

## Pro-angiogenic and Angiostatic Compounds from Terrestrial and Marine Sources

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Rec date: May 23, 2014, Acc date: July 27, 2014, Pub date: July 29, 2014

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### Abstract

The formation of new blood vessels out of pre-existing capillaries or angiogenesis is a sequence of events that is of key importance in a broad array of physiologic and pathologic processes. In several diseases, excessive angiogenesis is a part of the pathology such as cancer (both solid and hematologic tumors), cardiovascular disease (atherosclerosis), chronic inflammation (rheumatoid arthritis, Crohn's disease), diabetes (proliferative diabetic retinopathy), neovascular wet age related macular degeneration, retinopathy of prematurity, psoriasis, and AIDS complications. These diseases may benefit from the therapeutic inhibition of angiogenesis. There has been a substantial progress made in research on natural products possessing several therapeutic actions as a result of which they have attracted attention of scientists, the world over and has profoundly influenced the course of discovery from traditional remedies. The present review entails such natural products from terrestrial and marine sources that have exhibited pro-angiogenic or antiangiogenic effects and offer subsequent potential for the development of novel pharmacological agents in the near future.

**Keywords:** Pro-angiogenic compounds; Angiostatic compounds

### Introduction

From several decades, much of the attention has been given to the approach of isolating novel chemical structures and compounds from natural resources, with immense pharmacological potential in order to counteract the pathological conditions of human body. Marine natural products bioprospecting has yielded a considerable number of drug candidates till date with 4 clinically approved drugs and 13 natural products (or derivatives thereof) in different phases of the clinical pipeline and a large number of marine chemicals in the preclinical pipeline [1]. Organisms in the marine source are majorly unexplored domain and can therefore, greatly account for the identification of compounds with higher potency and novel biological activities. The serendipitous isolation of the first bioactive marine compounds dates back more than 50 years whereby antiviral compounds, spongomydine and spongouridine were reported from the Caribbean sponge *Cryptotheca crypta* in the early 1950s and further studies on these compounds subsequently led to the development of antiviral compound, Ara-A and anticancer agent Ara-C [2]. From thereon, the search for pharmacologically active compounds from marine sources increased drastically and several novel therapeutic compounds were reported with time e.g. Blunt et al. reviewed 243 articles for the year 2003 and signified over 656 new marine compounds from the available literature with biological activities being reported for about 354 of them [3].

The bioactivity-guided fractionation of crude extracts has provided lead molecules for the discovery of novel drugs from traditionally used plants that continue to play an essential role in the human health care system and World Health Organization has earlier estimated that approximately 80% of the world's inhabitants rely mainly on traditional medicines for their primary health care needs [4]. There has been a substantial progress made in research on natural products possessing several therapeutic actions as a result of which they have

attracted attention of biologists, chemists and pharmacologists, the world over and has profoundly influenced the course of discovery from traditional remedies.

The formation of new blood vessels out of pre-existing capillaries or angiogenesis is a sequence of events that is of key importance in a broad array of physiologic and pathologic processes [5]. In several diseases, excessive angiogenesis is a part of the pathology such as cancer (both solid and hematologic tumors), cardiovascular disease (atherosclerosis), chronic inflammation (rheumatoid arthritis, Crohn's disease), diabetes (proliferative diabetic retinopathy), neovascular wet age related macular degeneration, retinopathy of prematurity, psoriasis, and AIDS complications [6]. These diseases may benefit from the therapeutic inhibition of angiogenesis. A growing tumor needs an extensive capillary network to provide nutrients and oxygen to the body tissues. In addition, the new intra-tumoral blood vessels provide a way for tumor cells to enter the circulation and to metastasize to distant organs. Thus, every organ system may involve diseases in which angiogenesis is an important component. Several compounds from terrestrial and marine sources are under clinical trials and have been shown to possess potent angiostatic effect in the pre-clinical phases e.g. squalamine. On the other hand pro-angiogenic compounds are those which stimulate the process of angiogenesis and may play a vital role in diseases where angiogenesis is found to be deficient such as in case of infertility, ulcers, heart diseases, scleroderma and stroke.

Several compounds isolated from terrestrial and marine sources have shown potent pro-angiogenic and antiangiogenic efficacy in the pre-clinical studies warranting their further development for use in humans and the present article entails such pro-angiogenic or angiostatic compounds.

## Angiostatic Compounds from Marine Sources

Squalamine is an aminosterol antibiotic synthesized from the tissues of the dogfish shark, *Squalus acanthias* [7]. It is a 7, 24-dihydroxylated, 24-sulfated cholestane steroid conjugated to a spermidine at C3 and has been reported to inhibit angiogenesis and solid tumor growth in vivo in the rabbit corneal micropocket assay [8,9]. It was later postulated that squalamine inhibited new blood vessel growth by selectively inhibiting the sodium-hydrogen antiporter sodium-proton exchangers (specifically the NHE3 isoform) causing inhibition of hydrogen ion efflux from endothelial cells with subsequent reduction of cellular proliferation [10]. Further studies reported its efficacy in the treatment of retinal neovascularization in a mouse model of oxygen induced retinopathy [11]. The phase I and pharmacokinetic studies of Squalamine in patients with advanced cancers demonstrated the efficacy and safety profile of the compound in humans [12]. The systemic administration of squalamine lactate significantly reduced choroidal neovascularization in a rat laser-induced choroidal neovascularization and is under investigation in phase II clinical trials for choroidal neovascularization due to age related macular degeneration [13,14]. Neovastat is another naturally occurring compound derived from the marine cartilage (dogfish) that possesses antiangiogenic potential mediated via the inhibition of matrix metalloproteinases (MMPs) specifically MMP-2, MMP-9 and MMP-12 [15,16]. Neovastat reached phase III clinical trials for the treatment of malignant diseases and was reported to inhibit vascular endothelial growth factor (VEGF) mediated angiogenesis as it significantly blocked VEGF-dependent microvessel sprouting from Matrigel-embedded rat aortic rings and also inhibited VEGF-induced endothelial cell tubulogenesis *in vitro* [17,18]. The presence of an endothelial-specific proapoptotic factor within neovastat was reported to contribute towards its antiangiogenic efficacy as it was able to interfere with several steps associated with angiogenesis through its ability to induce endothelial cell apoptosis [19].

A new antiangiogenic polysaccharide was reported from the marine algae *Grateloupia longifolia* that noticeably inhibited proliferation of human microvascular endothelial cells (HMEC-1) and human umbilical vein endothelial cells (HUVEC) in a dose dependent manner with IC50 values of 0.86 and 0.64 mg/ml, respectively. The observed inhibition was found to be VEGF-independent although tissue factor was down regulated at both mRNA and protein levels following the polysaccharide treatment of HMEC-1 thereby postulating the same to be the mechanism of the antiangiogenic effect. The polysaccharide also evinced significant antiangiogenic effect in the chick chorio-allantoic membrane assay also reduced the vessel density in Matrigel plugs implanted in mice [20]. A new purine analog, 1,3-dimethylisoguaninium was reported from the ethanolic extract of the Okinawan sponge *Amphimedon paravidis* that exhibited angiostatic effect via specific inhibition of the basic fibroblast growth factor (bFGF)-induced proliferation of bovine aorta endothelial cells (BAECs) in a time dependent manner [21].

The bacteria's associated with marine invertebrates are also rich sources of bioactive metabolites and this was revealed when the extract obtained from the bacterium (PB2) isolated from the primmorphs of the sponge *Suberites domuncula* was found to exhibit antiangiogenic activity in the chick chorio-allantoic membrane (CAM) assay with 50% activity at 5 µg/ml and 100% activity at 10 and 20 µg/ml concentrations [22]. A benzyl pyrrolidine derivative, streptopyrrolidine obtained from the fermentation broth of a marine bacterium, *Streptomyces* sp. KORDI-3973 isolated from the deep sea

sediment exhibited significant anti-angiogenic activity without any cytotoxicity against human umbilical vein endothelial cells (HUVECs) at the concentration of 100 µg/ml [23]. The unique chemical structure of streptopyrrolidine was distinct from the known angiogenesis small molecule inhibitors and its antiangiogenic activity at non-toxic threshold dose marks towards its further developments.

A marine-derived antitumour compound aplidine (dehydrodidemnin B) isolated from the Mediterranean tunicate *Aplidium albicans* evinced noticeable inhibition of spontaneous angiogenesis, angiogenesis elicited by exogenous angiogenic growth factors (VEGF and FGF-2) and angiogenesis induced by VEGF overexpressing IA9 ovarian carcinoma cells, in the in ovo chick CAM assay [24]. Tong et al. isolated a novel sulfated saponin Philinopside A from the sea cucumber *Pentacta quadrangulari* that exhibited significant inhibition of the proliferation, migration and tube formation of human microvascular endothelial cells in a dose dependent manner with average IC50 values of  $1.4 \pm 0.17$ ,  $0.89 \pm 0.23$  and  $0.98 \pm 0.19$  µM signifying its dual anti-angiogenic and anti-tumor effects in a series of *in vitro* and *in vivo* models [25]. A brominated compound (+)-Aeropylsinin-1 isolated and purified from marine sponge *Aplisina aerophoba* exhibited significant antiangiogenic activity as the compound evinced dose-dependent inhibitory effect in the in ovo CAM assay, showing potent apoptosis-inducing activity in the developing endothelium and the inhibitory effect of the compound was further confirmed in the in vivo Matrigel plug assay [26]. Castro et al. isolated puupehenone and 11 related compounds from marine sponges and evaluated their anti-angiogenic efficacy using Matrigel and chick chorio-allantoic membrane assay [27]. Three of these compounds isozonanol, 8-epipuuehedione and 8 epi-9,11-dihydropuuehedione completely inhibited angiogenesis in the chick CAM assay at doses equal or lower than 30 nmol/egg thereby signifying their potential of further evaluations. Two novel sulfated sterols lembehsterols A and B, isolated from the marine sponge *Petrosia strongylata* exhibited inhibitory activity against thymidine phosphorylase, an enzyme related to angiogenesis in solid tumors [28]. Wrasidlo et al. reported the antiangiogenic potential of a lipopeptide, somocystinamide A derived from *Lyngbya majuscula* [29]. Systemic treatment of zebrafish or local treatment of the chick chorio-allantoic membrane with the compound exhibited dose dependent inhibition of angiogenesis suggesting the future development of the agent as an anti-angiogenic drug. Fucoidans are a group of marine sulfated polysaccharides in the cell-wall matrix of brown algae with main skeleton consisting of α1,3-linked-L-fucose-4-sulfate moiety. Cumashi et al. reported the antiangiogenic activity of nine different fucoidans from brown seaweeds. *Laminaria saccharina*, *Laminaria digitata*, *Fucus evanescens*, *Fucus serratus* and *Fucus distichus* potentially inhibited human umbilical vein endothelial cell (HUVEC) tubulogenesis *in vitro* and this significantly correlated with the decreased levels of Plasminogen-activator inhibitor-1 in HUVEC supernatants, thereby suggesting the possible mechanism of fucoidan-induced inhibition of tubulogenesis [30].

Recently, a screening program carried out by Gupta et al. evaluated the antiangiogenic efficacy of twenty two marine invertebrates extracts of phylum mollusca using in ovo and in vivo models of angiogenesis such as CAM assay, corneal neovascularization assay in rats and oxygen induced retinopathy in rat pups and it was found that among all the extracts, the methanolic extract of *Telescopium telescopium* evinced most noticeable antiangiogenic activity in all the tested models that was mediated via the inhibition of vascular endothelial growth factor [31].

### Angiostatic Compound from Medicinal Plants

The antiangiogenic efficacy of two newer sapogenins viz. 20(S)-protopanaxadiol and 20(S)-protopanaxatriol that were obtained by alkaline hydrolysis of an extract of American ginseng *Panax quinquefolium* L. were evaluated in human umbilical vein endothelial cells (HUVEC) whereby both the compounds evinced dose dependent antiproliferatory activity envisioning their potential for development as novel antiangiogenic drug candidates [32]. The antiangiogenic potential of two naturally occurring *sesterterpenes*, *leucosterterpenone* and *leucosterlactone* isolated from the Himalayan plant *Leucosceptrum canum* Sm was evaluated using the *in vitro* and *in vivo* angiogenic assays and cultures of large (bovine aortic endothelial cells) and small endothelial cells (human dermal microvascular endothelial cells) whereby these derived compounds showed noticeable antiangiogenic activity exhibited via the specific inhibition of the fibroblast growth factor-2 induced angiogenesis [33]. Taraboletti et al. reported a seco taxane derivative IDN 5390 to inhibit *in vivo* fibroblast growth factor-2 induced angiogenesis in Matrigel implants and exhibited efficacy in the *in vitro* tubulin polymerization assay as it caused a concentration dependent increase in the fraction of polymerized tubulin and a parallel decrease in soluble tubulin [34]. The methanolic and chloroform extracts of *Sphenocentrum jollyanum* Pierre (menispermaceae) exhibited significant anti-angiogenic efficacy in a dose dependent manner in the chick chorio-allantoic membrane assay bringing to the fore, the need for further studies towards confirming the antiangiogenic potentials of the plant as well as identifying and characterizing the active principles for drug development [35].

The ethanolic extract of the whole plant of *Andrographis paniculata* (Acanthaceae) and its major component andrographolide (extracted from dried plant powder) were reported to exert significant antiangiogenic effects in both *in vitro* and *in vivo* models of angiogenesis whereby they inhibited the tumor specific angiogenesis by regulating the production of various pro- and anti-angiogenic factors such as pro-inflammatory cytokine, nitric oxide, VEGF, IL-2 and TIMP-1 [36]. Kwak et al. investigated the anti-angiogenic activities of the herbal extracts of *Cnidium officinale* Makino and *Tabanus bovinus* using cultured glomerular capillary endothelial cells, CAM and rat cornea [37]. The herbal extracts conspicuously inhibited the neovascularization and the blood vessels patterns in CAMs treated with extracts ran parallel to each other without much branching and the oral administration of herbal extracts (20 mg/kg per day) for 4 weeks significantly inhibited the rat corneal neovascularization induced by suture and the length of the blood vessels was conspicuously lower than that in control animals. Yoon et al. investigated the antiangiogenic efficacy of Soamsan, a traditional Korean herbal remedy, using CAM and rat corneal neovascularization assays and reported the blood vessels in CAM treated with Soamsan were with less branching and the length of blood vessels in Soamsan-treated rat cornea were conspicuously low as compared to control thereby implicating the antitumor efficacy of the herbal remedy via the suppression of angiogenesis and growth factor transcription [38]. Huh et al. isolated 1,2,3,4,6-penta-O-galloyl-beta-D-glucose from the gallnut of *Rhus chinensis* Mill and reported the compound to possess anticancer activity via the inhibition of angiogenesis through COX-2 and MAPK-dependent pathways [39]. The compound effectively disrupted the basic fibroblast growth factor induced neovascularization in the chick CAM assay and in matrigel plugs in the mice suggesting the scope of development of a novel non-toxic chemopreventive agent. Torilin, a sesquiterpene compound isolated

and purified from the fruits of *Torilis japonica* (Umbelliferae) was reported to decrease both neovascularization of chick embryos in the chorio-allantoic membrane assay and basic fibroblast growth factor-induced vessel formation in the mouse Matrigel plug assay [40]. Wu et al. reported the ethyl acetate fraction from fresh whole plants of *Bidens pilosa* Linn. var. *radiata* (Compositae) from Taiwan to exhibit significant anti-cell proliferation and anti-tube formation activities against human umbilical vein endothelium cells (HUVEC) [41]. Two polyacetylenes, 1,2-dihydroxytrideca-5,7,9,11-tetrayne and 1,3-dihydroxy-6(E)-tetradecene-8,10,12-triyne were isolated from the ethyl acetate fraction of *Bidens pilosa* using bioassay-guided fractionation, that manifested highly specific and significant activities against HUVEC proliferation with IC50 values of 2.5 and 0.375 µg/ml, respectively, however the first compound exhibited more potent effect on preventing tube formation of HUVEC than the latter at a dose of 2.5 µg/ml.

Cardenas et al. evaluated the anti-angiogenic potential of aloemodin, a hydroxyanthraquinone from *Aloe vera* and reported the compound to possess significant inhibitory effects in the *in ovo* chick CAM assay with two main possible targets of the anti-angiogenic action namely the urokinase secretion and tubule formation of endothelial cells [42]. A tanshinone derivative dihydrotanshinone I extracted from a traditional Chinese medicinal plant *Salvia miltiorrhiza* Bunge (Labiatae) was investigated for its antiangiogenic capacity in human umbilical vein endothelial cell migration, invasion and tube formation detected by wound healing, Transwell invasion and Matrigel tube formation assays, respectively. The compound inhibited angiogenesis through suppressing endothelial cell proliferation, migration, invasion and tube formation indicating its potential for further development as a novel anti-angiogenic agent [43]. Earlier another compound from the same plant, cryptotanshinone was reported to inhibit basic fibroblast growth factor-induced angiogenesis of bovine aortic endothelial cells at 10 µmol ranges *in vitro* without cytotoxicity and demonstrated in the structure, the double bond at the C-15 position of the dihydrofuran ring to play a crucial role in the anti-angiogenic activity [44].

Genistein (4',5,7-trihydroxy isoflavone) occurring in the plant family Leguminosae, including soybean (*Glycine max*) was evaluated for its antitumor and antiangiogenic potential in mouse models of melanoma and breast cancers. *In vivo*, intraperitoneal administration of genistein at a dose of 10 mg/kg/day reduced tumor induced angiogenesis in syngenic mice implanted with B16 or F311 cells and similar antiangiogenic effects were observed with the soybean-based diet [45]. Mathur et al. reported the anti-angiogenic efficacy of a traditionally used indigenous medicinal plant in the Indian system of medicine, *Withania somnifera* Dunal (Solanaceae) [46]. The hydroalcoholic extract of the roots was preliminarily investigated for the anti-angiogenic potential using the chick chorio-allantoic membrane assay wherein a significant inhibition ( $p < 0.0001$ ) of vascular endothelial growth factor induced neovascularization was recorded. The effect was further confirmed using *in vivo* mouse sponge implantation method. The antiangiogenic activity of resveratrol, a natural polyphenol compound found in various plants including grapes, was examined in several *in vivo* models of angiogenesis including the mouse corneal model, the chick chorio-allantoic membrane assay, a wound healing model and a tumor model wherein the compound significantly inhibited angiogenesis-dependent physiological and pathological processes including wound healing and tumor growth [47]. The antiangiogenic effect of resveratrol was attributed towards direct inhibition of capillary endothelial cell growth

via suppression of the phosphorylation of the mitogen-activated kinase, a pathway common to fibroblast growth factor-2 and vascular endothelial growth factor-induced angiogenesis suggesting the beneficial effects of consumption of various plant products containing polyphenol based compounds and adequate amount of red wine in the prevention of cancer. Inokuchi et al. reported the *in vitro* antiangiogenic activity of vitamin E compounds with particular emphasis on tocotrienol which is a minor constituent of plants with high levels occurring in palm oil, cereal grains and rice bran [48]. Tocotrienol inhibited both the proliferation and tube formation of bovine aortic endothelial cells with  $\delta$ -tocotrienol exhibiting the highest activity as it reduced the vascular endothelial growth factor-stimulated tube formation by human umbilical vein endothelial cells directing towards its potential use as a therapeutic dietary supplement for minimizing tumor angiogenesis.

Liu et al. tested the aqueous extracts of leaves of *Rubus suavissimus* S. Lee (*Rosaceae*) for antiangiogenic activity in a human tissue-based fibrin-thrombin clot angiogenesis assay and subjected the crude extract for further activity guided fractionation [49]. The extract significantly inhibited initiation of the angiogenic response and subsequent neovessel growth at 0.1% w/v concentration and gallic acid, elucidated as one of the active angiogenesis inhibitors in one of the fractions exhibited inhibition at 1 mM concentration warranting further bioassay directed identification of other responsible compounds present in the extract. Noni, the juice of the fruit from *Morinda citrifolia* L. was tested in a three-dimensional fibrin clot matrix model using human placental vein and human breast tumor explants as sources for angiogenesis vessel development. Noni in concentrations of 5% (v/v) significantly inhibited the initiation of new vessel sprouts from placental vein explants and also reduced the growth rate and proliferation of newly developing capillary sprouts whereas 10% noni juice in media effectively inhibited capillary initiation in explants from human breast tumors [50]. Demirci et al. examined the essential oil from the aerial parts of *Phlomis linearis* Boiss. and Bal. (*Lamiaceae*) for possible anti-angiogenic effect on chick chorio-allantoic membrane and reported very weak effect at a concentration of 100  $\mu$ g/pellet [51]. Nasunin, delphinidin-3-(*p*-coumaroylrutinoside)-5-glucoside, isolated from the eggplant peels exhibited significant antiangiogenic effect as it suppressed microvessel outgrowth in an *ex vivo* angiogenesis assay using a rat aortic ring as well suppressed HUVEC proliferation in a dose dependent manner at a concentration ranging from 50-200  $\mu$ M implicating its usefulness for the prevention of angiogenesis-related diseases [52]. *Yoysungnoen* et al. reported the dose dependent anti-angiogenic effects of tetrahydrocurcumin on tumor angiogenesis compared with curcumin using both *in vitro* and *in vivo* models of human hepatocellular carcinoma cell line (HepG2) wherein the more beneficial effect of tetrahydrocurcumin treatment was observed over curcumin as it exerted its antiangiogenic effect without any cytotoxic activities to HepG2 cells even at higher doses [53]. Curcumin is a phenolic compound isolated from *Curcuma longa* that was earlier expressed significant antiangiogenic activity in the hepatocellular carcinoma cells implanted nude mice [54]. The aqueous extracts of black cumin seeds (*Nigella sativa*) and green tea leaves (*Camellia sinensis*) were reported to express marked anti-angiogenic effects on endothelial cells of rat's aorta augmenting the efficacies of the extracts as potential remedies for angiogenesis related diseases [55]. Agarwal et al. evaluated the *in vitro* antiangiogenic efficacy of grape seed extract on HUVEC proliferation, survival, matrix metalloproteinases secretion and capillary tube formation [56]. Grapes (*Vitis vinifera*) and grape seeds are rich in

polyphenols, commonly known as procyanidins and commercial preparations for dietary supplement of grape seed polyphenols are marketed as 'grape seed extract' with 95% standardized procyanidins [57]. Grape seed extract have been reported to significantly inhibit cell growth and viability of HUVEC, induce apoptotic cell death in HUVEC, decrease secreted levels of matrix metalloproteinase-2 (MMP-2) from HUVEC and also inhibit capillary tube formation on Matrigel by endothelial cells in a dose dependent manner suggesting the possible association of anti-angiogenic potential of grape seed extract with its antiproliferative, proapoptotic and matrix metalloproteinase inhibitory activities.

### Antiangiogenic Compounds from Bacteria and Algae

Kaur et al. reported a peptide tubulysin A, isolated from a strain of myxobacteria *Archangium geophyra* to depolymerize microtubules and induce mitotic arrest [58]. The compound exhibited significant *in vitro* anti-angiogenic activity as judged by both cell migration and cord formation using HUVEC (human umbilical-vein endothelial cells). Fucoxanthin, a major carotenoid extracted and refined from edible brown algae (*Undaria pinnatifida*) and its deacetylated product, fucoxanthinol were examined for any antiangiogenic effects using human umbilical vein endothelial cells (HUVEC) proliferation and tube formation assays in addition to the *ex vivo* angiogenesis assay using a rat aortic ring [59]. Fucoxanthin significantly expressed HUVEC proliferation and tube formation at more than 10  $\mu$ M concentration and both the compounds suppressed the microvessel outgrowth in the *ex vivo* angiogenesis assay in a dose-dependent manner.

### Proangiogenic Compounds from Natural Sources

A sulfated steroid sokotrasterol sulfate isolated from the sponge *Topsentia ophirhaphidites* was reported for its pro-angiogenic potential as it promoted endothelial sprouting *in vitro*, new blood vessels formation on the chick chorio-allantoic membrane and accelerated angiogenesis and reperfusion in a mouse hindlimb ischemia model [60]. A novel angiogenic factor  $\beta$ -sitosterol was derived from the Aloe vera gel that evinced angiogenic activity in the chick chorio-allantoic membrane assay as well as stimulated neovascularization in the presence of heparin in the mouse Matrigel plug assay and the motility of human umbilical vein endothelial cells in an *in vitro* wound migration assay implicating its potential pharmaceutical applications for the future management of chronic wounds [61]. Matou et al. reported the angiogenic property of an oversulfated exopolysaccharide derived from a polysaccharide secreted by the mesophilic bacterium *Alteromonas infernos* [62]. The oversulfated exopolysaccharide enhanced human umbilical vein endothelial cell proliferation, migration and differentiation induced by basic fibroblast growth factor or vascular endothelial growth factor and also increased the density of tubular structures on Matrigel in the presence of FGF-2 or VEGF thereby suggesting its potential to accelerate vascular wound healing or for promoting the growth of collateral blood vessels in ischemic tissues.

### Conclusion

In the search of newer pharmacologically active substances from natural sources, scientists have constantly been engaged into chemical studies on the bioactive compounds including structural elucidation, synthesis, elucidation of pharmacophore by analysis of structure-activity relationship, action mechanisms and search for target proteins.

Angiogenesis is the formation of new blood capillaries from pre-existing blood vessels and the switch to the angiogenic phenotype involves a local equilibrium between positive regulators of angiogenesis such as vascular endothelial growth factor, basic fibroblast growth factor etc. and negative regulators of angiogenesis such as angiostatin, endostatin etc. Under pathological conditions, this equilibrium may be disturbed leading to abnormal angiogenesis which is frequently the final pathway leading to the vast majority of diseases such as cancer and may even result in catastrophic loss of vision in some ocular diseases such as diabetic retinopathy, retinopathy of prematurity and wet age related macular degeneration. Therefore the substances that inhibit or promote angiogenesis have a considerable potential to become therapeutic agents. The concept of an anti-angiogenic approach as a promising strategy for the treatment of a variety of neovascular diseases in humans led to the discovery of many natural compounds with promising anti-angiogenic properties and of these only a few have been approved clinically. Therefore, there is a pressing need for the search of newer angiostatic agents for the treatment of neovascular diseases and also for pro-angiogenic agents for the treatment of diseases where angiogenesis is lying deficient.

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