Review on Angiogenesis Modulation by Natural Compounds as Therapeutic Potential and Mechanisms

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Abstract

Angiogenesis is induced when there is any imbalance in the equilibrium due to either up regulation of pro-angiogenic factors or down regulation of anti-angiogenic mediators. Recent interest in identifying and modulating antiangiogenic pathways and antiangiogenic drug development has added advantage for therapeutic purposes. Many naturally occurring compounds have been indicated as inhibitors of tumor specific angiogenesis. This review was covers the topics including pathophysiology of angiogenesis, angiogenesis modulating compounds from plants, antiangiogenic potential of culinary herbs. The anti-angiogenic potential of the plants may be due to the prese.nce of terpenoids and flavonoids. The molecular mechanisms responsible for the antiangiogenic activity may be associated with inhibition of several steps of angiogenesis including proliferation, migration and tube formation of vascular endothelial cells. Since there is a close relationship between tumor growth and angiogenesis mechanism, various anti-angiogenic compounds for use in cancer treatment have been studied. Angiogenic modulators would be an ideal choice for future chemotherapeutics.

Keywords: Angiogenesis, Angiogenic modulators, Therapeutic potential, Medicinal plants

Significance | Compounds derived from plants that have antiangiogenic effects could be used in the development of drugs that target this stage of angiogenesis.

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1. Introduction

The mechanism of angiogenesis was first studied by Folkman in the process of tumor angiogenesis (Folkman and Klagsbrun, 1987). The term "Angiogenesis" refers to the growth of new capillaries from pre-existing vasculature and is a fundamental process required for tissue differentiation in embryogenesis, it is rare in adults except during reproductive cycle and wound healing (Walsh and Pearson, 2001, Lok et al. 2017). Angiogenesis is a tightly controlled complex process with several steps, where the pro and anti-angiogenic factors are in equilibrium to neutralize one another. Any imbalance in the equilibrium due to either up regulation of pro-angiogenic factors or down regulation of anti-angiogenic mediators induces angiogenesis (Distler *et al.*, 2003).

Many diseases are caused by persistent unregulated angiogenesis, tumor growth is angiogenesis-dependent and that every increment of tumor growth requires an increment of vascular growth (Wang *et al.*, 2004). In addition to this the growth of new capillaries is often triggered in conditions of pathological cellular proliferation, ichemia or chronic inflammation (Pugh and Ratecliffe, 2003).

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Recent interest in identifying and modulating antiangiogenic pathways and antiangiogenic drug development has added advantage for therapeutic purposes. Further, induction of therapeutic angiogenesis by various methods has recently been developed to treat ischemic diseases (Baumgartner *et al*., 1998; Rosengart *et al*., 1999). Natural compounds contain a range of developed to treat ischemic diseases (Baumgartner *et al*., 1998; Rosengart *et al*., 1999). Natural compounds contain a range of complex organic chemicals that may have synergistic effect on various physiological process in normal and disease state by interacting multiple pathways (Yance and Sagar, 2006). Many naturally occurring compounds have been indicated as inhibitors of tumor specific angiogenesis (Leyon and Kuttan, 2003; Sunila and Kuttan, 2006). One of the first isolated antiangiogenic agents is a phytochemical (Yance and Sagar, 2006). A recent report indicated that red wine polyphenolic compounds and green tea polyphenols were able to inhibit several key events of angiogenic process such as proliferation, migration of endothelial cells, vascular smooth muscle cells, expression of two major proangiogenic factors, VEGF and matrix metalloproteinases (Oak *et al*., 2005). Anthocyanidins present in fruits especially, delphinidin was found to be most potent angiogenic inhibitor (Lamy *et al*., 2006). Quercetin was found to inhibit several steps of angiogenesis including proliferation, migration, and tube formation of human microvascular dermal endothelial cells in a dose-dependent manner (Tan *et al*., 2003). Xanthophylls from maize seeds effectively inhibited the process of vessel formation, in chick yolk sac membrane and chorioallantoic membrane (CAM) suggesting a potential role of such compounds in the prevention of diseases associated with vascular dysfunction (Shirley *et al*., 2009). Numerous bioactive compounds from vegetables and fruits are recently being tested for antiangiogenic potential (Md Shamsuddin et al. 2019, Arif et al. 2018, Mansoureh et al. 2019) . Radiotherapy can be used in the up-front treatment of cancer with focused ultrasound energy as antiangiogenic therpay (Pegah et al. 2017). Angiogenesis is also can be targeted and treated with different immune biomarkers for different catgtory of disease such as uterine diseases, kidney, obesity (Mahfoudh et al 2017, Md Shamsuddin 2017, Sarah 2017, Elham 2017, Suzana 2017, Dhamraa 2017).

Angiogenesis

Angiogenesis is the process of neovascularization in which new capillary blood vessels are formed, this rarely occurs in normal physiological condition except for embryogenesis, formation of corpus luteum and wound healing (Wang *et al*., 2004). There are ten sequential steps involved in the process of angiogenesis, (i) release of angiogenic factors after tissue injury or hypoxia, (ii) binding of angiogenic factors to the receptors on endothelial cells (ECs), (iii) EC activation after receptor binding, (vi) release of protease to dissolve the basement membrane, (v) migration and proliferation of EC, (vi) adhesion molecules (integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$) help to pull the sprouting blood vessel forward, (vii) production of matrix metalloproteinases (MMPs) to dissolve extracellular matrix and initiate remodelling, (viii) angiopoietin-Tie-2 interaction modulates tubule formation, (ix) EphB-ephrinB system regulates loop formation, (x) pericytes are incorporated to stabilize the newly formed blood vessel (Tai-Ping *et al*., 2006).

Pathophysiology of angiogenesis

The Angiogenesis Foundation has declared angiogenesis as a "common denominator" in the most important diseases of society, in many disease conditions the body loses control of angiogenesis (Manoj *et al*., 2010). Angiogenesis is strictly controlled by selected positive and negative regulators and this rarely occurs in adults except for embryogenesis, placentation, endometrial repair and wound healing (Folkman and Klagsbrun, 1987; Tonnesen *et al*., 2000). In menstrual cycle it occurs in the corpus lutea and endometrium with rapid growth and regression (Brown *et al*., 1992: Gargett and Rogers, 2001).

In disease such as cancer and age-related macular degeneration, psoriosis and endometriosis, excessive angiogenesis occurs when disease cell produce large amounts of angiogenesis factors (e.g vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and hepatocyte growth factor) overwhelming the effects of natural angiogenesis inhibitors (e.g. angiostatin, endostatin and thrombospondin) (Tai-ping *et al*., 2006). Other disease conditions (e.g obesity and asthma) are associated with excessive angiogenesis. In these conditions, new blood vessels feed diseased tissue and destroy normal tissues; in cancer, tumor cells use the new vessels to escape into the circulation and lodge in other organs (tumor metastases). In early stages of tumorigenesis, tumors are not angiogenic, but when reaches vascular phase it switches to angiogenic phenotype an extensive vascular network is constructed through sprouting or non-sprouting angiogenic mechanisms. Angiogenesis is important for the progressive growth of solid tumors and also permits the shedding of metastatic tumors from the primary site.

In tumor-associated angiogenesis, angiogenic factors from tumors stimulate endothelial cells within a venule to degrade the vascular basement membrane and to migrate into surrounding tissues towards the tumor mass and to promote the proliferation of endothelial cells in a capillary sprout. There is much evidence that angiogenesis is important for the progressive growth of solid tumors (Folkman and Klagsbrun, 1987). The VEGF is secreted in large amounts and by tumor cells and stimulates angiogenesis leading to tumor growth and subsequent metastatis (Bergers and Benjamin, 2003; Raghu, 2003).

Angiogenesis-modulating compounds from plants

A wide range of plants contain compounds with angiogenesis-modulating properties (Table 1). The discovery started in early 1970's with the invention of Taxol® from Pacific yew tree (*Taxus brevifolia*) Taxol® kills proliferating cancer cells by disrupting their microtubule cytoskeleton (Mans *et al*., 2000), recently it was proven low picomolar concentration of Taxol® is antiangiogenic, inhibiting

Table 1 Plant derived antiangiogenic compounds. (Source: Tai-ping *et al*., 2006)

Plant species	Compound	Mechanism
Glycine max (soybean)	Genistein	Suppresses VEGF and FGF-2 expression; inhibits receptor tyrosine kinase; inhibits activation of NF-kB and Akt signaling pathways.
Camellia sinensis (green tea)	EGCG	Abrogates VEGF signaling by interfering with formation of VEGF receptor 2 complex.
Vitis spp.(grape)	Resveratrol	Disrupts Src-dependent VE cadherin tyrosine phosphorylation.
P. ginseng	Ginsenosides Rb1, Rb2 and Rg3	Inhibit VEGF production by tumor cells Inhibits tube formation
Glycyrrhiza uralensis (liquorice)	Isoliquiritin	

VEGF production (Avramis *et al*., 2001). Camptothecin isolated from *Camptotheca acuminatas* an anticancer agent used for the past 15 years, Clement *et al* (1998) showed that camptothecin inhibited human EC growth *in vitro.* Angiogenic functional foods provide a good strategy for the prevention of degenerative disease (Losso *et al*., 2005).

Antiangiogenic properties of culinary herbs

Angiogenesis is required for proper nourishment and removal of metabolic wastes from tumor sites. Angiogenesis may be a relevant target to inhibit tumor progression The anti-angiogenic molecules reported to date many are plant compounds, peptides, chemokines, cytokines, nanoparticles siRNA, flavonoids and chalcones monoclonal antibodies, soluble, to vascular growth factors receptors, soluble receptors and fragments derived from extracellular matrix protein. Modulation of angiogenesis is considered as therapeutic strategies of great importance for human health.

Numerous bioactive compounds from plants sources and other anti-angiogenic compounds have anti-angiogenic potential. Those compounds inhibit angiogenesis and metastasis through regulation of multiple signaling pathways. They regulate gene expression of VEGF, MMP'S, EGFR and inhibit NFkB, ERK signaling pathways. Therapeutic angiogenesis, which is aimed at stimulating neovascularization with growth factors is being developed to reverse these conditions. Kaempferol is a natural flavonoid present in many fruits and vegetables, mildly inhibits cell viability but significantly reduces the VEGF gene expression at mRNA and protein levels in both ovarian cancer cell lines. HIF-1α, a regulator of VEGF is down regulated by kaempferol treatment by, and it represses AKT phosphorylation. It inhibits angiogenesis and VEGF expression in human ovarian cancer lines through both HIF-dependent (Akt/KIF) and HIF-independent (ESRRA) pathways (Haitao *et al*., 2009).

A variety of herbs that are traditionally used for anticancer treatment also exhibit antiangiogenic activity through multiple interdependent processes (effects on gene expression, signal processing and enzyme activities). *Artemisia annua, Viscum album, Curcuma longa (curcumin), Scutellaria baicalensis, Magnolia officinalis, Camellia sinensis, Gingko biloba, Poria cocos, Zingiber officinalis, Panax ginseng, Rabdosia rubescens.* For example, *Crinum asiaticum* leaf methanol extract widely investiagted for anti-angiogenesis as a possible mechanism of action for anti-tumour activity (Yusoff et al. 2017). Curcumin decreased migration of EC and down-regulated NFkB and inhibits Ikb kinaes there by suppressing proliferation and inducing apoptosis. The chemo- preventive efficacy of polyphenon-B from tea, on DMBA-dimethylbenzathracene -induced carcinogenesis was reported. Dietary administration of polyphenols reduced the incidence of carcinomas by modulating markers of cell proliferation, cell survival, tumor infiltration, angiogenesis, angiogenesis and apoptosis. Antiangiogenic tripolide isolated from *Tripterygium wilfordi* manifested most potent antiangiogenic activity against vessel formation, m RNA expression of *angiopoeitin* (*angpt)*2 (Ming *et al*., 2009).

The structural differences in angiogenic factors and inhibitors are attributable to differences in receptor-binding affinities, pharmacology, and mechanisms of actions. Ginsenosides, the components from *Panax Ginseng* have pro-angiogenic effects and antiangiogenic effects. Minor structural differences in the ginsenosides enable them to interact differentially with the nuclear receptors leading to opposing effects on angiogenesis. Investigations would lead to the development of specific ligands for the modulation angiogenesis. Simulation of angiogenesis using angiogenesis peptides has produced encouraging results in clinical trials in treating coronary artery diseases.

Blocking angiogenesis with antibodies / peptides / nanoparticles / siRNA /flavonoids/ chalcones of angiogenic factors or with enzyme inhibitors is effective for treating malignancy. Genestein from soyabean exerted angiogenic effect by Inhibiting EC proliferation, suppressing VEGF and FGF-2 expression, inhibiting tyrosine kinase receptor, inhibiting activation of NF-Kb (Peter *et al*., 2004). Epigallocatechin-3-gallate (EGCG) from green tea suppresses oxidant-induced production of the proangiogenic cytokine IL-8, inhibits VEGF-induced Akt activation and VE cadherin phosphorylation at physiological doses (Johnson *et al*., 2010). Pterogynidine (Pt), an alkaloid isolated from the Brazilian flora, *Alchornea glandulosa,* resulted in a drastic reduction in the percentage of EC proliferation and a 17-fold increase in apoptotic cells as compared to controls. Antiproliferative and pro-apoptotic effects of other alkaloids and plant extracts have already been described in cancer cells implying that a similar mechanism is probably occurring in EC as well. Pt reduced EC invasion and indicated the potential of this compound as an anti-angiogenic agent. Squalamine, a natural product isolated from shark *Squalus acanthias*, inhibited angiogenesis and tumor growth in part, by blocking nitrogen-induced proliferation and migration of EC, thus preventing neovascularization of the tumor. Sinomenine (Sn) an alkaloid extracted from Chinese medicinal plant *Sinomenium acutum* disrupted tube formation on the Matrigel (Shanshan *et al*., 2004; Manoj *et al.,* 2011).

Conclusion

Results from our previous studies indicated that Mentha *spicata*, *Ocimum basilicum and Centella asiatica* were able to suppress angiogenesis by markedly inhibiting the vessel growth sprouting from the rat aortic explants. The percentage inhibition of vessel growth for the rat aortic explants treated with *Mentha spicata* was found to be 100% indicating the highest anti-angiogenic potential of the plant. Among the plants investigated, *Mentha spicata* extracts were found to possess the highest antiangiogenic activity, hence the plants were further tested to determine the ability to inhibit HUVEC cell proliferation. *Mentha spicata* extracts were found to inhibit the HUVEC cell growth stating that the antiangigenic mechanism may be by the mode of inhibition of epithelial cell growth.

The reported anti-angiogenic potential of the plants investigated may be due to the presence of terpenoids and flavonoids which was confirmed by preliminary phytochemical and chemical analysis. The molecular mechanisms responsible for the antiangiogenic activity may be associated with inhibition of several steps of angiogenesis including proliferation, migration and tube formation of vascular endothelial cells. Since there is a close relationship between tumor growth and angiogenesis mechanism, various anti-angiogenic compounds for use in cancer treatment have been studied. Angiogenic modulators would be an ideal choice for future chemotherapeutics. The chemo preventive compounds that selectively interfere with particular biochemical alterations occurring in tumor cells or those acting on the highly specialized biology of endothelial cells during neo-vascularization and need to be studied. Understanding the basic principles by which flavonoids inhibit angiogenesis may lead to the development of new therapeutic strategies, in addition to supporting the role of polyphenols as cancer chemo preventive agent. In the present study, *Mentha spicata*, *Ocimum basilicum* and *Centella asiatica* extracts exhibited both cytotoxic and antiangiogenic potential, hence further molecular investigations are warranted to understand the basic principles of the reported activities as well to recommend the plants as suitable candidates for cancer chemotherapeutics and antiangiogenic modulators. Moreover, the plants investigated are culinary herbs, inclusion in the diet may have additional nutritive benefits.

Author contribution

J.R.N., S.S., S.R., H.W.J.C., S.R.N. conceptualized, wrote, reviewed, and edited the manuscript. All authors read and agreed to the published version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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