HHS Public Access

Author manuscript

Angiogenesis. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

Angiogenesis. 2016 July ; 19(3): 287–295. doi:10.1007/s10456-016-9512-y.

Plants and their active compounds: natural molecules to target angiogenesis

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Abstract

Angiogenesis, or new blood vessel formation, is an important process in the pathogenesis of several diseases and thus has been targeted for the prevention and treatment of many disorders. However, the anti-angiogenic agents that are currently in use are mainly synthetic compounds and humanized monoclonal antibodies, which are either expensive or toxic, thereby limiting their use in many patients. Therefore, it is necessary to identify less toxic, inexpensive, novel and effective anti-angiogenic molecules. Several studies have indicated that natural plant products can meet these criteria. In this review, we discuss the anti-angiogenic properties of natural compounds isolated from plants and the molecular mechanisms by which these molecules act. Finally, we summarize the advantages of using plant products as anti-angiogenic agents. Compared with currently available anti-angiogenic drugs, plant products may not only have similar therapeutic potential but are also inexpensive, less toxic and easy to administer. However, novel and effective strategies are necessary to improve their bioavailability for clinical use.

Keywords

Plants; Natural compounds; Angiogenesis; Therapy

Introduction

The process of forming new blood vessels from existing vasculature, which involves adult endothelial cells (ECs), is known as angiogenesis [1]. Angiogenesis plays a critical role in the pathogenesis of several diseases, such as rheumatoid arthritis, psoriasis, diabetic retinopathy and cancer [2–4]. Therefore, targeting angiogenesis has been an important therapeutic approach for the treatment of several diseases [5,6]. However, the anti-angiogenic agents presently in use are mainly synthetic chemicals or humanized monoclonal

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

antibodies that target either angiogenic factors or tyrosine kinases involved in the regulation of angiogenic pathways [7, 8]. Although these drugs have shown promise, their high cost, their serious systemic toxicities and the development of resistance necessitate identifying other novel and effective anti-angiogenic molecules that are inexpensive and have minimal or no side effects [9, 10].

Plant products have been used in traditional medicine for many years, and their anti-inflammatory, anti-allergic and anti-infective properties are well-established [11–13]. Recent reports have indicated that these natural compounds also have angiogenesis-modulating effects [14–16]. In this review, we describe the angiogenic process and summarize the data concerning medicinal plants that demonstrate angiogenesis-modulating activities based on their active compounds. A comparison of natural plant products and synthetic anti-angiogenic agents revealed the advantages and disadvantages of these natural products as possible future drugs targeting the angiogenic process.

Angiogenesis is necessary for both physiological conditions and pathological disorders

Angiogenesis is essential for normal physiological activities, such as embryonic development, wound healing and the menstrual cycle, but it is also important for the pathogenesis of several diseases [17, 18]. It is well-established that dysregulation of angiogenesis plays a critical role in the initiation and progression of many diseases such as malignant tumors and age-related macular degeneration (AMD) [18–20]. Rapidly proliferating malignant tumors require an increased blood supply to support their growth; thus, angiogenesis is critical for the initiation, growth and metastasis of these tumors [6,20].

Angiogenesis is a tightly regulated process

Because angiogenesis requires a critical balance between multiple pro-angiogenic and anti-angiogenic factors (Table 1), and a shift in this balance can lead to pro- or anti-angiogenic effects [21,22], angiogenesis can be initiated by a reaction to inflammation, hypoxia, and other conditions and is mediated by angio-modulatory factors that are released by tumors and other diseased cells [23,24]. In chronic allergic inflammatory diseases, eosinophils are recruited to the sites of inflammation. Eosinophils can regulate angiogenesis as a reaction to hypoxia, which is commonly observed in these sites [25]. In the case of tumors, monocytes are recruited from the peripheral blood to the tumor microenvironment. These cells are then reprogrammed into tumor-associated macrophages (TAM) that sense hypoxia in avascular regions within the tumor and secrete multiple pro-angiogenic factors, such as vascular endothelial growth factor-A (VEGF), basic fibroblast growth factor (bFGF), thymidine phosphorylase (TP), urokinase-type plasminogen activator (uPA) and adrenomedullin (ADM), to activate the angiogenic switch [26]. TAM is also a major source of metalloproteinase-9 (MMP9), which degrades the extracellular matrix, thereby releasing bioactive VEGF [26].

Currently used anti-angiogenesis agents

Because VEGF is one of the most important factor responsible for inducing angiogenesis and because its activities are largely mediated through its VEGFR-2 receptors, the anti-angiogenic agents currently in use predominantly target either VEGF or VEGFR-2 [27, 28]. Anti-VEGF agents, such as bevacizumab, pegaptanib and ranibizumab, are currently in use for the treatment of age-related macular degeneration (AMD), choroidal neovascularization (CNV), and multiple solid and hematological malignancies [29–31]. Recent studies have demonstrated that anti-VEGF agents are also potential therapeutics for diabetic macular edema (DME), asthma and chronic obstructive pulmonary disease (COPD) [32–34]. Tyrosine kinase inhibitors, such as sunitinib, sorafenib, regorafenib and axitinib, can target VEGFR-2 receptors. Moreover, several fusion proteins also inhibit the activities of these angiogenic molecules by effectively trapping them and other molecules that suppress the synthesis of these factors by inhibiting the mTOR, cyclooxygenase (COX) and heat-shock protein 90 (HSP90) pathways [35–37].

Although these anti-angiogenic agents are effective in inhibiting pathological angiogenesis, they also have serious side effects that preclude their use in many patients, thereby depriving these patients of the optimum and positive effects of anti-angiogenic therapy [7, 9, 38]. Intravitreal injections of anti-VEGF agents in AMD patients have been associated with cardiovascular toxicity and an increased risk of bleeding [9,39]. Both transient and sustained elevations of the intra-orbital pressure have been observed in these patients following anti-VEGF therapy [9,40]. Serious adverse effects, such as malignant hypertension and cutaneous, renal, hepatic and hematological toxicities, have also been reported in cancer patients receiving anti-angiogenic therapies [41]. Accordingly, the high cost and serious toxicities of the presently used anti-angiogenic drugs have prompted a search of alternative strategies. Researchers have focused on effective naturally occurring anti-angiogenic molecules derived from plant products because these inexpensive compounds, which have low or minimal toxicity, have been used for centuries in different parts of the world for the treatment of many disorders [42].

Plants and their active compounds as angiogenesis-modulating agents

A wide variety of plant-based compounds have been reported to exhibit anti-angiogenic properties through different molecular pathways (Table 1 and Fig. 1). These plant-derived compounds are predominantly phytochemicals that have significant physiological effects in the body [43]. These molecules act as antioxidants, stimulate enzyme activities, mimic hormones, interfere with DNA replication or bind to cell walls. In addition, they can prevent malignant transformation and heart diseases [44]. Several reports have also described the synergistic effects of plant-based medicinal compounds as anti-angiogenic agents when used in combination with other anti-neoplastic drugs [45–47].

Natural anti-angiogenic compounds derived from plants

Polyphenols

Polyphenols are members of a large family of chemical compounds that are found in several plants and fruits, including the catechins found in tea, curcumin in *Curcuma longa* and resveratrol in grapes and berries [48]. These natural compounds have anti-proliferative effects on both tumor cells and tumor-associated stromal cells, including ECs, and suppress tumorigenesis through their anti-angiogenic, anti-oxidant and anti-proliferative properties [42,49, 50].

Resveratrol (3,4,5-trihydroxy-trans-stilbene), a polyphenol present in grapes, berries and other plant sources, affects tumor angiogenesis via multiple mechanisms [42,51,52]. Animal studies have indicated that oral administration of 5.7 μg/ml of resveratrol can retard tumor growth in T241 murine fibrosarcoma-bearing C57BL6 mice by inhibiting endothelial cell migration, proliferation and new blood vessel formation. The underlying mechanism of resveratrol is through the inhibition of FGF2 and VEGF receptor-mediated activation of MAPK in endothelial cells [51]. *In vitro* studies also indicate that resveratrol can significantly inhibit VEGF expression in A2780/CP70 and OVCAR-3 human ovarian cancer cells [52]. Cao *et al.* further demonstrated that 50 μM of resveratrol can significantly inhibit both basal and IGF-1-mediated HIF-1 alpha expression in human ovarian cancer cells [52]. Resveratrol mediates its actions through the inhibition of Akt and MAPK–driven basal and IGF-1-mediated HIF-1 alpha expression via stimulation of proteasomal degradation of HIF-1 alpha [52]. In addition, resveratrol also acts as an inhibitor of protein translational regulators, such as the M_r 70000 ribosomal protein S6 kinase 1, S6 ribosomal protein, eukaryotic translation initiation factor 4E-binding protein 1 and eukaryotic initiation factor 4E [52]. Furthermore, it has been reported that HS-1793, a resveratrol analog can reprogram pro-angiogenic M2 macrophages into anti-tumoral M1 phenotype through up-regulation of interferon gamma [53].

Catechin derivatives, such as epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG), are present in green tea [42]. Thearubigins and theaflavins are found in black tea [42]. Low concentrations of EGCG inhibited both VEGF production and capillary EC proliferation [42]. EGCG (40 mg/L) and green tea extracts (GTE) significantly decreased VEGF production in MDA-MB231 human breast cancer cells, and this action of GTE was correlated with suppression of protein kinase C, c-fos and c-jun RNA transcripts, indicating that AP-1-responsive regions present in the human VEGF promoter may be involved in this process [54]. EGCG also inhibited VEGF production in human head and neck squamous cell carcinoma and breast cancer cells by inhibiting Stat3 and NF-kappa B activation in these cells [55]. Jung *et al.* further reported that 30 μM of EGCG can retard angiogenesis through suppression of Erk-1/2 phosphorylation and inhibition of VEGF expression in HT29 human colon cancer cells [56]. These authors also demonstrated that intraperitoneal injection of 1.5 mg of EGCG for approximately 20 days can significantly inhibit angiogenesis and tumor growth in HT29-bearing nude mice [56]. Also, treatment of 4T1 murine breast cancer bearing mice with 10mg/kg of EGCG for 30 days suppressed tumor growth by inhibiting tumor-associated

macrophage infiltration and M2 macrophage polarization. The mechanism of this action of EGCG was due to exosome-mediated transfer of microRNA-16 from tumor cells to macrophages [57]. In another study, EGCG (0.75–25 μM) was shown to inhibit migration of neutrophils and thereby polymorphonuclear neutrophil-induced angiogenesis in a dose-dependent manner [58].

Curcumin, a small molecular weight polyphenol isolated from turmeric (*Curcuma longa*), a commonly used spice, has both anti-cancer and anti-inflammatory properties [59,60]. Curcumin inhibited bFGF (1 ng/ml)-induced endothelial cell proliferation *in vitro* in a concentration (0.5 to 10 μM)-dependent manner [61]. These authors also reported that although 10 mg of curcumin inhibited bFGF (80 ng)-mediated corneal neovascularization in mice, it had no effect on phorbol ester-stimulated VEGF mRNA production [61]. However, other studies have indicated that oral administration of a curcumin solution (3000 mg/kg) significantly reduces tumor neocapillary density and serum VEGF levels in mice with HepG2 hepatocellular carcinoma [62]. Furthermore, although treatment of RAW264.7 macrophages with 1 mM of hydrazinocurcumin encapsulated nanoparticles induced polarization of macrophages from M2 to M1 phenotype through inhibition of STAT3 [63], 25 μmol/L of curcumin, on the contrary, stimulated polarization of these cells into M2 phenotype via activation of proliferator-activated receptor gamma and secretion of IL-4 or IL-13 [64. 65].

Flavonoids, including flavones, flavonols, flavanones, anthocyanins and isoflavones, comprise another class of polyphenols that demonstrates anti-angiogenic properties [49]. Genistein, an isoflavonoid derived from *Genista tinctoria*, can inhibit bFGF (2.5 ng/ml)-mediated endothelial cell tube formation *in vitro* at a concentration of approximately 150 μM by suppressing production of plasminogen activator (PA) and PA inhibitor-1 [66]. However, a lower concentration of genistein (30 μM) has also been reported to inhibit proliferation of endothelial cells stimulated by 100 ng/ml of bFGF [67].

Other polyphenolic flavonoids, such as silymarin and silibinin isolated from the fruits and seeds of *Silybum marianum* (milk thistle), can also inhibit angiogenesis [68,69]. Silymarin at a concentration of 50–100 μg/ml downregulated VEGF expressions in human DU145 prostate cancer and MDA-MB-468 breast cancer cells. It also inhibited endothelial MMP-2 secretion [68]. Additionally, mice fed 0.05% and 0.1% (w/w) silibinin showed inhibited growth of human DU145 prostate tumor xenografts due to suppression of VEGF and CD31 expression [69]. Moreover, oral dose of 742 mg/kg of silibinin (5 days/ week for 10 weeks) also significantly inhibited the incidence and growth of urethane-induced lung adenocarcinoma in A/J mice by decreasing numbers of tumor-associated macrophages [70].

Alkaloids

Castanospermine, an alkaloid present in *Castanospermum austral* and the pods of *Alexa leiopetala*, is a glucosidase inhibitor [71]. A previous report indicated that 4 μg/ml of castanospermine inhibited both migration and invasion of ECs through the basement membrane. Furthermore, 2.5~50 mg/mouse of castanospermine was reported to suppress tumor growth in a xenograft model and neovascularization in matrigel assay [71]. In

addition, this molecule also blocked the morphological differentiation of these cells *in vitro* by altering the structures of their cell surface oligosaccharides [71].

Sanguinarine, a benzophenanthridine alkaloid derived from the roots of *Sanguinaria canadensis*, has been reported to markedly suppress VEGF-induced EC migration and sprouting *in vitro* and blood vessel formation *in vivo* by blocking VEGF-induced Akt phosphorylation in a dose-dependent manner (10–300 nM) [72]. Similarly, brucine, an indole alkaloid derived from *Strychnos nux-vomica*, inhibited VEGF-mediated angiogenesis both *in vitro* and *in vivo* by suppressing downstream protein kinases, including Src, FAK, Erk, Akt and mTOR, at a concentration of 40 μM. In addition, brucine also inhibited VEGF, nitric oxide (NO), IL-6, IL-8, TNF-α and IFN-γ in human umbilical vein cells [73]. Another indole alkaloid, 6′-debromohamacanthin A, which is found in marine sponges, and tylophorine, a phenanthroindolizidine alkaloid isolated from *Tylophora indica*, inhibited VEGF and VEGFR-2 mediated-angiogenesis at a concentration of ≤10 μM via similar mechanisms through the PI3K/Akt/mTOR signaling pathway [74, 75]. Furthermore, norisoboldine, an alkaloid isolated from *Radix Linderae*, demonstrated Notch1-mediated anti-angiogenic effects in an experimental rheumatoid arthritis model at a dose of 7.5 mg/kg [76]. Colchicine and vinblastine are two alkaloids derived from *Colchicum autumnale* and *Catharanthus roseus*, respectively [77]. Although colchicine significantly inhibits angiogenesis *in vitro* at concentration of 10^{-6}~10^{-8} M, the effective anti-angiogenic dose is toxic to human subjects [77]. However, continuous administration of vinblastine at a dose of 2.0 mg/kg/week produced inhibitory effects on VEGF-mediated angiogenesis in mammalian models, but the mechanisms underlying the anti-angiogenic actions of these compounds are still unknown [77, 78].

Terpenoids and tannins

Ginsenosides, including ginsenoside-Rg3 and ginsenoside-Rb2, are found in the roots of red ginseng (*Panax ginseng*). These natural plant products significantly decreased the number of neovessels in murine B16 melanomas at an intravenous dose of 10 μg per mouse or oral dose of 100~1000 μg per mouse [79,80]. In contrast, there is also a report indicating that a mixture of saponins derived from ginseng at concentrations between 10–100 μg/ml stimulated EC migration, proliferation and tube formation and wound healing at a dose of 25 mg in 1 ml of 0.3% collagen [81].

Taxol is a complex polyoxygenated diterpene isolated from the bark of the Pacific yew tree (*Taxus brevifolia*). Taxol kills malignant tumor cells by disrupting their microtubule cytoskeleton [82] and exhibits anti-angiogenic properties at low concentrations between 25–100 nM by inhibiting VEGF production and the expression of HIF1 alpha (HIF-1α) [82,83].

Other plant extracts

Triphala churna (THL) is a mixture of three myrobalan fruits, those of *Emblica officinalis* Gaertn (Amla), *Terminalia chebula* Retz (Haritaki) and *Terminalia belerica* Roxb (Bibhitaki), in equal proportions [16]. This medicinal mixture has been extensively used for many years in a traditional Indian system of medicine, Ayurveda, for the treatment of gastrointestinal and cardiovascular disorders [16]. Interestingly, our recent studies

demonstrated that 40 μg/ml of THL and particularly its active tannin compounds chebulinic acid and chebulagic acid at a concentration of 2 μM significantly inhibited VEGF-induced angiogenesis by blocking VEGFR-2 phosphorylation [16, 84].

Conclusion

Angiogenesis plays an important role in the development of many diseases. Disruption of the balance between pro-angiogenic and anti-angiogenic factors leads to either excessive or inadequate levels of angiogenesis [21,22]. Treatments targeting angiogenesis are effective for many diseases [5,7,10]. However, the anti-angiogenic agents that are currently in use, such as anti-VEGF-A antibodies and tyrosine kinase inhibitors, have many serious adverse effects [9,34]. In contrast, some crude plant extracts and their active ingredients appear to be safer, with low or no systemic effects, than the currently used synthetic medicines and antibodies with anti-angiogenic properties [85]. Importantly, many of these natural plant products can be administered orally and thus will be more acceptable to patients. Several of the natural plant products have shown comparable or improved anti-angiogenic effects in experimental models compared with the anti-angiogenic agents currently in use [14,42, 85].

Several problems need to be resolved before these natural products can be successfully used in the clinic. One of the major concerns is the bioavailability of these compounds because many of these molecules have poor solubility in water and low absorption rates; therefore, only negligible concentrations of these natural compounds can reach the peripheral circulation and the desired disease sites [48]. Accordingly, two approaches to improve their bioavailability are presently being studied, one of which is the use of nano-carriers [86]. Natural compounds can be packed into biodegradable polymeric nanoparticles and prepared as solid or liquid formulations. These formulations retain the activities of the native compounds and improve their targeting to the desired tissue sites because the nano-compounds have better pharmacokinetic profiles [87]. For example, a nano-carrier encapsulating EGCG had the same pro-apoptotic and anti-angiogenic effects as the unencapsulated compound but with a 10-fold dosage advantage [86], and nano-encapsulated curcumin, kaempferol and berberine had increased anti-angiogenic and anti-tumor effects *in vivo* compared with those of their unencapsulated forms [87–89]. Another effective method to improve the bioavailability of these compounds is to develop synthetic derivatives of these compounds by either adding or removing functional groups to or from these molecules to increase their solubilities and rates of absorption without changing their biological effects [90, 91].

Acknowledgments

This study was supported by grants from the National Institutes of Health [R01DK098045 (S.B) and R01CA169158 (S.B.)]. We apologize to colleagues whose studies were not cited because of space limitation.

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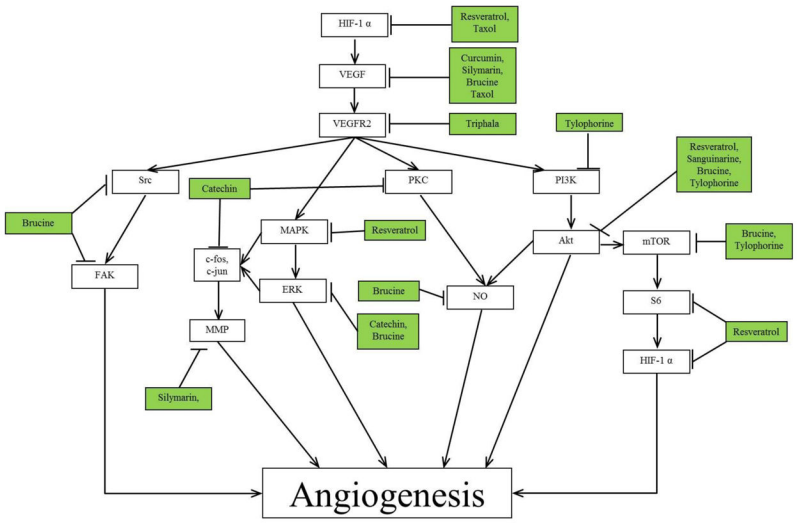

Fig.1.

The major angiogenesis pathways targeted by plants and plant-based compounds

Table 1

Angiogenesis-inhibitory plants and their active molecules

Active compounds		Plant species	In vivo dose and model	In vitro concentration and cells	Anti-angiogenesis Target	Reference
Polyphenols	Resveratrol	Grapes, berries etc.	5.7 μg/ml on T241 fibrosarcoma xenografts, 1.5mg/kg of HS-1793 on FM3A breast cancer xenografts	50 μM on A2780/CP70 and OVCAR-3 cells	Akt, MAPK phosphorylation, S6 protein, HIF-1α expression, Secretion of IFN-γ and programming of TAM	[51], [52], [53]
	Catechin derivatives	Tea.	1.5 mg of EGCG on HT29 xenografts, 10mg/kg of EGCG on 4T1 breast cancer xenografts	40 mg/L EGCG on MDA-MB231 cells, 30 μM EGCG on HT29 cells, 0.75~25 μM EGCG on neutrophils	protein kinase C, c-fos and c-jun, Stat3 and NF-kappa B, Erk-1/2 phosphorylation, TAM infiltration and polarization, neutrophil migration	[54], [55], [56], [57], [58]
	Curcumin	Curcuma longa	3000 mg/kg on HepG2 xenografts, 10 mg on mouse corneal,	0.5~10 μM on primary endothelial cells, 1 mM of hydrazinocurcumin encapsulated nanoparticles on RAW264.7 macrophages, 25 μmol/L of curcumin on macrophages	VEGF production, Stat3, proliferator-activated receptor gamma, IL-4, IL-13 production, TAM polarization	[61], [62], [63], [64], [65]
	Flavonoids	Berries, tree fruits, Nuts and Beans	Unknown	30, 150 μM on endothelial cells	PA, PAI-1,	[66], [67]
	Silymarin, silibinin	Silybum marianum	0.05% and 0.1% (w/w) on DU145 prostate tumor xenografts, 742 mg/kg of silibinin on urethane-induced lung adenocarcinoma in A/J mice	50~100 μg/ml on DU145 and MDA-MB-468 cells	VEGF expression, MMP2 secretion, TAM infiltration	[68], [69], [70]
Alkaloids	Castanospermine	Castanospermum austral, Alexa leipetala	2.5~50 mg/mouse on matrigel assay, 2.5 mg/mouse on EHS-BAM and Tsu-pr1 tumor xenografts	4 μg/ml on BAEC	EC surface glycoproteins and EC differentiation	[71]
	Sanguinarine	Sanguinaria Canadensis	100 nM on matrigel assay, 100 ng on CAM assay	10~300 nM on HUVECs	Akt phosphorylation	[72]
	Brucine	Strychnos nux-vomica	20 or 40 μM on rat aortic ring assay, 10 mg/kg on matrigel assay and EAC tumor xenografts	5~40 μM on HUVECs	Src, FAK, Erk, Akt and mTOR phosphorylation, VEGF, NO production	[73]
	Tylophorine	Tylophora indica	7.5 mg/kg on EAC tumor xenografts	2.5~20 μM on HUVECs	PI3K/Akt/mTOR signaling	[75]
	Colchicine, vinblastine	Colchicum autumnale, Catharanthus roses	2.0 mg/kg week of vinblastine on rat mesentery model	10^{-6}~10^{-8} M of colchicine on thrombin clot-based assay	Unknown	[77], [78]

Active compounds		Plant species	In vivo dose and model	In vitro concentration and cells	Anti-angiogenesis Target	Reference
Terpenoids and tannins	Ginsenosides	Panax ginseng	10 μg/mouse i.v. or 100~1000 μg/mouse p.o. on lung metastasis model	Unknown	Unknown	[79], [80]
	Taxol	Taxus brevifolia	Unknown	25~100 nM on 1A9 and MDA-MB-231 cells	VEGF and HIF-1α production	[82], [83]
	Triphala churna	Emblica officinalis, Terminalia chebula, Terminalia belerica	100 mg/kg on matrigel assay, 40 μg/ml on CAM assay	40 μg/ml on HUVECs	VEGFR2 phosphorylation	[16]