Angiogenesis (2016) 19:287–295
DOI 10.1007/s10456-016-9512-y

REVIEW PAPER

Plants and their active compounds: natural molecules to target angiogenesis

Kai Lu[1] · **Madhavi Bhat**[1] · **Sujit Basu**[1,2]

Received: 21 December 2015 / Accepted: 1 May 2016 / Published online: 6 May 2016

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 for 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 for several diseases [5, 6]. However, the anti-angiogenic agents presently in use are mainly synthetic chemicals or humanized monoclonal 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.

✉ Sujit Basu
sujit.basu@osumc.edu

[1] Department of Pathology, Ohio State University, Columbus, OH 43210, USA

[2] Division of Medical Oncology, Department of Internal Medicine, Ohio State University, Columbus, OH 43210, USA

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, 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 factors 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 for 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 for 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; 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 antineoplastic drugs [45–47].

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	References
Polyphenols					
Resveratrol	Grapes, berries, etc	5.7 μg/ml on T241 fibrosarcoma xenografts, 1.5 mg/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	[51–53]
Catechin derivatives	Tea	1.5 mg of EGCG on HT29 xenografts, 10 mg/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	[54–58]
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	[61–65]
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	[68–70]
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]
Terpenoid 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]

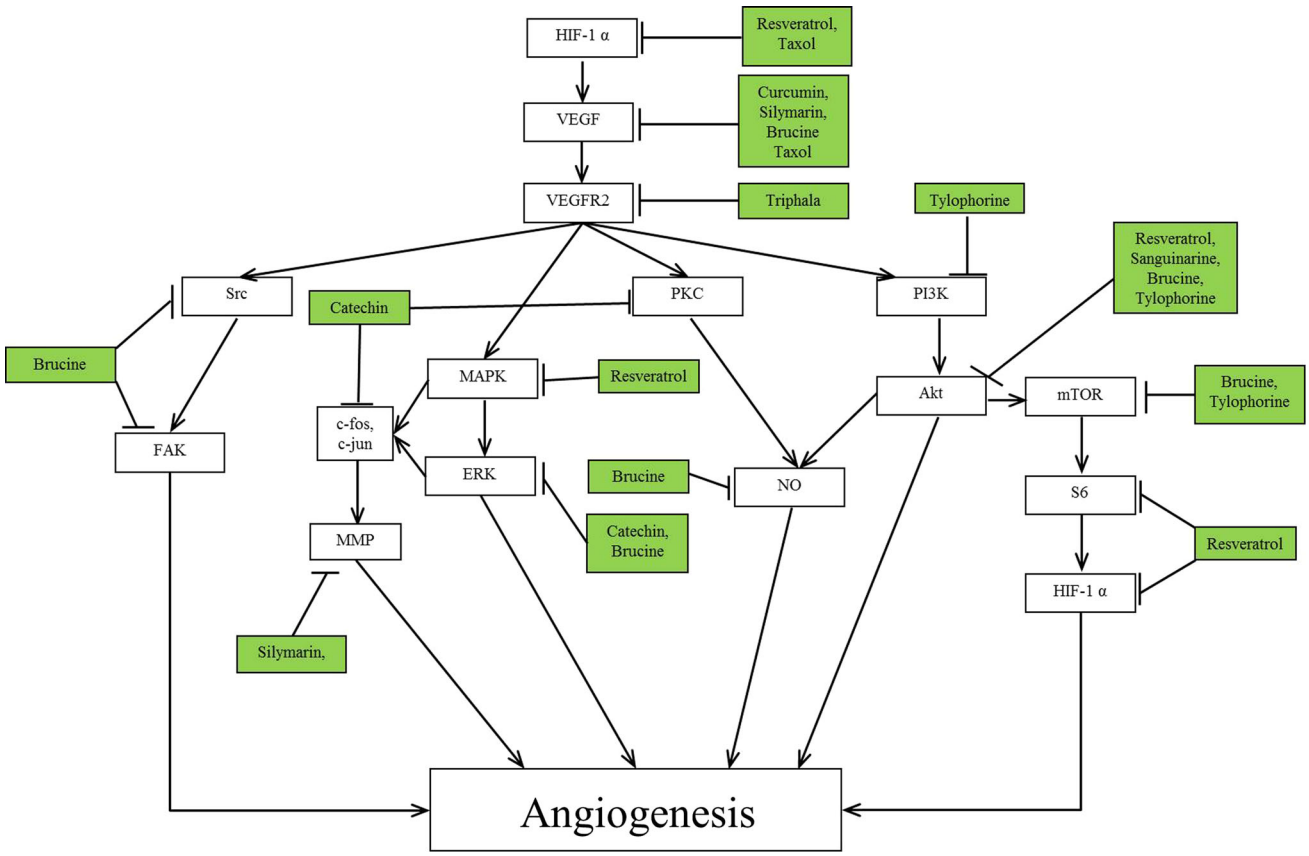

Fig. 1 Major angiogenesis pathways targeted by plants and plant-based compounds

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, antioxidant, 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. [52] 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. 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 70,000 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. [56] 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. 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 for 4T1 murine breast cancer-bearing mice with 10 mg/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 (*C. longa*), a commonly used spice, has both anticancer and anti-inflammatory properties [59, 60]. Curcumin inhibited bFGF (1 ng/ml)-induced endothelial cell proliferation in vitro in a concentration (0.5–10 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 nanoparticle-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 the 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 down-regulated 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 the 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 PI3 K/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 a 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 and 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 and 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 for 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.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Risau W (1997) Mechanisms of angiogenesis. Nature 386(6626):671–674
2. Chung AS, Ferrara N (2011) Developmental and pathological angiogenesis. Annu Rev Cell Dev Biol 27:563–584
3. Paleolog EM (2002) Angiogenesis in rheumatoid arthritis. Arthritis Res 4(Suppl 3):S81–S90
4. Heidenreich R, Rocken M, Ghoreschi K (2009) Angiogenesis drives psoriasis pathogenesis. Int J Exp Pathol 90(3):232–248
5. Ferrara N, Kerbel RS (2005) Angiogenesis as a therapeutic target. Nature 438(7070):967–974
6. Folkman J (1996) Fighting cancer by attacking its blood supply. Sci Am 275(3):150–154
7. Al-Husein B, Abdalla M, Trepte M, Deremer DL, Somanath PR (2012) Antiangiogenic therapy for cancer: an update. Pharmacotherapy 32(12):1095–1111
8. Kubota Y (2012) Tumor angiogenesis and anti-angiogenic therapy. Keio J Med 61(2):47–56
9. Elice F, Rodeghiero F (2012) Side effects of anti-angiogenic drugs. Thromb Res 129(Suppl 1):S50–S53
10. Samant RS, Shevde LA (2011) Recent advances in anti-angiogenic therapy of cancer. Oncotarget 2(3):122–134
11. Recio MC, Andujar I, Rios JL (2012) Anti-inflammatory agents from plants: progress and potential. Curr Med Chem 19(14):2088–2103
12. Tewtrakul S, Subhadhirasakul S (2007) Anti-allergic activity of some selected plants in the Zingiberaceae family. J Ethnopharmacol 109(3):535–538
13. Cowan MM (1999) Plant products as antimicrobial agents. Clin Microbiol Rev 12(4):564–582
14. Sagar SM, Yance D, Wong RK (2006) Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-Part 1. Curr Oncol 13(1):14–26
15. Wen W, Lu J, Zhang K, Chen S (2008) Grape seed extract inhibits angiogenesis via suppression of the vascular endothelial growth factor receptor signaling pathway. Cancer Prev Res (Phila) 1(7):554–561
16. Lu K, Chakroborty D, Sarkar C, Lu T, Xie Z, Liu Z, Basu S (2012) Triphala and its active constituent chebulinic acid are natural inhibitors of vascular endothelial growth factor-a mediated angiogenesis. PLoS One 7(8):e43934
17. Carmeliet P (2003) Angiogenesis in health and disease. Nat Med 9(6):653–660
18. Carmeliet P, Jain RK (2000) Angiogenesis in cancer and other diseases. Nature 407(6801):249–257
19. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M (2006) Angiogenesis in cancer. Vasc Health Risk Manage 2(3):213–219
20. Adair TH, Montani JP (2010) Angiogenesis. Integrated systems physiology: from molecule to function to disease. Morgan & Claypool Life Sciences, San Rafael, CA
21. Gupta K, Zhang J (2005) Angiogenesis: a curse or cure? Postgrad Med J 81(954):236–242
22. Bouis D, Kusumanto Y, Meijer C, Mulder NH, Hospers GA (2006) A review on pro- and anti-angiogenic factors as targets of clinical intervention. Pharmacol Res 53(2):89–103
23. Nyberg P, Xie L, Kalluri R (2005) Endogenous inhibitors of angiogenesis. Cancer Res 65(10):3967–3979
24. Folkman J, Klagsbrun M (1987) Angiogenic factors. Science 235(4787):442–447
25. Nissim Ben Efraim AH, Levi-Schaffer F (2014) Roles of eosinophils in the modulation of angiogenesis. Chem Immunol Allergy 99:138–154
26. Riabov V, Gudima A, Wang N, Mickley A, Orekhov A, Kzhyshkowska J (2014) Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis. Front Physiol 5:75
27. Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA (2004) Vascular endothelial growth factor and angiogenesis. Pharmacol Rev 56(4):549–580
28. Weis SM, Cheresh DA (2011) Tumor angiogenesis: molecular pathways and therapeutic targets. Nat Med 17(11):1359–1370
29. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS (2014) Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev 8:CD005139
30. Hefner L, Gerding H (2014) Intravitreal anti-VEGF treatment of choroidal neovascularization (CNV) in pathological myopia (PM): a review. Klin Monbl Augenheilkd 231(4):414–417
31. Marinaccio C, Nico B, Maiorano E, Specchia G, Ribatti D (2014) Insights in hodgkin lymphoma angiogenesis. Leuk Res 38(8):857–861
32. Arevalo JF (2014) Diabetic macular edema: changing treatment paradigms. Curr Opin Ophthalmol 25(6):502–507
33. Bandello F, Casalino G, Loewenstein A, Goldstein M, Pelayes D, Battaglia Parodi M (2014) Pharmacological approach to diabetic macular edema. Ophthalmic Res 51(2):88–95
34. Olivieri D, Chetta A (2014) Therapeutic perspectives in vascular remodeling in asthma and chronic obstructive pulmonary disease. Chem Immunol Allergy 99:216–225
35. Lockhart AC, Rothenberg ML, Dupont J, Cooper W, Chevalier P, Sternas L, Buzenet G, Koehler E, Sosman JA, Schwartz LH, Gultekin DH, Koutcher JA, Donnelly EF, Andal R, Dancy I, Spriggs DR, Tew WP (2010) Phase I study of intravenous vascular endothelial growth factor trap, aflibercept, in patients with advanced solid tumors. J Clin Oncol 28(2):207–214
36. Zhong H, Chiles K, Feldser D, Laughner E, Hanrahan C, Georgescu MM, Simons JW, Semenza GL (2000) Modulation of hypoxia-inducible factor 1alpha expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. Cancer Res 60(6):1541–1545
37. Mabjeesh NJ, Post DE, Willard MT, Kaur B, Van Meir EG, Simons JW, Zhong H (2002) Geldanamycin induces degradation of hypoxia-inducible factor 1alpha protein via the proteosome pathway in prostate cancer cells. Cancer Res 62(9):2478–2482
38. Faruque LI, Lin M, Battistella M, Wiebe N, Reiman T, Hemmelgarn B, Thomas C, Tonelli M (2014) Systematic review of the risk of adverse outcomes associated with vascular endothelial growth factor inhibitors for the treatment of cancer. PLoS One 9(7):e101145
39. Thulliez M, Angoulvant D, Le Lez ML, Jonville-Bera AP, Pisella PJ, Gueyffier F, Bejan-Angoulvant T (2014) Cardiovascular events and bleeding risk associated with intravitreal antivascular endothelial growth factor monoclonal antibodies: systematic review and meta-analysis. JAMA Ophthalmol 132(11):1317–1326
40. SooHoo JR, Seibold LK, Kahook MY (2014) The link between intravitreal antivascular endothelial growth factor injections and glaucoma. Curr Opin Ophthalmol 25(2):127–133
41. Ishak RS, Aad SA, Kyei A, Farhat FS (2014) Cutaneous manifestations of anti-angiogenic therapy in oncology: review with focus on VEGF inhibitors. Crit Rev Oncol Hematol 90(2):152–164
42. Wang Z, Dabrosin C, Yin X, Fuster MM, Arreola A, Rathmell WK, Generali D, Nagaraju GP, El-Rayes B, Ribatti D, Chen YC, Honoki K, Fujii H, Georgakilas AG, Nowsheen S, Amedei A, Niccolai E, Amin A, Ashraf SS, Helferich B, Yang X, Guha G, Bhakta D, Ciriolo MR, Aquilano K, Chen S, Halicka D,

Mohammed SI, Azmi AS, Bilsland A, Keith WN, Jensen LD (2015) Broad targeting of angiogenesis for cancer prevention and therapy. Semin Cancer Biol 35(Suppl):S224–S243
43. Liu RH (2003) Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 78(3 Suppl):517S–520S
44. Huang WY, Cai YZ, Zhang Y (2010) Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. Nutr Cancer 62(1):1–20
45. Sak K (2012) Chemotherapy and dietary phytochemical agents. Chemother Res Pract 2012:282570
46. Wang CZ, Luo X, Zhang B, Song WX, Ni M, Mehendale S, Xie JT, Aung HH, He TC, Yuan CS (2007) Notoginseng enhances anti-cancer effect of 5-fluorouracil on human colorectal cancer cells. Cancer Chemother Pharmacol 60(1):69–79
47. Sugiyama T, Sadzuka Y (1998) Enhancing effects of green tea components on the antitumor activity of adriamycin against M5076 ovarian sarcoma. Cancer Lett 133(1):19–26
48. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L (2004) Polyphenols: food sources and bioavailability. Am J Clin Nutr 79(5):727–747
49. Fotsis T, Pepper MS, Aktas E, Breit S, Rasku S, Adlercreutz H, Wahala K, Montesano R, Schweigerer L (1997) Flavonoids, dietary-derived inhibitors of cell proliferation and in vitro angiogenesis. Cancer Res 57(14):2916–2921
50. Fotsis T, Pepper M, Adlercreutz H, Hase T, Montesano R, Schweigerer L (1995) Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. J Nutr 125(3 Suppl):790S–797S
51. Brakenhielm E, Cao R, Cao Y (2001) Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes. FASEB J 15(10):1798–1800
52. Cao Z, Fang J, Xia C, Shi X, Jiang BH (2004) Trans-3,4,5′-Trihydroxystibene inhibits hypoxia-inducible factor 1alpha and vascular endothelial growth factor expression in human ovarian cancer cells. Clin Cancer Res 10(15):5253–5263
53. Jeong SK, Yang K, Park YS, Choi YJ, Oh SJ, Lee CW, Lee KY, Jeong MH, Jo WS (2014) Interferon gamma induced by resveratrol analog, HS-1793, reverses the properties of tumor associated macrophages. Int Immunopharmacol 22(2):303–310
54. Sartippour MR, Shao ZM, Heber D, Beatty P, Zhang L, Liu C, Ellis L, Liu W, Go VL, Brooks MN (2002) Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells. J Nutr 132(8):2307–2311
55. Masuda M, Suzui M, Lim JT, Deguchi A, Soh JW, Weinstein IB (2002) Epigallocatechin-3-gallate decreases VEGF production in head and neck and breast carcinoma cells by inhibiting EGFR-related pathways of signal transduction. J Exp Ther Oncol 2(6):350–359
56. Jung YD, Kim MS, Shin BA, Chay KO, Ahn BW, Liu W, Bucana CD, Gallick GE, Ellis LM (2001) EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. Br J Cancer 84(6):844–850
57. Jang JY, Lee JK, Jeon YK, Kim CW (2013) Exosome derived from epigallocatechin gallate treated breast cancer cells suppresses tumor growth by inhibiting tumor-associated macrophage infiltration and M2 polarization. BMC Cancer 13:421
58. Donà M, Dell'Aica I, Calabrese F, Benelli R, Morini M, Albini A, Garbisa S (2003) Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. J Immunol 170(8):4335–4341
59. Naksuriya O, Okonogi S, Schiffelers RM, Hennink WE (2014) Curcumin nanoformulations: a review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. Biomaterials 35(10):3365–3383
60. Aggarwal BB, Gupta SC, Sung B (2013) Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br J Pharmacol 169(8):1672–1692
61. Arbiser JL, Klauber N, Rohan R, van Leeuwen R, Huang MT, Fisher C, Flynn E, Byers HR (1998) Curcumin is an in vivo inhibitor of angiogenesis. Mol Med 4(6):376–383
62. Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H, Patumraj S (2006) Effects of curcumin on tumor angiogenesis and biomarkers, COX-2 and VEGF, in hepatocellular carcinoma cell-implanted nude mice. Clin Hemorheol Microcirc 34(1–2):109–115
63. Zhang X, Tian W, Cai X, Wang X, Dang W, Tang H, Cao H, Wang L, Chen T (2013) Hydrazinocurcumin Encapsuled nanoparticles "re-educate" tumor-associated macrophages and exhibit anti-tumor effects on breast cancer following STAT3 suppression. PLoS One 8(6):e65896
64. Chen F, Guo N, Cao G, Zhou J, Yuan Z (2014) Molecular analysis of curcumin-induced polarization of murine RAW264.7 macrophages. J Cardiovasc Pharmacol 63(6):544–552
65. Gao S, Zhou J, Liu N, Wang L, Gao Q, Wu Y, Zhao Q, Liu P, Wang S, Liu Y, Guo N, Shen Y, Wu Y, Yuan Z (2015) Curcumin induces M2 macrophage polarization by secretion IL-4 and/or IL-13. Mol Cell Cardiol 85:131–139
66. Fotsis T, Pepper M, Adlercreutz H, Fleischmann G, Hase T, Montesano R, Schweigerer L (1993) Genistein, a dietary-derived inhibitor of in vitro angiogenesis. Proc Natl Acad Sci USA 90(7):2690–2694
67. Koroma BM, de Juan E Jr (1994) Phosphotyrosine inhibition and control of vascular endothelial cell proliferation by genistein. Biochem Pharmacol 48(4):809–818
68. Jiang C, Agarwal R, Lu J (2000) Anti-angiogenic potential of a cancer chemopreventive flavonoid antioxidant, silymarin: inhibition of key attributes of vascular endothelial cells and angiogenic cytokine secretion by cancer epithelial cells. Biochem Biophys Res Commun 276(1):371–378
69. Singh RP, Sharma G, Dhanalakshmi S, Agarwal C, Agarwal R (2003) Suppression of advanced human prostate tumor growth in athymic mice by silibinin feeding is associated with reduced cell proliferation, increased apoptosis, and inhibition of angiogenesis. Cancer Epidemiol Biomark Prev 12(9):933–939
70. Tyagi A, Singh RP, Ramasamy K, Raina K, Redente EF, Dwyer-Nield LD, Radcliffe RA, Malkinson AM, Agarwal R (2009) Growth inhibition and regression of lung tumors by silibinin: modulation of angiogenesis by macrophage-associated cytokines and nuclear factor-kappaB and signal transducers and activators of transcription 3. Cancer Prev Res (Phila) 2(1):74–83
71. Pili R, Chang J, Partis RA, Mueller RA, Chrest FJ, Passaniti A (1995) The alpha-glucosidase I inhibitor castanospermine alters endothelial cell glycosylation, prevents angiogenesis, and inhibits tumor growth. Cancer Res 55(13):2920–2926
72. Eun JP, Koh GY (2004) Suppression of angiogenesis by the plant alkaloid, sanguinarine. Biochem Biophys Res Commun 317(2):618–624
73. Saraswati S, Agrawal SS (2013) Brucine, an indole alkaloid from *Strychnos nux-vomica* attenuates VEGF-induced angiogenesis via inhibiting VEGFR2 signaling pathway in vitro and in vivo. Cancer Lett 332(1):83–93
74. Kim GD, Cheong OJ, Bae SY, Shin J, Lee SK (2013) 6″-Debromohamacanthin A, a bis (indole) alkaloid, inhibits angiogenesis by targeting the VEGFR2-mediated PI3K/AKT/mTOR signaling pathways. Mar Drugs 11(4):1087–1103
75. Saraswati S, Kanaujia PK, Kumar S, Kumar R, Alhaider AA (2013) Tylophorine, a phenanthraindolizidine alkaloid isolated from *Tylophora indica* exerts antiangiogenic and antitumor activity by targeting vascular endothelial growth factor receptor 2-mediated angiogenesis. Mol Cancer 12:82

76. Lu Q, Lu S, Gao X, Luo Y, Tong B, Wei Z, Lu T, Xia Y, Chou G, Wang Z, Dai Y (2012) Norisoboldine, an alkaloid compound isolated from *Radix Linderae*, inhibits synovial angiogenesis in adjuvant-induced arthritis rats by moderating Notch1 pathway-related endothelial tip cell phenotype. Exp Biol Med (Maywood) 237(8):919–932
77. Stafford SJ, Schwimer J, Anthony CT, Thomson JL, Wang YZ, Woltering EA (2005) Colchicine and 2-methoxyestradiol inhibit human angiogenesis. J Surg Res 125(1):104–108
78. Albertsson P, Lennernas B, Norrby K (2008) Dose effects of continuous vinblastine chemotherapy on mammalian angiogenesis mediated by VEGF-A. Acta Oncol 47(2):293–300
79. Mochizuki M, Yoo YC, Matsuzawa K, Sato K, Saiki I, Tono-oka S, Samukawa K, Azuma I (1995) Inhibitory effect of tumor metastasis in mice by saponins, ginsenoside-Rb2, 20(R)- and 20(S)-ginsenoside-Rg3, of red ginseng. Biol Pharm Bull 18(9):1197–1202
80. Sato K, Mochizuki M, Saiki I, Yoo YC, Samukawa K, Azuma I (1994) Inhibition of tumor angiogenesis and metastasis by a saponin of *Panax ginseng*, ginsenoside-Rb2. Biol Pharm Bull 17(5):635–639
81. Morisaki N, Watanabe S, Tezuka M, Zenibayashi M, Shiina R, Koyama N, Kanzaki T, Saito Y (1995) Mechanism of angiogenic effects of saponin from ginseng Radix rubra in human umbilical vein endothelial cells. Br J Pharmacol 115(7):1188–1193
82. Foa R, Norton L, Seidman AD (1994) Taxol (paclitaxel): a novel anti-microtubule agent with remarkable anti-neoplastic activity. Int J Clin Lab Res 24(1):6–14
83. Escuin D, Kline ER, Giannakakou P (2005) Both microtubule-stabilizing and microtubule-destabilizing drugs inhibit hypoxia-inducible factor-1alpha accumulation and activity by disrupting microtubule function. Cancer Res 65(19):9021–9028
84. Lu K, Basu S (2015) The natural compound chebulagic acid inhibits vascular endothelial growth factor A mediated regulation of endothelial cell functions. Sci Rep 5:9642
85. Chatterjee S, Bhattacharjee B (2012) Use of natural molecules as anti-angiogenic inhibitors for vascular endothelial growth factor receptor. Bioinformation 8(25):1249–1254
86. Siddiqui IA, Adhami VM, Bharali DJ, Hafeez BB, Asim M, Khwaja SI, Ahmad N, Cui H, Mousa SA, Mukhtar H (2009) Introducing nanochemoprevention as a novel approach for cancer control: proof of principle with green tea polyphenol epigallocatechin-3-gallate. Cancer Res 69(5):1712–1716
87. Wang L, Li H, Wang S, Liu R, Wu Z, Wang C, Wang Y, Chen M (2014) Enhancing the antitumor activity of berberine hydrochloride by solid lipid nanoparticle encapsulation. AAPS PharmSciTech 15(4):834–844
88. Luo H, Jiang B, Li B, Li Z, Jiang BH, Chen YC (2012) Kaempferol nanoparticles achieve strong and selective inhibition of ovarian cancer cell viability. Int J Nanomedicine 7:3951–3959
89. Gou M, Men K, Shi H, Xiang M, Zhang J, Song J, Long J, Wan Y, Luo F, Zhao X, Qian Z (2011) Curcumin-loaded biodegradable polymeric micelles for colon cancer therapy in vitro and in vivo. Nanoscale 3(4):1558–1567
90. Saha SK, Khuda-Bukhsh AR (2013) Molecular approaches towards development of purified natural products and their structurally known derivatives as efficient anti-cancer drugs: current trends. Eur J Pharmacol 714(1–3):239–248
91. Mori M, Supuran CT (2015) Editorial: challenging organic syntheses and pharmacological applications of natural products and their derivatives. Curr Pharm Des 21(38):5451–5452