development of angiosuppressive drugs becomes one of the focuses in pharmaceutical industry. As proposed, by inhibiting angiogenesis, tumor tissues cannot obtain enough nutrients for the active metabolism. Moreover, malignant tumor cells have no way to metastasize through the newly formed blood vessels. Therefore, antiangiogenic therapy has become one of the promising methods for cancer treatment. Avastin® is the first drug approved for cancer or angiogenic disorders (e.g., diabetic retinopathy) treatments by acting as an angiosuppressive agent. As we know, marine contains huge amount of valuable materials, some of them or their derivatives would be the promising drug candidates such as bryostatin-1, panobinostat, plitidepsin, marizomib, and plinabulin, whereas they are being tested in phase I, phase II, and phase III clinical trials (Wang and Miao 2013). Up to now, two of four approved marine-derived drugs, cytarabine and ecteinascidin, are approved for cancer treatment in 1969 and 2007, respectively (Mayer et al. 2010; Abraham et al. 2012). In this review, we will summarize the marine-originated compounds which have been shown for the angiosuppressive activities (Fig. 1).

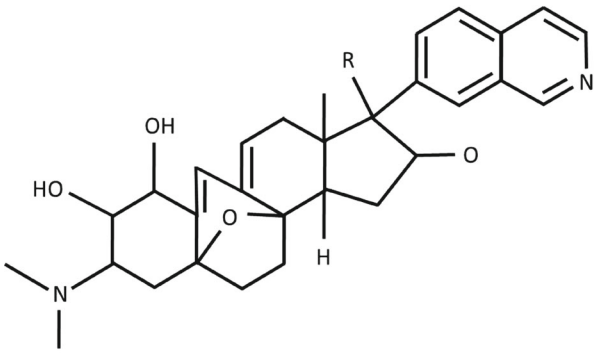
Angiogenesis

General background

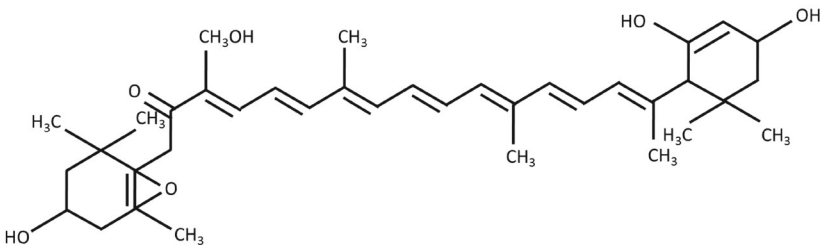
Angiogenesis, the formation of neovessels from preexisting vasculature, is a complex process that



Cortistatins A, B (Cortistatin A: R = H; Cortistatin B: R = OH)



Cortistatins C, D (Cortistatin C: R = H; Cortistatin D: R = OH)



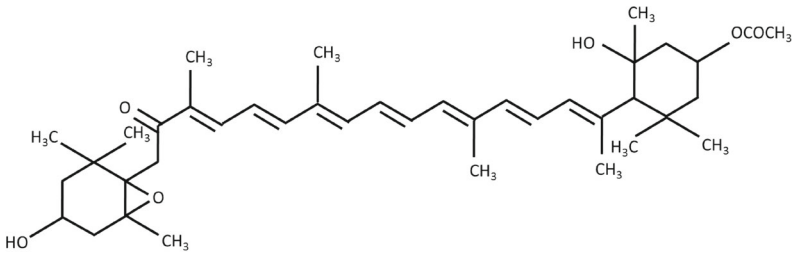
Siphonaxantin

Fig. 1 (continued)

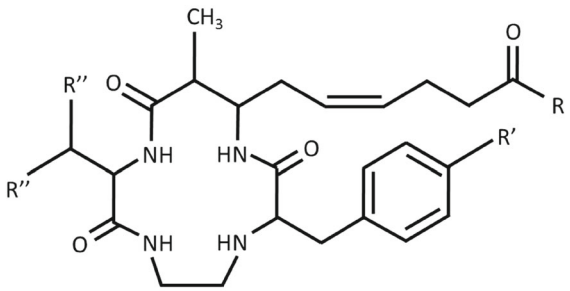
comprises endothelial cell (EC) activation by angiogenic growth factors, protease secretion to digest the extracellular matrix, EC chemotactic migration and invasion, EC tube formation, and neovessel stabilization. During the normal situation, angiogenesis is closely under control by a series of angiogenic stimulators and inhibitors. Indeed, this process has been shown to contribute for pathogenesis of many diseases such as cancer, atherosclerosis, diabetic retinopathy, and rheumatoid arthritis (Folkman and Klagsbrun 1987).

Angiogenesis as a therapeutic target

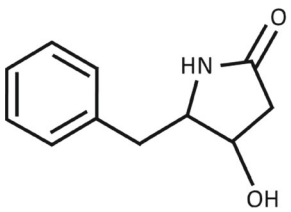
Angiotherapy is a newly developed clinical treatment strategy that targets the angiogenesis in pathological situation. This strategy can be applied for either promoting or suppressing angiogenesis. For case of promotion, becaplermin (Regranex™), a recombinant human platelet-derived growth factor (PDGF), has been used for treating diabetic foot ulcers by enhancing angiogenesis (Nagai and Embil 2002; Papanas and Maltezos



Fucoxanthinol



Azumamides A-E (A (R= NH2, R' = H, R"= CH3); B (R= NH2, R' = OH, R"= CH3); C (R= OH, R' = OH, R"= CH3); D (R= NH2, R' = H, R"= H); E (R= OH, R' = H, R"= CH3))



Streptopyrrolidine

Fig. 1 (continued)

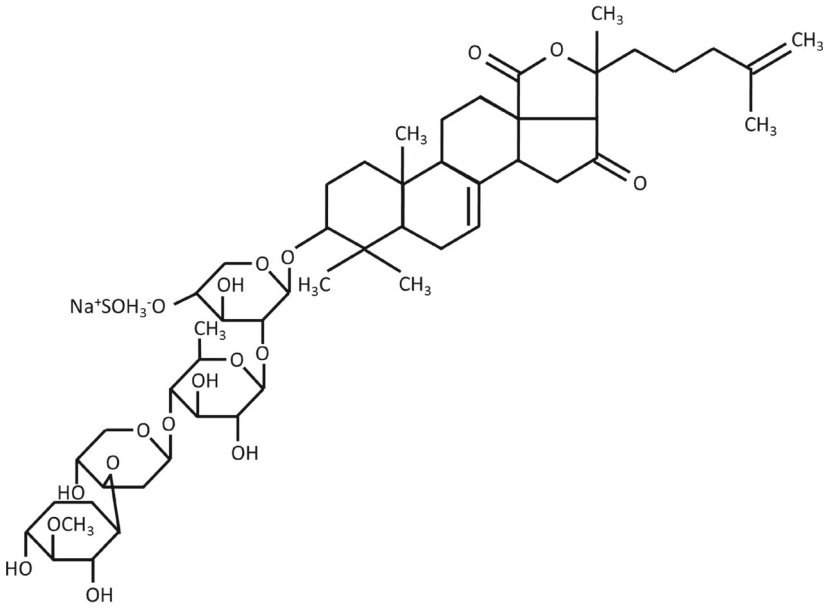
2007). Conversely, for the case of suppression, bevacizumab (Avastin®), a recombinant humanized monoclonal body of vascular endothelial growth factor A (VEGF-A), has been used for treating various types of cancer by suppressing neovessel formation (Kerbel 2000; Brekken et al. 2002; Ruoslahti 2002). In fact, the effort of angiosuppression is more appreciated in the field of biomedical and clinical applications. Many evidences have shown the capability of different angiosuppressive agents in pathological situation (Amit et al. 2013; Mayer et al. 2010). Thus, in this review, mainly the marine-derived angiosuppressive agents are discussed.

Angiosuppressive effects of marine-derived compounds

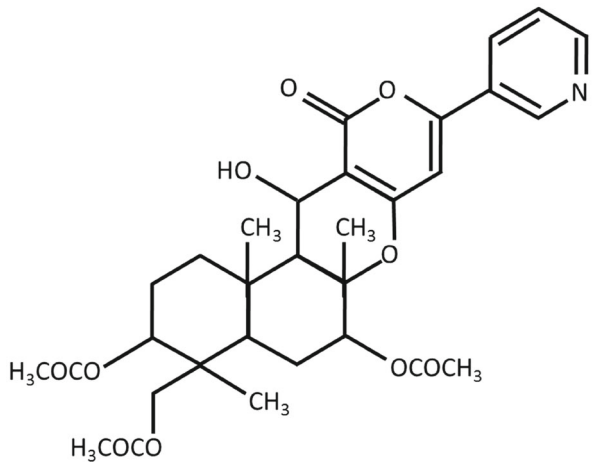
Previous literatures show that a lot of marine-derived compounds can exert inhibitory effects on neovessel formation in vitro, in vivo, and ex vivo. As shown in Table 1, they can be categorized into different groups according to chemical nature of the compounds (Fig. 1).

Alkaloids

Alkaloids, a group of naturally occurring chemical compounds, are commonly produced by many different types of



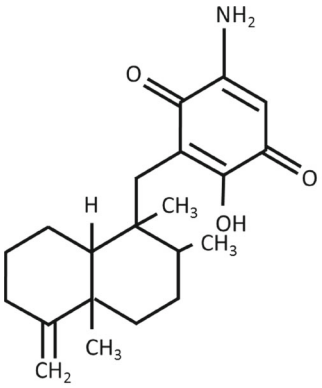
Philinopside E



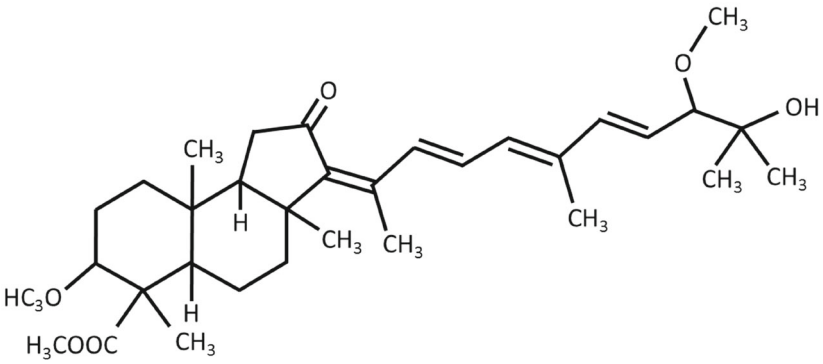
Pyripyropenes

Fig. 1 (continued)

organisms including bacteria, fungi, plants, and animals. It is well known that alkaloids exhibit a wide range of pharmacological activities such as anticancer, antibacterial, antiasthma, antihyperglycemic, vasodilatory, and analgesic activities. Fascaplysin, a bis-indole alkaloid of the marine sponge *Fascaplysinopsis bergquist*, has been recognized as a potent cyclin-dependent kinase-4 (CDK-4) inhibitor with IC_{50} at 350 nM (Bharate et al. 2012). Zheng et al. (2010)) demonstrated that fascaplysin at the concentration of 1.3 μM could induce apoptosis on human umbilical vein endothelial cells (HUVECs) directly. This response was confirmed by detecting caspase-3, Bax, Bcl-2, procaspase-8, and Bid activities (Zheng et al. 2010). Moreover, microarray data further showed that fascaplysin could modulate genes that are involved in cell cycle arrest (Cdc7, E2f1), apoptosis (Bid), actin cytoskeleton formation (Cdc42), and cell adhesion (Vcam1, Pecam1) (Yan et al. 2011). For the neolamellarin, it is a metabolite isolated from the marine sponge *Dendrilla nigra*. This



Smenospongine



Globostellatic acid

Fig. 1 (continued)

pyrrole-derived alkaloid has been shown to inhibit hypoxia-inducible factor-1 (HIF-1) (Arafeh and Ullah 2009). Upon treating with 7-hydroxyneolamellarin A (IC_{50} at 1.9 μM), HIF-1 activation was inhibited and VEGF secreted level was reduced in T47D cells human breast cancer cells (Liu et al. 2007). Bastadin-6 is a macrocyclic tetramer of a brominated tyrosine derivative that extracted from *Ianthella* species. With the IC_{50} set at 0.052 μM, it has been shown to suppress VEGF- or bFGF-induced HUVEC proliferation in 20- to 100-fold when compared with normal fibroblasts or tumor cells. Upon the drug treatment, apoptotic cell death was observed. Moreover, it could suppress VEGF-induced tube formation and migration of HUVECs at 0.1 and 1 μM, respectively. In mice corneal assay, bastadin-6 inhibited VEGF- or basic fibroblast growth factor (bFGF)-induced neovessel formation completely (Aoki et al. 2006a; Kotoku et al. 2008a). Another class of antiangiogenic alkaloid is extracted from marine sponge *Cortisium simplex*, called cortiostatin, which contains 12 types of cortiostatin (A–L) (Chen and Tseng 2010). Among them, cortiostatins A–D were well tested for the angiosuppressive activity that they all could exhibit growth inhibition on HUVECs with high selectivity. Among them, cortiostatin A has been shown as the most potent one, with IC_{50} at 0.0018 mM on HUVECs. When comparing with normal fibroblasts or tumor cell lines such as Neuro2A, K562, NHDF, and KB3-1, the selective index was found to over 3000-fold difference (Aoki et al. 2006a). It also suppressed HUVECs chemotactic migration (0.2–2 μM) and tube formation (2–200 nM in a dose-dependent manner (Aoki et al. 2007a; Sato et al. 2008). Lastly, aeroplysinin-1, brominated tyrosine metabolite extracted from marine sponge *Aplysina cavernicola*, has been shown to exhibit effective angiosuppressive ability (Córdoba et al. 2007). Rodríguez-Nieto et al. (2002)) indicated that aeroplysinin-1 could inhibit the proliferation of actively growing HUVECs and bovine aortic endothelial cells (BAECs) in a dose-dependent manner. In Matrigel tube formation assay, treatment with aeroplysinin-1 at dose of 0.7 μM, BAEC alignment and cord formation were completely inhibited, while HUVEC differentiation on Matrigel was stopped at 3 μM. In Boyden chamber assay, same concentration of aeroplysinin-1 could result in a 50 % inhibition of BAEC invasion. Moreover, the addition of

Table 1 Common examples of angiosuppressive marine-derived compounds

Marine-derived compounds	Compound nature	Sources	References
Fucoidans	Polysaccharides	Brown algae	Matsubara et al. (2005); Matou et al. (2002) Boisson-Vidal et al. (2007); Delma et al. (2015)
Oligomannurarate sulfate		Semi-synthetic	Ma et al. (2008); Zhao et al. (2006)
Fascaplysin	Alkaloids	Marine algae	Bharate et al. (2012); Zheng et al. (2010); Yan et al. (2011)
Neolamellarins		Marine sponge	Liu et al. (2007)
Bastadin-6		Marine sponge	Kotoku et al. (2008a); Aoki et al. (2006a)
Cortistatins		Marine sponge	Chen and Tseng (2010); Sato et al. (2008); Aoki et al. (2006a, 2007a)
Aeroplysinin-1		Marine sponge	Martínez-Poveda (2013); 'Córdoba et al. (2007); González-Iriarte et al. (2003); Rodríguez-Nieto et al. (2002)
Siphonaxantin	Carotenoids	Green algae	Ganesan et al. (2010)
Fucoxanthinol		Brown algae	Sugawara et al. (2006)
Azumamides	Peptides	Marine sponge	Nakao et al. (2008); Izzo et al. (2006)
Plitidepsin (Aplidin®)		Synthetic	Straight et al. (2006); Taraboletti et al. (2004); Plummer et al. (2013); Barboza et al. (2012)
Streptopyrrolidine	Amines	Marine bacteria	Shin et al. (2008)
Philinopsides A and E	Saponins	Sea cucumber	Tian et al. (2007, 2005); Tong et al. (2005)
Dieckol	Phenols	Brown algae	Li et al. (2015)
Pyripyropenes	Terpenoids	Marine fungus	Hayashi et al. (2009)
Smenospongine		Marine sponge	Kong et al. (2011)
Globostellatic acid		Marine sponge	Kotoku et al. (2008b); Aoki et al. (2007a)
Organic extracts	Others	Green algae	Kyadari et al. (2013)
Lysozyme			Ye et al. (2008)
Spongistatin 1		Marine sponge	Rothmeier et al. (2009)

aeroplysinin-1 (6 and 15 nM) could cause severe disorganization of the preexisting vessels and a complete suppression of neovessel formation in the area covered by the methylcellulose disks (Rodríguez-Nieto et al. 2002; González-Iriarte et al. 2003). Mechanistic study showed that this compound effectively downregulated matrix metalloproteinase (MMP)-1, MMP-2, urokinase, thrombospondin 1 (TSP-1), and monocyte chemoattractant rotein-1 (MCP-1) production (Rodríguez-Nieto et al. 2002; Martínez-Poveda et al. 2013a; Martínez-Poveda et al. 2013b).

Polysaccharides

Polysaccharides refer to carbohydrate molecules link up in polymer form with linear to highly branched structure. Natural saccharides are heterogeneous, due to the diverse in building blocks and their structural arrangement; they have distinct properties and biological functions. For instance, cellulose and chitin are used as structural and supporting purpose, while starch and glycogen are used for energy reservation. Fucoidan, extracted from brown algae or seaweed (e.g., mozuku, kombu, bladderwrack, wakame, and hijiki), has been found to modulate angiogenesis in a dipolar manner. Even though it has been shown to inhibit HUVEC tube formation and MMP-2 and MMP-9 secretions of pancreatic cancer cells at the concentration of 100–400 μg/ml, proangiogenic effect has been demonstrated (Delma et al. 2015; Matsubara et al. 2005). From the in vitro and ex vivo study, fucoidan has been shown to enhance HUVEC migration, fibroblast growth factor-2 (FGF-2)-induced vascular tube formation (Matou et al. 2002; Matsubara et al. 2005). Moreover, fucoidan might also modulate the mobilization of endothelial progenitor cells and their incorporation in ischemic tissues, in which it is believed as a critical step for angiogenesis (Boisson-Vidal et al. 2007). Oligomannurarate sulfates JG3 and JG6 are the novel semisynthesized marine-derived oligosaccharides that exhibited inhibitory effects on lung metastasis in the murine B16F10 experimental metastasis model, and MDA-MB-435s orthotopic xenografts in athymic mice, whereas their angiosuppressive effects have been shown in bioassays and molecular studies (Wen et al. 2013; Zhang et al. 2010). These oligosaccharides (10, 50, and 100 μg/ml) could significantly suppress tube formation of endothelial cells in a dose-dependent manner. In the ex vivo and in vivo studies, endothelial sprouting of rat aortic ring and neovessel

formation in chicken chorioallantoic membrane were arrested as well. Enzymatic study showed that JG3 and JG6 (2, 10, 50, and 100 μg/ml) are effective on the phosphorylation of protein tyrosine kinase (PTK) inhibition. In addition, data indicated that HER2, EGFR, VEGFR, PDGFR, c-Kit, FGFR1, and c-Src could be inhibited upon the treatment of JG3 and JG6 (Ma et al. 2008). Zhao et al. (2006) showed that JG3 could shut down heparanase-driven HUVEC invasion and migration and suppress the secretion of heparin sulfate-sequestered bFGF from extracellular matrix (ECM) and lead to angiosuppression (Zhao et al. 2006). Obviously, oligomannurarate sulfate is not only potent for cancer therapy anticancer but also effective in antiangiogenesis.

Carotenoids

They are a group of organic pigments which are commonly found in the chloroplasts of plants and some photosynthetic microorganisms such as bacteria and fungi. Obviously, cartotenoids play an important role in plants and algae through absorbing light energy for photosynthesis. They have vitamin A activity that can be converted to retinal and are important in protecting the macula of the retina. Siphonaxantin and fucoxanthinol, both are carotenoid in nature, are extracted from green (*Codium fragile*) and brown algae (edible seaweed such as *Undaria pinnatifida* and *Hijikia fusiformis*), respectively. The former (2.5, 10, and 25 μM) exhibits inhibition on HUVECs proliferation and tube formation in a dose-dependent manner (Ganesan et al. 2010). Ex vivo study also indicated the reduction of microvessel outgrowth from rat aortic fragments (Ganesan et al. 2010). Fucoxanthinol (10–20 μM) presented similar effects in vitro and ex vivo. In addition, it could inhibit the differentiation of endothelial progenitor cells into endothelial cells and lead to the neovessel formation (Sugawara et al. 2006).

Peptides

This class of biological molecules appears normally in a form of dipeptides and tripeptides, followed by polypeptides through linking up different numbers of amino acid monomers. Azumamides A-E are a group of cyclic tetrapeptide and depsipeptide, extracted from sponge *Mycale izuensis* that have been shown to exert impressive antiproliferative properties on cancers via inhibiting histone deacetylase (HDAC) (Izzo et al. 2006; Nakao et al. 2006). Among them, azumamides E is the most powerful carboxylic acid containing natural histone deacetylase (HDAC) inhibitor (Maulucci et al. 2007). Nakao et al. (2008)) has evaluated the angiosuppressive effect of various azumamides; similarly, azumamides E (1.9 μM) was found to exert strong inhibition on *in vitro* vascular organization model that using mouse pluripotent stem (iPS) cells. Besides, Plitidepsin (also known as Aplidin), is a cyclic depsipeptide isolated from the Mediterranean tunicate *Aplidium albicans*. Currently, this marine-derived antitumor agent is undergoing clinical trial on multiple myeloma and lymphoma (Plummer et al. 2013; Barboza et al. 2012). This antineoplastic drug candidate has been found to inhibit angiogenesis in various cancer models. In human leukemia cells MOLT-4 and anaplastic thyroid cancer xenograft models, aplidin (0.5–1 mg/kg/day) was found to suppress VEGF secretion, block VEGF-VEGFR-1 autocrine loop, VEGF receptor (FLT-1), and MMP production, respectively (Straight et al. 2006). Taraboletti et al. (2004) demonstrated angiosuppressive activity of aplidin in vitro and in vivo. In chick embryo allantoic membrane (CAM) assay, aplidin (10 nM) attenuated spontaneous neovessels formation and angiogenesis elicited by exogenous VEGF and FGF-2 and induced by VEGF overexpressing 1A9 ovarian carcinoma cells. In cellular study, aplidine (0.03–10 nM) suppressed VEGF and FGF-2-induced endothelial cell proliferation, migration, invasion, and tube formation significantly. Moreover, it inhibited the production of MMP-2 and MMP-9 by endothelial cells at the range of 1.25 to 20 nM) (Taraboletti et al. 2004).

Amines

Amines, derivatives of ammonia, are naturally found organic compounds; their functional groups usually contain a basic nitrogen atom, and the common examples are amino acids. Streptopyrrolidine, a benzyl pyrrolidine derivative, was isolated from the fermentation broth of a marine *Streptomyces* presented in the deep sea sediment. Shin et al. (2008) showed that streptopyrrolidine could significantly suppress capillary tube formation of HUVECs without exerting any cytotoxicity. Moreover, it was found that its potency is compactable as well-known angiogenic inhibitor SU11248 (Shin et al. 2008).

Saponins

This group of amphipathic glycosides commonly carries one or more hydrophilic glycoside moieties and linked with a lipophilic triterpene derivative. They were believed to be found in different plant species with particular abundance; indeed they are also extracted from marine organism. Among different types of saponin, ginsenosides are the most well-known and studied one. They are abundant in *Panax* ginseng and have been claimed as its pharmacological active ingredient. Of course, angiomodulatory effect is one of the research focus, in which Yue's group has demonstrated the proangiogeic and

angiosupressive effects of different protopanaxatriol and protopanaxadiol (Chan et al. 2009, 2013; Kwok et al. 2012; Yue et al. 2005, 2006, 2007; Fan et al. 2006). Previously, two novel philinopsides, A and E, that were isolated from the sea cucumber *Pentacta quadrangular*is, have been shown to exert dual antiangiogenic and antitumor activities in vitro and in vivo. Tong et al. (2005) demonstrated that philinopside A could effectively suppress the proliferation (IC_{50} at 1.4 μM), migration (IC_{50} at 0.89 μM), and tube formation (IC_{50} at 0.98 μM) of human microvascular endothelial cells (HMECs) in a dose-dependent manner. In rat aortic sprouting assay and CAM assay, it inhibited the neovessel formation in the concentrations of 2, 5, and 10 μM significantly. Western blotting analysis data showed that the angiosuppressive effect of philinopside A would be acted through suppressing the angiogenesis-related receptor tyrosine kinases (RTKs) including epithelial growth factor receptor, fibroblast growth factor receptor-1, PDGF receptor-beta, and VEGF receptor activations (Tong et al. 2005). For the philinopside E, it has been shown to inhibit cell migration, cell adhesion, and tube formation of both HMECs and HUVECs in the similar dose range. At the dose range of 1.25 to 5 μM, it could also inhibit the KDR phosphorylation and downstream signaling by interacting with KDR extracellular domain specifically to block its interaction with VEGF and the downstream signaling. Tian et al. (2005) and Tian et al. (2007) further demonstrated that philinopside E could inhibit alpha(v)beta(3) integrin-driven downstream signaling and resulted in the disruption of the actin cytoskeleton organization and decreased cell adhesion to vitronectin in HMECs (Tian et al. 2005; 2007).

Terpenoids

Terpenoids are the largest group of natural compounds found in living things. They are diverse structural difference that not only found in functional groups but also in their basic carbon skeletons. They are widely found in plant species; common examples are camphor and salvinorin A in the *Salvia divinorum*, and ginkgolide in *Ginkgo biloba*. They form cyclic structures such as steroids and sterols and play a role in traditional herbal remedies for many pharmaceutical functions including antibacterial and antineoplastic. Tomoda's group isolated pyripyropenes A–R from fermentation broth of *Aspergillus fumigatus* since 1993 (Kim et al. 1994; Tomoda et al. 1995, 1996). It has been shown that pyripyropenes A, B, and D could exhibit antiproliferative effect against HUVECs with IC_{50} of range of 0.1–1.8 μM. Among them, pyripyropenes A could significantly suppress VEGF-induced migration and tube formation of HUVECs (Hayashi et al. 2009). For the smenospongine, a sesquiterpene aminoquinone that extracted from marine sponge *Dactylospongia elegans*; it has been shown to suppress HUVECs proliferation (0.1–50 μM), migration, and tubulogenesis (0.5–2.5 μM) in a dose-dependent manner (Kong et al. 2011). Moreover, isomalabaricane triterpenes and their derivatives, globostellatic acids (GA) (A-D) and 13Z,17Z-, 13Z,17E-, 13E,17Z-, and 13E,17E-globostellatic acids X methyl esters were isolated from marine sponge *Stelletta globostellata* and *Rhabdastrella globostellata*, respectively. They have been shown to exhibit angiosuppressive effect on different in vitro models (Aoki et al. 2007a). Data showed that 13E,17E-globostellatic acids X methyl ester could suppress angiogenesis more significantly, in which it suppressed HUVEC proliferation in 80- to 250-fold selectively in comparing with KB3-1, K562, and Neuro2A cells. Moreover, in Matrigel tube formation assay and chemotaxical chamber model, it (0.03–0.1 μM) could inhibit the in vitro tubulogenesis and VEGF-induced cell migration in a dose-dependent manner (Aoki et al. 2007a; Kotoku et al. 2008a).

Hydroxyl group compounds

Phenolic compounds are refer to a class of organic chemical compounds which consist of a hydroxyl group (–OH) bonded to an aromatic hydrocarbon group directly. Most of these phenolic compounds appear in nature, for instant, gallic acid from galls and cannabinoids from cannabis, while synthetic phenolic compounds are bisphenol A and butylated hydroxytoluene (BHT). In general, phenolic compounds have strong antibacterial and antiseptic activities and act as nerve stimulants and immunostimulants. Dieckol, isolated from *Ecklonia cava* or *Ecklonia stolonifera*, has been shown to exert potent antiproliferative and angiosuppressive effects. It could inhibit VEGF-induced EA.hy926 human endothelial cell proliferation and migration through suppressing MMP-2 and MMP-9 genes and proteins expression. Moreover, data further showed that dieckol-induced angiosuppression could be mediated by inhibiting mitogen-activated protein kinase (MAPK) signaling pathway molecules including ERK and p38 (Li et al. 2015).

Others

Apart from the purified compounds, algae extract and marine lysozyme have also been suggested as angiosuppressive agents. Lysozyme, also known as 1,4-β-N-acetylmurmidase, has been recognized as a powerful antibacterial agent. Marine-derived lysozyme is a new class biological active material extracted from marine invertebrates (Nilsen et al. 1999; Nilsen and Myrnes 2001). Unexpectedly, these lysozymes showed special activity when comparing with vertebrate-derived one. Previously, Ye et al. (2008) showed that marine-derived lysosome suppress ECV304 endothelial cells

proliferation in a dose-dependent manner. In vivo CAM assay results further showed that lysozyme could suppress neovessel formation that created an avascular zone (Ye et al. 2008). On the other hand, organic extracts from plants have been found to contain a lot of biologically active ingredients. Recently, algal extract from *Chlorella pyrenoidosa* has been shown to exhibit antiangiogenic activity, in which these extracts could suppress neovascularization in in ovo CAM assay and in vivo corneal model (Kyadari et al. 2013). The last reported angiosuppressive drug candidate is spongistatin 1 which is a cyclic lactone extracted from marine sponge *Spongia* sp. Rothmeier et al. (2009) showed that it would be potent in inhibiting angiogenesis in vitro and in vivo. Spongistatin 1 could induce IC_{50} of cytotoxicity and growth on HUVECs 50 nM and 100 pM, respectively. For the in vitro cell migration, tubulogenesis, and chemotaxis of HUVECs, the IC_{50} were found at the concentrations of 1 nM. In mouse corneal micropocket assay and aortic ring assay, spongistatin 1 suppressed the neovessel formation and endothelial sprouting for 50 % at 10 μg/kg and 500 pM, respectively (Rothmeier et al. 2009).

Concluding remarks

This review summarizes some representative marine-derived angiosuppressive agents. These natural compounds and their derivatives are isolated from marine flora including algae and seaweed and fauna such as sponges and sea cucumber. Apart from the valuable nutritional values, in recent decades, dozens of these marine-derived compounds have been shown to exhibit promising angiosuppressive activity and could be acted as drug candidates. With the increasing exploration of marine resources, it is expected that more new angiosuppressive compounds will be searched and subsequently developed as the potent angiosuppressive drugs for clinical use.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

References

Abraham I, El Sayed K, Chen ZS, Guo H (2012) Current status on marine products with reversal effect on cancer multidrug resistance. Mar Drugs 10(10):2312–2321

Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S (2013) The impact of Bevacizumab (Avastin) on survival in metastatic solid tumors—a meta-analysis and systematic review. PLoS One 8(1), e51780

Aoki S, Cho SH, Ono M, Kuwano T, Nakao S, Kuwano M, Nakagawa S, Gao JQ, Mayumi T, Shibuya M, Kobayashi M (2006a) Bastadin 6, a spongean brominated tyrosine derivative, inhibits tumor angiogenesis by inducing selective apoptosis to endothelial cells. Anticancer Drugs 17(3):269–278

Aoki S, Sanagawa M, Watanabe Y, Setiawan A, Arai M, Kobayashi M (2007a) Novel isomarabarican triterpenes, exhibiting selective antiproliferative activity against vascular endothelial cells, from marine sponge Rhabdastrella globostellata. Bioorg Med Chem 15(14): 4818–4828

Aoki S, Watanabe Y, Tanabe D, Arai M, Suna H, Miyamoto K, Tsujibo H, Tsujikawa K, Yamamoto H, Kobayashi M (2007b) Structure-activity relationship and biological property of cortistatins, antiangiogenic spongean steroidal alkaloids. Bioorg Med Chem 15(21):6758–6762

Arafeh KM, Ullah N (2009) Synthesis of neolamellarin A, an inhibitor of hypoxia-inducible factor-1. Nat Prod Commun 4(7):925–926

Barboza NM, Medina DJ, Budak-Alpdogan T, Aracil M, Jimeno JM, Bertino JR, Banerjee D (2012) Plitidepsin (Aplidin) is a potent inhibitor of diffuse large cell and Burkitt lymphoma and is synergistic with rituximab. Cancer Biol Ther 13(2):114–122

Bharate SB, Manda S, Mupparapu N, Battini N, Vishwakarma RA (2012) Chemistry and biology of fascaplysin, a potent marine-derived CDK-4 inhibitor. Mini Rev Med Chem 12(7):650–664

Boisson-Vidal C, Zemani F, Caligiuri G, Galy-Fauroux I, Colliec-Jouault S, Helley D, Fischer AM (2007) Neoangiogenesis induced by progenitor endothelial cells: effect of fucoidan from marine algae. Cardiovasc Hematol Agents Med Chem 5(1):67–77

Brekken RA, Li C, Kumar S (2002) Strategies for vascular targeting in tumors. Int J Cancer 100(2):123–130

Chan LS, Yue PY, Mak NK, Wong RN (2009) Role of microRNA-214 in ginsenoside-Rg1-induced angiogenesis. Eur J Pharm Sci 38(4):370–377

Chan LS, Yue PY, Wong YY, Wong RN (2013) MicroRNA-15b contributes to ginsenoside-Rg1-induced angiogenesis through increased expression of VEGFR-2. Biochem Pharmacol 86(3):392–400

Chen DY, Tseng CC (2010) Chemistry of the cortistatins—a novel class of anti-angiogenic agents. Org Biomol Chem 8(13):2900–2911

Córdoba R, Tormo NS, Medarde AF, Plumet J (2007) Antiangiogenic versus cytotoxic activity in analogues of aeroplysinin-1. Bioorg Med Chem 15(15):5300–5315

Delma CR, Somasundaram ST, Srinivasan GP, Khursheed M, Bashyam MD, Aravindan N (2015) Fucoidan from Turbinaria conoides: a multifaceted 'deliverable' to combat pancreatic cancer progression. Int J Biol Macromol 74:447–457

Fan TP, Yeh JC, Leung KW, Yue PY, Wong RN (2006) Angiogenesis: from plants to blood vessels. Trends Pharmacol Sci 27(6):297–309

Folkman J, Klagsbrun M (1987) Angiogenic factors. Science 235(4787): 442–447

González-Iriarte M, Carmona R, Pérez-Pomares JM, Macías D, Angel Medina M, Quesada AR, Muñoz-Chápuli R (2003) A modified chorioallantoic membrane assay allows for specific detection of endothelial apoptosis induced by antiangiogenic substances. Angiogenesis 6(3):251–254

Ganesan P, Matsubara K, Ohkubo T, Tanaka Y, Noda K, Sugawara T, Hirata T (2010) Anti-angiogenic effect of siphonaxanthin from green alga. Codium fragile Phytomedicine 17(14):1140–1144

Hayashi A, Arai M, Fujita M, Kobayashi M (2009) Pyripyropenes, fungal sesquiterpenes conjugated with alpha-pyrone and pyridine moieties, exhibits anti-angiogenic activity against human umbilical vein endothelial cells. Biol Pharm Bull 32(7):1261–1265

Izzo I, Maulucci N, Bifulco G, De Riccardis F (2006) Total synthesis of azumamides A and E. Angew Chem Int Ed Engl 45(45):7557–7560

Kerbel RS (2000) Tumor angiogenesis: past, present and the near future. Carcinogenesis 21(3):505–515

Kim SK, Ravichandran YD, Khan SB, Kim YT (2008) Prospective of the cosmeceuticals derived from marine organisms. Biotechnol Bioprocess Engine 13:511–523

Kim YK, Tomoda H, Nishida H, Sunazuka T, Obata R, Omura S (1994) Pyripyropenes, novel inhibitors of acyl-CoA:cholesterol acyltransferase produced by Aspergillus fumigatus. II. Structure elucidation of pyripyropenes A, B, C and D. J Antibiot (Tokyo) 47(2):154–162

Kim SK, Wijesekara I (2010) Development and biological activities of marine-derived bioactive peptides: a review. J Functional Foods 2(1):1–9

Kotoku N, Hiramatsu A, Tsujita H, Hirakawa Y, Sanagawa M, Aoki S, Kobayashi M (2008a) Structure-activity relationships study of bastadin 6, an anti-angiogenic brominated-tyrosine derived metabolite from marine sponge. Arch Pharm (Weinheim) 341(9):568–577

Kotoku N, Tamada N, Hayashi A, Kobayashi M (2008b) Synthesis of BC-ring model of globostellatic acid X methyl ester, an anti-angiogenic substance from marine sponge. Bioorg Med Chem Lett 18(12):3532–3535

Kwok HH, Guo GL, Lau JK, Cheng YK, Wang JR, Jiang ZH, Keung MH, Mak NK, Yue PY, Wong RN (2012) Stereoisomers ginsenosides-20(S)-Rg_3 and -20(R)-Rg_3 differentially induce angiogenesis through peroxisome proliferator-activated receptor-gamma. Biochem Pharmacol 83(7):893–902

Kong D, Yamori T, Kobayashi M, Duan H (2011) Antiproliferative and antiangiogenic activities of smenospongine, a marine sponge sesquiterpene aminoquinone. Mar Drugs 9(2):154–161

Kyadari M, Fatma T, Azad R, Velpandian T (2013) Evaluation of antiangiogenic and antiproliferative potential of the organic extract of green algae Chlorella pyrenoidosa. Indian J Pharmacol 45(6): 569–574

Li YX, Li Y, Je JY, Kim SK (2015) Dieckol as a novel anti-proliferative and anti-angiogenic agent and computational anti-angiogenic activity evaluation. Environ Toxicol Pharmacol 39(1):259–270

Liu N, Fang H, Li Y, Xu W (2009) Recent research in selective cyclin-dependent kinase 4 inhibitors for anti-cancer treatment. Curr Med Chem 16(36):4869–4888

Liu R, Liu Y, Zhou YD, Nagle DG (2007) Molecular-targeted antitumor agents. 15. Neolamellarins from the marine sponge Dendrilla nigra inhibit hypoxia-inducible factor-1 activation and secreted vascular endothelial growth factor production in breast tumor cells. J Nat Prod 70(11):1741–1745

Ma J, Xin X, Meng L, Tong L, Lin L, Geng M, Ding J (2008) The marine-derived oligosaccharide sulfate (MdOS), a novel multiple tyrosine kinase inhibitor, combats tumor angiogenesis both in vitro and in vivo. PLoS One 3(11), e3774

Matou S, Helley D, Chabut D, Bros A, Fischer AM (2002) Effect of fucoidan on fibroblast growth factor-2-induced angiogenesis in vitro. Thromb Res 106(4–5):213–221

Matsubara K, Xue C, Zhao X, Mori M, Sugawara T, Hirata T (2005) Effects of middle molecular weight fucoidans on in vitro and ex vivo angiogenesis of endothelial cells. Int J Mol Med 15(4): 695–699

Maulucci N, Chini MG, Micco SD, Izzo I, Cafaro E, Russo A, Gallinari P, Paolini C, Nardi MC, Casapullo A, Riccio R, Bifulco G, Riccardis FD (2007) Molecular insights into azumamide e histone deacetylases inhibitory activity. J Am Chem Soc 129(10):3007–3012

Martínez-Poveda B, García-Vilas JA, Cárdenas C, Melgarejo E, Quesada AR, Medina MA (2013a) The brominated compound aeroplysinin-1 inhibits proliferation and the expression of key pro-inflammatory molecules in human endothelial and monocyte cells. PLoS One 8(1), e55203

Martínez-Poveda B, Rodríguez-Nieto S, García-Caballero M, Medina MÁ, Quesada AR (2013b) The antiangiogenic compound aeroplysinin-1 induces apoptosis in endothelial cells by activating the mitochondrial pathway. Mar Drugs 11(8):3046–3067

Mayer AM, Glaser KB, Cuevas C, Jacobs RS, Kem W, Little RD, McIntosh JM, Mukherji SK (2010) Bevacizumab (Avastin). AJNR Am J Neuroradiol 31(2):235–236

Nagai MK, Embil JM (2002) Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers. Expert Opin Biol Ther 2(2):211–218

Nakao Y, Narazaki G, Hoshino T, Maeda S, Yoshida M, Maejima H, Yamashita JK (2008) Evaluation of antiangiogenic activity of azumamides by the in vitro vascular organization model using mouse induced pluripotent stem (iPS) cells. Bioorg Med Chem Lett 18(9):2982–2984

Nakao Y, Yoshida S, Matsunaga S, Shindoh N, Terada Y, Nagai K, Yamashita JK, Ganesan A, van Soest RW, Fusetani N (2006) Azumamides A-E: histone deacetylase inhibitory cyclic tetrapeptides from the marine sponge Mycale izuensis. Angew Chem Int Ed Engl 45(45):7553–7557

Nilsen IW, Myrnes B (2001) The gene of chlamysin, a marine in vertebratetype lysozyme, is organized similar to vertebrate but different from invertebrate chicken-type lysozyme genes. Gene 69:27–32

Nilsen IW, Overbo K, Sandsdalen E, Sandaker E, Sletten K, Myrnes B (1999) Protein purification and gene isolation of chlamysin, a cold-active lysozyme-like enzyme with antibacterial activity. FEBS Lett 464:153–158

Papanas N, Maltezos E (2007) Growth factors in the treatment of diabetic foot ulcers: new technologies, any promises? Int J Low Extrem Wounds 6(1):37–53

Plummer R, Lorigan P, Brown E, Zaucha R, Moiseyenko V, Demidov L, Soriano V, Chmielowska E, Andrés R, Kudryavtseva G, Kahatt C, Szyldergemajn S, Extremera S, de Miguel B, Cullell-Young M, Calvert H (2013) Phase I-II study of plitidepsin and dacarbazine as first-line therapy for advanced melanoma. Br J Cancer 109(6):1451–1459

Pomponi SA (1999) The bioprocess–technological potential of the sea. J Biotech 70(1–3):5–13

Rothmeier AS, Ischenko I, Joore J, Garczarczyk D, Fürst R, Bruns CJ, Vollmar AM, Zahler S (2009) Investigation of the marine compound spongistatin 1 links the inhibition of PKCalpha translocation to nonmitotic effects of tubulin antagonism in angiogenesis. FASEB J 23(4):1127–1137

Rodríguez-Nieto S, González-Iriarte M, Carmona R, Muñoz-Chápuli R, Medina MA, Quesada AR (2002) Antiangiogenic activity of aeroplysinin-1, a brominated compound isolated from a marine sponge. FASEB J 16(2):261–263

Ruoslahti E (2002) Specialization of tumour vasculature. Nat Rev Cancer 2(2):83–90

Sato Y, Kamiyama H, Usui T, Saito T, Osada H, Kuwahara S, Kiyota H (2008) Synthesis and anti-angiogenic activity of cortistatin analogs. Biosci Biotechnol Biochem 72(11):2992–2997

Shin HJ, Kim TS, Lee HS, Park JY, Choi IK, Kwon HJ (2008) Streptopyrrolidine, an angiogenesis inhibitor from a marine-derived Streptomyces sp. KORDI-3973. Phytochemistry 69(12): 2363–2366

Straight AM, Oakley K, Moores R, Bauer AJ, Patel A, Tuttle RM, Jimeno J, Francis GL (2006) Aplidin reduces growth of anaplastic thyroid cancer xenografts and the expression of several angiogenic genes. Cancer Chemother Pharmacol 57(1):7–14

Sugawara T, Matsubara K, Akagi R, Mori M, Hirata T (2006) Antiangiogenic activity of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. J Agric Food Chem 54(26): 9805–9810

Taraboletti G, Poli M, Dossi R, Manenti L, Borsotti P, Faircloth GT, Broggini M, D'Incalci M, Ribatti D, Giavazzi R (2004) Antiangiogenic activity of aplidine, a new agent of marine origin. Br J Cancer 90(12):2418–2424

Tian F, Zhang X, Tong Y, Yi Y, Zhang S, Li L, Sun P, Lin L, Ding J (2005) PE, a new sulfated saponin from sea cucumber, exhibits anti-angiogenic and anti-tumor activities in vitro and in vivo. Cancer Biol Ther 4(8):874–882

Tian F, Zhu CH, Zhang XW, Xie X, Xin XL, Yi YH, Lin LP, Geng MY, Ding J (2007) Philinopside E, a new sulfated saponin from sea cucumber, blocks the interaction between kinase insert domain-containing receptor (KDR) and alphavbeta3 integrin via binding to the extracellular domain of KDR. Mol Pharmacol 72(3):545–552

Tomoda H, Tabata N, Yang DJ, Namatame I, Tanaka H, Omura S, Kaneko T (1996) Pyripyropenes, novel ACAT inhibitors produced by Aspergillus fumigatus. IV. Structure elucidation of pyripyropenes M to R. J Antibiot (Tokyo) 49(3):292–298

Tomoda H, Tabata N, Yang DJ, Takayanagi H, Nishida H, Omura S, Kaneko T (1995) Pyripyropenes, Novel ACAT inhibitors produced by Aspergillus fumigatus. III. Structure elucidation of pyripyropenes E to L. J Antibiot (Tokyo) 48(6):495–503

Tong Y, Zhang X, Tian F, Yi Y, Xu Q, Li L, Tong L, Lin L, Ding J (2005) Philinopside A, a novel marine-derived compound possessing dual anti-angiogenic and anti-tumor effects. Int J Cancer 114(6):843–853

Wang YQ, Miao ZH (2013) Marine-derived angiogenesis inhibitors for cancer therapy. Mar Drugs 11(3):903–933

Wen WW, Xie S, Xin XL, Geng MY, Ding J, Chen Y (2013) Oligomannurarate sulfate inhibits CXCL12/SDF-1-mediated proliferation and invasion of human tumor cells in vitro. Acta Pharmacol Sin 34(12):1554–9.1

Yan X, Chen H, Lu X, Wang F, Xu W, Jin H, Zhu P (2011) Fascaplysin exert anti-tumor effects through apoptotic and anti-angiogenesis pathways in sarcoma mice model. Eur J Pharm Sci 43(4):251–259

Ye J, Wang C, Chen X, Guo S, Sun M (2008) Marine lysozyme from a marine bacterium that inhibits angiogenesis and tumor growth. Appl Microbiol Biotechnol 77(6):1261–1267

Yue PY, Mak NK, Cheng YK, Leung KW, Ng TB, Fan DT, Yeung HW, Wong RN (2007) Pharmacogenomics and the Yin/Yang actions of ginseng: anti-tumor, angiomodulating and steroid-like activities of ginsenosides. Chin Med 2:6

Yue PY, Wong DY, Wu PK, Leung PY, Mak NK, Yeung HW, Liu L, Cai Z, Jiang ZH, Fan TP, Wong RN (2006) The angiosuppressive effects of 20(R)-ginsenoside Rg3. Biochem Pharmacol 72(4):437–445

Yue PY, Wong DY, Ha WY, Fung MC, Mak NK, Yeung HW, Leung HW, Chan K, Liu L, Fan TP, Wong RN (2005) Elucidation of the mechanisms underlying the angiogenic effects of ginsenoside Rg(1) in vivo and in vitro. Angiogenesis 8(3):205–216

Zhao H, Liu H, Chen Y, Xin X, Li J, Hou Y, Zhang Z, Zhang X, Xie C, Geng M, Ding J (2006) Oligomannurarate sulfate, a novel heparanase inhibitor simultaneously targeting basic fibroblast growth factor, combats tumor angiogenesis and metastasis. Cancer Res 66(17):8779–8787

Zhang J, Chen Y, Xin XL, Li QN, Li M, Lin LP, Geng MY, Ding J (2010) Oligomannurarate sulfate blocks tumor growth by inhibiting NF-kappaB activation. Acta Pharmacol Sin 31(3):375–381

Zheng YL, Lu XL, Lin J, Chen HM, Yan XJ, Wang F, Xu WF (2010) Direct effects of fascaplysin on human umbilical vein endothelial cells attributing the anti-angiogenesis activity. Biomed Pharmacother 64(8):527–533