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The Role of Medicinal Herbs in Angiogenesis Related Diseases

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Abstract: Angiogenesis, the development of new blood vessels from existing one, is essential in normal growth processes. Uncontrolled angiogenesis is a main contributor to a number of disease states such as asthma, AIDS, bacterial infections, autoimmune disease, cirrhosis, diabetes, obesity, multiple sclerosis and endometriosis, Angiogenesis also considered a key step in tumour growth, invasion and metastasis. Angiogenesis is required for suitable nourishment and removal of metabolic wastes from tumour sites. Therefore, modulation of angiogenesis is considered as therapeutic strategies of great importance for human health. Numerous bioactive plant extracts are recently tested for their anti-angiogenic potential. Among the most frequently studied are plants rich with polyphenols and terpens present in fruits, vegetables and other plants which have high antioxidant compounds. Plant polyphenols inhibit angiogenesis and metastasis through regulation of multiple signaling pathways. Specifically, flavonoids regulate expression of Vascular Endothelial Growth Factor (VEGF), matrix metalloproteinase (MMPs), Epidermal Growth Factor Receptor (EGFR) and inhibit nuclear factor _B (NF_B), phosphatidylinositol-3-kinase (PI3-K/Akt) and Extra Cellular Signal-Regulated Kinases 1 and 2 (ERK1/2) signaling pathways, thereby causing strong anti-angiogenic effects. This review focuses on the antiangiogenic plants.

Key words: Angiogenesis, natural products, anti angiogenic plants, antioxidants, polyphenolic compounds

INTRODUCTION

Medicines from plants: Since, ancient times, plants have been used to treat many diseases. However, it was not until the 1800s that pure compounds were isolated from plants, paving the way for modern pharmaceuticals (Fan *et al*., 2006). Isolation of salicylic acid from the bark of the willow tree (*Salix alba*), Felix Hoffmann synthesized aspirin in 1897. Ephedrine was isolated from the Chinese herb mahuang (Ephedra) in 1887 and became popular with American physicians in 1924 for its bronchodilatating and decongestant properties. Sodium cromoglyate, first used in 1968, is a khellin derivative that was isolated from Egyptian khella seeds (*Ammi visnaga*) by Roger Altounyan. The antimalarial drug artemisinin was developed in 1972 from the Chinese herb qinghao (sweet wormwood, *Artemisia annua* L.). These examples illustrate the rich history of plant-based medicines (Fan *et al*., 2006). Angiogenesis is the growth of neovessels from existing vasculature. Usually, angiogenesis is tightly controlled by a balance of angiogenesis factors and inhibitors and occurs only in embryonic development, wound healing and the female menstrual cycle (Folkman, 1971). Angiogenic diseases result from new blood vessels growing either excessively (e.g., cancer, diabetic retinopathy and psoriasis) or insufficiently (e.g., chronic wounds and ischemic heart disease). To date, the stimulation of angiogenesis using angiogenesis peptides has produced encouraging clinical results in treating coronary artery disease. Inhibiting angiogenesis with antibodies of angiogenesis factors or with enzyme inhibitors is effective for treating malignancy. Of particular application to this article is the fact that some of the plant-derived anticancer drugs (e.g., Taxol, camptothecin and combretastatin) are antiangiogenic (Murphy and Docherty, 1992). In traditional Chinese medicine (TCM), many herbs are used in the healing of angiogenic diseases such as chronic wounds and rheumatoid arthritis. Thus, it is important to explore these medicinal plants as a source of new angiomodulators. In this study, many plants were reviewed plant-based angiotherapy.

Essential steps in angiogenesis: The process of angiogenesis can be divided into the following four main steps: (1) degradation of the basement membrane of

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existing blood vessels, (2) migration of these endothelial cells toward the angiogenic stimulus, (3) proliferation of the endothelial cells leading to the creation of solid endothelial cell sprouts in the stromal space and (4) organization of endothelial cells into capillary tubes and vascular loops with the formation of tight junctions and the deposition of new basement membrane (Klagsbrun and Moses, 1999). Angiogenic stimuli lead to increased endothelial cell permeability through dissolution of adherens junctions (Pepper, 2001). Endothelial cell proliferation occurs early in angiogenesis and continues as the new capillary grow elongates. Activation of Phosphoinositide 3-kinase PI3K/Akt promotes endothelial cell survival and proliferation through modulation of numerous cell cycle regulators, including cyclinD1, p27 and Bcl-X2. MAPK signaling pathways (ERK1/2, p38 and JNK) mediate growth factor and mechanical force-induced proliferation of endothelial cells (Pages *et al*., 2000). Proteolysis of basement membrane matricellular components is necessary to encourage endothelial cell invasion into the surrounding interstitial matrix. The degradation of the extracellular matrix is under control of proteolytic enzymes and their inhibitors. The balance between proteases and their inhibitors determines if controlled lyses, leading to angiogenesis, can happen (Vassalli *et al*., 1991). The composition of the extracellular matrix is another vital factor, facilitating or inhibiting angiogenesis. The most important proteolytic enzymes, involved in the process of angiogenesis, belong to two families: the serine proteases, in particular the plasminogen activator/plasmin system and the matrix metalloproteinases (MMPs) (Murphy and Docherty, 1992). MMPs have a great affinity for fibronectin, laminins, elastin and collagens which are the major extra cellular matrix components found in endothelial cell basement membrane and interstitial spaces (Murphy and Docherty, 1992). However, some MMPs act efficiently as fibrinolysins through a plasminogen activator independent pathway (Hiraoka *et al*., 1998). Most MMPs are secreted from the cell as latent enzymes that required cleavage of their amino-terminal propeptide to become active. Plasmin is a potent activator of most MMPs, whereas several active MMPs can also activate latent MMPs (Nagase, 1997). The regulation of MMPs occurs at the transcription level, proenzyme activation and inhibition by specific inhibitors, the TIMPs (Brew *et al*., 2000). The gelatinases MMP-2 and MMP-9 are thought to be major MMPs. MMP-2 is expressed as a latent zymogene, pro-MMP-2, by vascular smooth muscle cells (VSMCs), endothelial cells and macrophages (Pasterkamp *et al*., 2000) and its activation occurs through membrane-type MMPs (MT-MMPs) (Visse and Nagase, 2003). The new sprouts form a lumen by the process of intracellular vascular fusion or by stabilization of several cells around a central lumen. The final step is stabilization of the embryonic capillaries. Angiogenesis is a process requiring the synchronizing action of a variety of growth factors and cell-adhesion molecules in endothelial and mural cells (Bouis *et al*., 2006).

Tumour angiogenesis as a therapeutic target: Angiogenesis is considered a key step in tumour growth, invasion and metastasis. Tumour remain avascular and dormant for years; however, tumour growth can be initiated by neoangiogenesis (Bergers and Benjamin, 2003). The idea of blocking tumour growth by the inhibition of new blood vessels generation was take in consideration. Table 1 shows the diseases characterized by abnormal angiogenesis (Carmeliet, 2003).

Phytochemicals as antiangiogenic compounds: Several hypotheses have been suggested to explain beneficial effects of increased eating of vegetables and fruits on human health. An attractive hypothesis is that vegetables and fruits contain compounds that have protective

Table 1: Diseases characterized by abnormal angiogenesis

Body system	Disease characterized by abnormal angiogenesis
Numerous organs	Cancer and metastasis; infectious diseases; vasculitis and angiogenesis in autoimmune disorders
Blood/lymph vessels	Vascular malformations; DiGeorge syndrome; hereditary hemorrhagic telangiectasia; cavernous hemangioma; cutaneous hemangioma; lymphatic malformations; transplant arteriopathy and atherosclerosis
Adipose tissue	Obesity
Skin psoriasis	Allergic dermatitis; scar keloids; pyogenic granulomas; blistering disease; kaposi's sarcoma in AIDS patients; systemic sclerosis
Eye persistent hyperplastic vitreous syndrome	Diabetic retinopathy; retinopathy of prematurity; choroidal neovascularization
Lung	Primary pulmonary hypertension; asthma; nasal polyps; rhinitis; chronic airway inflammation; cystic fibrosis
GIT	Inflammatory bowel disease and periodontal disease; ascites, peritoneal adhesions; liver cirrhosis
Reproductive system	Endometriosis; uterine bleeding; ovarian cysts; ovarian hyper stimulation
Bone, joints	Arthritis and synovitis; osteomyelitis; osteophyte formation; HIV-induced bone marrow angiogenesis
Kidney	Diabetic nephropathy

effects, independent of those of known nutrients and micronutrients (Lee and Lee, 2006). Plant polyphenols, a large group of natural antioxidants ever-present in a diet high in vegetables and fruits, certainly are serious candidates (Lee and Lee, 2006). They constitute one of the largest and most ubiquitous group of phytochemicals. They are formed to protect plants from photosynthetic stress, reactive oxygen species and herbivory. Polyphenols are an important part of the human diet, with flavonoids.

Flavonoids: Flavonoids are a group of phenolic compounds with antioxidant activity that have been well-known in fruits and vegetables. Although flavonoids are generally considered to be non-nutritive agents, interest in flavonoids has increase because of their potential role in the avoidance of major chronic diseases. More than 6000 different flavonoids have been identified (Harborne and Williams, 2000). Current interest is focusing on the beneficial health effects of flavonoids, because these compounds have many biological activities including antioxidative (Moridani *et al*., 2003) anti-inflammatory (Park *et al*., 2007) gastro-protective (Mojzis *et al*., 2001), cardio-protective (Zern *et al*., 2005) and anticancer (Ren *et al*., 2003). Moreover, it was also found that plant polyphenols may also influence some steps in cancer angiogenesis. Oak *et al*. (2005) documented that Red Wine Polyphenolic Compounds (RWPCs) and Green Tea Polyphenols (GTPs) were able to hinder several key events of the angiogenic process such as proliferation and migration of endothelial cells and vascular smooth muscle cells and the expression of two major pro-angiogenic factors, VEGF and matrix metalloproteinases. Antiangiogenic properties of polyphenols have also been observed in the chick embryo chorioallantoic membrane since the local application of RWPCs and GTPs strongly inhibited the formation of new blood vessels. Red wine polyphenolic compounds can propagate their antiangiogenic effects via inhibition of the platelet-derived growth factor-induced VEGF expression by preventing the redox-sensitive activation of the p38 MAPK pathway (Oak *et al*., 2004) also documented effect of RWPCs on MMP-2 activity. The scientist found that MMP-2 activation by thrombin was strongly prevented by RWPCs in a concentration-dependent manner. Moreover, addition of RWPCs directly to membrane type 1-MMP inhibited its metalloproteinase activity. Finally, RWPCs also inhibited matrix invasion of vascular smooth muscle cells as efficiently as a broad-spectrum MMP inhibitor. Later, they found that from RWPCs, anthocyanins presenting a hydroxyl residue at position 3_ were able to inhibit some steps of angiogenesis. In the anthocyanin class, only delphinidin and cyanidin prevented VEGF release. Both anthocyanines also inhibited phosphorylation of p38 MAPK and JNK in vascular smooth muscle cells (Oak *et al*., 2006). As mentioned above, MMPs degrade extracellular matrix components and contribute to angiogenesis. Green tea polyphenols inhibited gelatinases MMP-2 and MMP-9 from glioblastoma and pituitary tumours and the macrophage elastase MMP-12, but not pancreatic elastase, with low IC_{50s} of 10, 0.6 and 0.3 mg mL^{-1}, respectively. Epigallocatechin-3-gallate EGCG had low IC_{50} values of 0.8 and 6 mM for MMP-9 (Demeule *et al*., 2000). Later, it was observed that EGCG reduced membrane type 1MMP (MT1-MMP) responsible for proMMP-2 activation. The inhibitory effect of EGCG on MT1-MMP was demonstrated by the down-regulation of MT1-MMP transcript levels and by the inhibition of MT1-MMP-driven cell migration of transfected COS-7 cells (Annabi *et al*., 2002). Ability of green tea catechins to influence cancer neovascularization was also documented by Sartippour *et al*. (2002), who found that both mixed green tea extract as well as its individual catechin components are effective in inhibiting breast cancer and endothelial cell proliferation *in vitro*. Cao and Cao (1999) demonstrated inhibition of endothelial growth and angiogenesis in the chorioallantoic membrane assay with epigallocatechin-3-gallate (EGCG) (20 M). They also showed that oral administration of 1.25% green tea to mice inhibited corneal neovascularization stimulated by VEGF. Epigallocatechin-3-gallate was also shown to inhibit the expression of VEGF by colon carcinoma cells, head and neck squamous cells, breast carcinoma cells (Jung *et al*., 2001) investigated the effects of green tea catechins on intracellular signalling and VEGF induction *in vitro* in serum-derived HT29 human colon cancer cells. In this study EGCG Inhibited Erk1 and Erk2 activation in a dose-dependent manner. Moreover, EGCG also inhibited the increase of VEGF expression.

ROLE OF DIET IN ANGIOGENESIS AND CANCER

Dietary habits have been considered as one of the essential etiologic factors that lead to the wide variations in the risk and incidence of cancers (Hong and Sporn, 1997; Chan *et al*., 1998; Lippman and Hong, 2002). It has been shown through epidemiological studies that consumption of fiber rich diet with low lipid content and yellow-green vegetables is associated with the reduced risk of cancer (Hong and Sporn, 1997; Chan *et al*., 1998; Singh and Lippman, 1998; Sporn and Suh, 2000; Gupta and Dubois, 2000; Lippman and Hong, 2002). Dietary factors could be an important component in

regulating tumor dormancy as they have an important impact on cellular physiology and homeostasis and hence could influence the equilibrium between anti- and pro-angiogenic factors. It has also been shown that energy rich diets composed of meat, dairy products, processed food with refined carbohydrates and less fibers along with lower consumption of fruits and vegetables are directly correlated with higher incidence and death of cancer (Yu *et al*., 1995; Whittemore *et al*., 1995; Hong and Sporn, 1997; Chan *et al*., 1998; Clinton *et al*., 1988; Gupta and Dubois, 2000; Tsubono *et al*., 2001; Lippman and Hong, 2002). Dietary restrictions in various studies on animal models with limitation of fat or carbohydrate consumption reduce the levels of IGF-1 in circulation and suppress VEGF expression and tumor angiogenesis in prostate cancer (Mukherjee *et al*., 1999). It has been reported that high microvascular blood is associated with high glucose uptake and tumor angiogenesis in human gliomas (Aronen *et al*., 2000). Dietary restriction has shown to suppress angiogenesis and induce apoptosis in mouse tumor models (Mukherjee *et al*., 2002). Omega-3-fatty acid-rich diets suppress tumour growth and angiogenesis while Omega-6-fatty acid-rich diets promote tumor growth (Clinton *et al*., 1988; Rose and Connolly, 1991; Wang *et al*., 1995; Rose and Connolly, 2000). Hence, the identification of pro- and anti-angiogenic dietary components could be a potential strategy for cancer prevention and control.

ANTIANGIOGENIC CANCER CHEMOPREVENTIVE AGENTS

Huge numbers of chemopreventive agents have been shown to possess anticancer activities in many studies. These agents achieve anticancer activities through different mechanisms by targeting different aspects of cancer progression and development. Since angiogenesis is pre-requisite for the growth of solid tumours, vascular targeting has been explored as a potential strategy to suppress tumor growth and metastasis. In this regard, many phytochemicals have been shown to target tumour angiogenesis using *in vitro* and *in vivo* model systems (Fotsis *et al*., 1997; Paper, 1998; Cao *et al*., 2002; Tosetti *et al*., 2002; Dorai and Aggarwal, 2004). An account of such studies showing antiangiogenic activity of various phytochemicals/ chemo-preventive agents is shown in Table 2.

Table 2: Antiangiogenic effects of various natural chemopreventive agents

Natural chemo preventive agents	Anti-angiogenic effect
Alpha-difluoromethylornithine	Inhibits *in vitro* growth of both HUVEC as well as angio-endothelial cells in human gastric cancer model Apigenin Inhibits hypoxia-inducible factor 1-alpha and VEGF expression in human ovarian cancer cells. Inhibits *in vitro* angiogenesis
Chrysobalanus icaco extract	Inhibits angiogenesis in chorioallantoic membrane assay
Curcumin	Down regulates transcript levels of VEGF and bFGF and suppresses VEGF, MMP-2 and MMP-9 expression, NF-jB, COX-2 and MAPKs activity
Deguelin	Inhibits endothelial cell growth, survival, migration, invasion and metalloprotease production
Epicatechin/epicatechin gallate	Inhibits *in vitro* and *in vivo* angiogenesis
Epigallocatechin-3-gallate	Inhibits ephrin-A1-mediated endothelial cell migration and tumor vasculature in HT29 xenograft Suppresses ERK1/2 activity and inhibits expression and secretion of VEGF in colon cancer cells. Suppresses MMP-2/9 expression and activation in TRAMP model, along with inhibition of COX-2 expression, iNOS and NF-jB activity in other tumor models Inhibits VEGF-induced tyrosine phosphorylation of Flk-1/KDR in endothelial cells
Fisetin/luteolin	Inhibit bFGF-induced corneal neo-vascularization
Flavopiridol	Inhibits endothelial cell growth via suppression of hypoxia-induced expression of VEGF in human neuroblastoma and monocytes
Genistein	Down-regulates MMP-9 and up-regulates TIMP-1 Suppresses endothelial cell proliferation, migration and invasion Inhibits VEGF and COX-2 expression and suppresses VEGF-induced tyrosine phosphorylation of receptor kinases
Green tea extract	Decreases transcript levels of bFGF in breast cancer cells and inhibit angiogenesis *in vitro* and *in vivo* models Inhibits uPA expression in TRAMP model
3'-Hydroxyflavone/3',4'-dihydroxyflavone/2', 3'-dihydroxyflavone	Suppresses *in vivo* angiogenesis
Isoliquiritin	Inhibits *in vitro* capillary tube formation and *in vivo* angiogenesis
Isomers of conjugated linoleic acid	Inhibit angiogenesis *in vitro* as well as *in vivo* by suppression of formation of microcapillary networks Suppression of both serum and mammary gland VEGF concentration in breast cancer model
Linomide	Inhibits angiogenesis induced by angiogenesis growth factors in matrigel assays in prostate, seminal vesicle and breast carcinoma rodent models Livistona chinensis (aquous extract) Inhibits *in vitro* proliferation of endothelial cells
Magnosalin	Inhibits *in vivo* angiogenesis
OXO [6-(1-oxobutyl)-5,8-dimethyl –1,4-napthoquinone]	Inhibits proliferation and capillary differentiation on HUVECs as well as downregulates hypoxia induced expression of HIF-1 and VEGF in lung cancer model

Table 2: Continued

Natural chemo preventive agents	Anti-angiogenic effect
Phenethyl isothiocyanate	Inhibits *ex vivo* angiogenesis in CAM assay Lowers survival rate of HUVEC cells, inhibits capillary-like tube formation and migration of HUVEC Cells Inhibits VEGF secretion and lowers VEGF-R expression levels Philinopside A Inhibits HMECs proliferation, migration and tube formation and receptor tyrosine kinases like VEGF-R
Polypodium leucotomos extract	Inhibits *in vivo* angiogenesis in mouse model
Quercetin	Inhibits MMP-2 and MMP-9 secretion from tumor cells and suppresses endothelial cell proliferation, migration and tube formation
Resveratrol/heyneol (tetramer of resveratrol)	Inhibits capillary-like tube formation by HUVEC and capillary differentiation and VEGF binding to HUVEC. It inhibits NF-jB signaling
Retenoic acid	Suppresses production of IL-8 in head and neck carcinoma Inhibits responsiveness of endothelial cells to angiogenic growth factors
Selenium	Suppresses VEGF expression, lowers microvessel density and inhibits genolytic activity of MMP-2 in rat mammary carcinoma Initiates apoptotic death in HUVEC cells
Silibinin	Inhibits growth and survival of endothelial cells via disrupting VEGF and IGF-1 signaling, Inhibits RTK signaling and MAPK/ERK1/2 activation in human epithelial carcinoma cells, Inhibits IKKa kinase activity and NF-jB activity in human prostate carcinoma DU145 cells, Inhibits MMP-2 expression and tube formation in HUVEC, Suppresses expression of uPA in A549 lung cancer cell line
Silymarin	Inhibits VEGF secretion in prostate and breast cancer cells and tube formation by endothelial cells, Inhibits RTK signaling and MAPK/ERK1/2 activation in human epithelial carcinoma cells, Inhibits MMP-2 expression and tube formation in HUVEC
Soy phytochemical concentrate	Inhibit tumor angiogenesis and cell proliferation in bladder carcinoma
Sulfated beta (1 > 4) galacto-oligosaccharides	Inhibit angiogenesis via interaction with FGF-2 in chorioallantoic membrane assay
Taxotrene	Inhibits endothelial cell migration and angiogenesis
Torilin	Inhibits neo-vascularization in bFGF-induced vessel formation in mouse and chorioallantoic membrane in chick embryo models, Down-regulates hypoxia-induced expression of VEGF and IGF-II in HepG2 human hepatoblastoma cells
Viscum album coloratum (aquous extract)	Inhibits angiogenesis in CAM assay and metastasis, Vitamin K2 Inhibits endothelial cell tubular formation and endothelial cell proliferation

Dietary conjugated linoleic acid has been shown to inhibit angiogenesis *in vivo* as well as *in vitro* (Masso-Welch *et al*., 2002, 2004). It has been found that conjugated linoleic acid isomers (c9, t11 and t10, c12) were equally effective in inhibiting the formation of micro-capillary networks by mammary stromal vascular cells *in vitro* and mixed conjugated linoleic acid isomer preparation has been shown to inhibit angiogenesis *in vivo*. Mixed conjugated linoleic acid isomer preparation also decreased both serum and mammary gland VEGF concentration *in vivo* in breast cancer model (Masso-Welch *et al*., 2004). An oriental herbal cocktail, ka-mi-kae-kyuktang (formula of ten oriental herbs) has been reported to suppress the vascular endothelial responses by inhibiting bFGF-induced ERK1/2 phosphorylation, cell migration as well as capillary tube formation in the Human Umbilical Vein Endothelial Cells (HUVEC) and it also decreases hypoxia-induced HIF-1alpha and VEGF expression in mouse Lewis Lung Carcinoma (LLC) cells *in vitro* and suppresses bFGF-induced angiogenesis in chick chorioallantoic membrane model and in the Matrigel plugs in mice (Lee *et al*., 2006, 2007). Phenyl isothiocyanate (PEITC), a constituent of many edible cruciferous vegetables, causes a decrease in the survival of HUVEC in a concentration and tissue-dependant manner. PEITC inhibits the capillary- like tube formation and migration via suppression of VEGF secretion and down-regulation of VEGF receptor (Xiao and Singh, 2007). Sulforaphane and aliphatic isothiocyanate present in cruciferous vegetables decrease newly formed micro-capillaries *in vitro* in HMEC1 (an immortalized human micro-vascular endothelial cell line) and also inhibits hypoxia-induced transcription of VEGF, HIF-1alpha along with the suppression of VEGF receptor KDR/flk1 and MMP-2 (Xu *et al*., 2005).

CONCLUSIONS

Phytochemicals-mediated antiangiogenic intervention is a future area of research that promises a useful cancer prevention strategy. Phytochemicals that inhibit the pathological angiogenesis could have potential applications in cancer prevention and therapy as well as in other diseases with similar etiology. Chemopreventive phytochemicals are generally non-toxic and hence will produce no or minimum side effects, if any. Also, endothelial cells lack induced drug resistance and therefore, angio-prevention could be favored strategy for cancer control in comparison to other therapies such as radiotherapy and chemotherapy (Al-Douh *et al*., 2010). Since, angiogenesis is critically important for wound-healing, acute injury healing, healing of chronic ulceration of the gastrointestinal mucosa and others, phytochemicals that inhibit tumor angiogenesis might also inhibit physiological angiogenesis and produce

critical side effects. Recently many plants in South East Asia particularly in Malaysia have been studied and approved as antiangiogenic plants using different extracts such as the methanolic leave extract of *Orthosiphon staminneus* Benth by Sahib *et al*. (2009a, b) Siddiqui *et al*. (2009) and Aisha *et al*. (2009) and the mechanisms of action have been verified but the data has not been published yet, in conclusion, antiangiogenic chemopreventive phytochemicals should be studied and analyzed for their selective targeting of tumor.

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