Medicinal herbs and their phytochemicals are potential novel leads for developing antiangiogenic drugs. This review aims to assess the current status of research with medicinal herbs and their phytochemicals for the development of antiangiogenic agents for cancer and other angiogenesis-related diseases including inflammation, diabetic retinopathy, endometriosis and obesity. Most studies reviewed have focused on vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor 2 (VEGFR-2) signaling for endothelial response processes and have led to the identification of many potential antiangiogenic agents. Since human clinical trials with antiangiogenic modalities targeting VEGF/VEGFR-2 signaling have shown limited efficacy and occasional toxic side effects, screening strategies for herbal phytochemicals based on other signaling pathways important for cancer-endothelial and stromal crosstalks should be emphasized in the future. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: medical herbs; phytochemicals; antiangiogenesis; angiogenic diseases; VEGF/VEGFR.

INTRODUCTION

Angiogenesis is the process involving the growth of new blood vessels from pre-existing vessels (Carmeliet and Jain, 2000). While physiological angiogenesis takes place mainly during wound healing and menstrual cycle events of the female reproductive tract (Gordon et al., 1995; Risau, 1997), pathological angiogenesis occurs in diseases such as cancer, rheumatoid arthritis (RA), endometriosis and diabetic retinopathy. An abnormal or excessive level of angiogenesis also contributes to vascular malformation, obesity, chronic inflammation, whereas insufficient angiogenesis is related to Alzheimer’s disease, coronary artery disease, stroke, myocardial infarction and ulcer formation (Carmeliet and Jain, 2000; Carmeliet, 2003).

Angiogenesis inhibitors and promoters are potential drugs for treating angiogenesis-related disorders. Because of the critical dependence of solid cancers on neo-angiogenesis for growth, progression and metastasis (Wary et al., 2003), it was no surprise that major academic and industrial research and development efforts have been made in the past two decades for angio-therapy modalities for cancer worldwide. Clinical trials in the past few years with antiangiogenic modalities targeting the vascular endothelial growth factor A (VEGF-A)/vascular endothelial growth factor receptor 2 (VEGFR-2) using inactivating monoclonal antibodies or VEGFR-2 kinase inhibitor drugs as single agents or in combination with chemotherapy have shown survival benefit in cancer patients of an increasing number of advanced stage malignancies with many major challenges ahead (Ellis and Hicklin, 2008). With these recent clinical developments as a backdrop, we review the antiangiogenic properties of some medicinal herbs and phytochemicals to highlight the current status of natural products research and to provide guidance on the development of angiogenesis inhibitors from medicinal plants in the future.

FUNDAMENTALS OF ANGIOGENESIS

The angiogenic responses involve many biochemical and molecular signaling events resulting in coordinated and complex cellular processes such as endothelial cell proliferation, directional migration, basement membrane degradation and remodeling by matrix metalloproteinase (MMP), especially MMP-2, capillary tube formation and differentiation, pericyte recruitment and maturation (Bussolino et al., 1997). Overproduction of angiogenic factors and/or down-regulation of angiogenesis inhibitors usually accompany and drive tumor angiogenesis. VEGF is a potent pro-angiogenic factor crucial for tumor vascular development (Keck et al., 1989; Ferrara and Davis-Smyth, 1997; Ellis and Hicklin, 2008) and strongly induced by hypoxia that is a common feature of solid cancer. Of the VEGF families of proteins, VEGF-A isoforms such as VEGF_{165} and VEGF_{121} exert mitogenic and pro-angiogenic actions on the
endothelial cells via binding to membrane protein tyrosine kinase-receptors expressed on endothelial cells, including VEGFR-1 (also known as Flt-1 for Fms-like tyrosine kinase-1) and VEGFR-2 (also known as Flk-1 for fetal liver kinase-1 or KDR for kinase insert domain containing receptor) (Bernatchez et al., 1999; Ellis and Hicklin, 2008; Fischer et al., 2008). VEGFR-2 is by far the most important receptor for VEGF-A signaling in vascular endothelial cells (Takahashi and Shibuya, 1997).

In addition to VEGFs being direct ligands for activating endothelial cells, many other growth factors produced by cancer cells and other cell types act in paracrine fashion as well as by the activated endothelial cells in autocrine or paracrine fashion stimulate angiogenesis, many through upregulating VEGF production. Many endogenous inhibitory proteins have been identified such as endostatin, thrombospondin etc (Furumatsu et al., 2002; Schuch et al., 2005; Zhang and Lawler, 2007; Mahapatra, 2008). The following section reviews briefly endothelial response processes and signaling pathways to provide a framework for evaluating published work concerning how herbs and phytochemicals have been evaluated for antiangiogenic activities.

ENDOTHELIAL RESPONSES AND ASSAY MODELS FOR SCREENING POTENTIAL ANTIANGIOGENIC AGENTS

As mentioned above, angiogenesis is a complex process involving many factors such as proliferation, migration and differentiation of endothelial cells, degradation of extracellular matrix (ECM) and basement membrane, and maturation of the new blood vessels (Bussolino et al., 1997; Carmeliet and Jain, 2000; Griffioen and Molema, 2000; Bergers and Benjamini, 2003). Various in vitro and in vivo assays have been utilized to analyse angiogenesis experimentally. In general, basic fibroblast growth factor (bFGF) and VEGF are widely used as angiogenic activators in both in vitro and in vivo studies. In vitro, human umbilical vein endothelial cells (HUVECs) are isolated from fresh human umbilical cord veins by collagenase treatment (Jaffe et al., 1973) and their proliferation is determined by viability assays such as 2, 3-bis (2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino) carbonyl]-2H-tetrazolium hydroxide (XTT) (Jost et al., 1992), 3-[4,5-dimethyl(thiazol-2-yl)-3,5-diphenyl] tetrazolium bromide (MTT) (Carmichael et al., 1987) or bromophenoluridine (BrDu) incorporation assay in the absence or presence of bFGF or VEGF. Chemotactic migration or motility of HUVECs is assayed by the wound-healing assay or microchemotaxis chambers (Choi et al., 2007) or transwell (Pyun et al., 2008). Differentiation is determined by tube formation assay using HUVEC seeded on Matrigel with or without angiogenic activator (Grant et al., 1992). In vivo, chorioallantoic membrane (CAM) assay is performed to measure the number of newly formed blood vessels around angiogenic factor treated disc (Folkman, 1984) as exemplified in our study (Huh et al., 2005). The Matrigel plug assay is widely performed in C57BL/6 mice subcutaneously inoculated with angiogenic factor-treated Matrigel and the content of hemoglobin is measured in the Matrigel plugs to indirectly quantify functional new blood vessel formation (Passaniti, 1992; Lee et al., 2006a). Similarly, tumor-induced angiogenesis assay can be assessed by the detection of neovascularization around intradermally inoculated tumor cells (Runkel et al., 1991). Taken together, these angiogenesis experimental tools can be useful for antiangiogenic activity screening with phytochemicals, herbal extracts and formulas.

CLINICAL EXPERIENCE WITH CURRENT ANTIANGIOGENICS

Clinical trials in the past few years with antiangiogenic modalities such as angiotatin, endostatin, solimastat, bevacizumab and angizyme targeting the VEGF-A/VEGFR-2 with inactivating monoclonal antibodies or VEGFR-2 kinase inhibitor drugs as single agents or in combination with chemotherapy have shown survival benefit in cancer patients of an increasing number of advanced stage malignancies (Ellis and Hicklin, 2008). For instance, the addition of bevacizumab to chemotherapy of metastatic colorectal cancer prolonged median progression free survival (PFS; HR 0.61, 95% CI 0.51–0.73) in five trials including 3101 patients (Wagner et al., 2009). However, major hurdles for clinical implementation include limited efficacy, rapid development of resistance to the antiangiogenic modalities and in rare cases severe toxicity, arising from VEGF-A/VEGFR-2 ablation-induced severe hypoxia and its complications (Ellis and Hicklin, 2008). On the other hand, VEGFR-1 is expressed in not only endothelial cells, but also in many other cell types, such as macrophages, stromal cells, pericytes, smooth muscle cells, tumor cells, dendritic cells, bone marrow progenitors and leukemic cells (Hoeben et al., 2004; Fischer et al., 2008). VEGFR-1 binds placental growth factor (PIGF) and VEGF-B in addition to VEGF-A. Naturally occurring soluble non-signaling VEGFR1 or genetically engineered VEGFR1 serve as traps for VEGF-A due to the much tighter binding than VEGFR-2 for VEGF-A (Hoeben et al., 2004; Fischer et al., 2008). As more mechanistic studies reveal that the ligand specificity and signaling consequences for the VEGFRs are not equivalent and important cross-talks among different ligand-VEGFR signaling cascades within and among endothelial and many other cell types comprise the tumor angiogenesis environment, approaches targeting other VEGFRs and ligand signaling may complement the existing VEGF/VEGFR-2 antiangiogenesis modalities to improve the cancer treatment efficacy and patient safety (Ellis and Hicklin, 2008; Fischer et al., 2008). While monoclonal antibodies and other biological agents are being developed and tested against these un-conventional targets (Fischer et al., 2008), small molecular compounds that target different VEGFRs may add to the arsenal of novel antiangiogenesis drug leads.

Although many medicinal herbals and phytochemicals have recently been evaluated for antiangiogenic properties (Table 1), most of the screening and investigations focused on VEGF-A/VEGFR-2- or bFGF-induced signaling and processes. Screening assays based on other targets (Fischer et al., 2008) are necessary to complement existing approaches.
<table>
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<td><em>Flavonol</em></td>
<td>Quercetin</td>
<td><em>Rosa multiflora</em></td>
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<td>$&gt;$100 µM</td>
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<td>Fisetin</td>
<td><em>Gleditsia japonica</em></td>
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<td>Inflammatory angiogenesis</td>
<td>$-2.0$ µM</td>
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<td>Endometriosis-related angiogenesis</td>
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<td>Apigenin</td>
<td><em>Hydnocarpus</em></td>
<td>Hydnocarpi Semen</td>
<td>Corneal neovascularization</td>
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<td>Morelloflavone</td>
<td><em>Hovnia dulcis</em></td>
<td>Hoveniae Semen Cum</td>
<td>Tumor angiogenesis</td>
<td>$&lt;$20 µM</td>
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<td>Jeon <em>et al.</em>, 2005</td>
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<td>Epigallocatechin gallate</td>
<td><em>Thea sinensis</em></td>
<td>Theae Follium</td>
<td>Tumor angiogenesis</td>
<td>6.5–25 µM</td>
<td>Dona <em>et al.</em>, 2003; Xu <em>et al.</em>, 2009; Büchler, 2004; Wang, 2005</td>
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<td><em>Isoflavone</em></td>
<td>Genistein</td>
<td><em>Pueraria lobata</em></td>
<td>Puerariae Radix</td>
<td>Tumor angiogenesis</td>
<td>$-10$ µM</td>
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<td><em>Punica granatum</em></td>
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<td><em>Geranium thunbergii</em></td>
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<td><em>Paeonia lactiflora</em></td>
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<td>Labrecque <em>et al.</em>, 2005</td>
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<td>Phenolic acids</td>
<td>Gallic acid</td>
<td><em>Euphorbia pekinensis</em></td>
<td>Paoniae Radix</td>
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<td>$=4$ µM</td>
<td>Lee, 2004; Huh <em>et al.</em>, 2005; Zhang <em>et al.</em>, 2009</td>
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<td>Ellagic acid</td>
<td>1,2,3,4,6-penta-O-galloyl-β-D-glucose (PGG)</td>
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<td>Other non-flavonoid polyphenolics</td>
<td>Resveratrol (Stilbene)</td>
<td><em>Veratum album</em></td>
<td><em>Veratrumae Radix</em></td>
<td>Tumor angiogenesis</td>
<td>0.7 ± 0.1 µM</td>
<td>Chen et al., 2006; Bishayee, 2009; Bertelli, 2001</td>
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<td>Morus alba</td>
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<td>Inflammatory angiogenesis</td>
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<td>Curcumin</td>
<td><em>Curcuma longa</em></td>
<td><em>Curcumae Longae Radix</em></td>
<td>Tumor angiogenesis</td>
<td>~40 µM</td>
<td>Lin, 2007; Kunnunakkara, 2008; Binion, 2008</td>
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<td></td>
<td><em>Curcuma zedoaria</em></td>
<td></td>
<td><em>Zedoariae Rhizoma</em></td>
<td>Adipokine-induced angiogenesis</td>
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<td>Ejaz et al., 2009</td>
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<td></td>
<td><em>Alpinia oxyphylla</em></td>
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<td><em>Alpiniae Fructus</em></td>
<td>Inflammatory angiogenesis</td>
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<td>TERPENES</td>
<td>Campesterol (Phytosterol)</td>
<td><em>Gastrodia elata</em></td>
<td><em>Gastrodiae Rhizoma</em></td>
<td>Tumor angiogenesis</td>
<td>~25 µM</td>
<td>Jackson, 2006</td>
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<td>INDOLES</td>
<td>Sulforaphane</td>
<td><em>Raphanus sativus</em></td>
<td><em>Raphani Semen</em></td>
<td>Tumor angiogenesis</td>
<td>~5 µM</td>
<td>Jackson, 2007; Yao et al., 2008</td>
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<td>PYRANOCOUMARINS AND SIMPLE COUMARINS</td>
<td>Decursin</td>
<td><em>Angelica gigas</em></td>
<td><em>Angelicae Gigantis Radix</em></td>
<td>Tumor angiogenesis</td>
<td>&lt;10 µM</td>
<td>Lee et al., 2009b; Jung et al., 2008; Son, 2009</td>
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<td>Decursinol angulate</td>
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<td>Tumor angiogenesis</td>
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<td>Scopolin</td>
<td><em>Scopolia japonica</em></td>
<td><em>Scopoliae Rhizoma</em></td>
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<td>Decurisnol</td>
<td><em>Morus alba</em></td>
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<td>Tumor angiogenesis</td>
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<td>MISCELLANEOUS</td>
<td>11,11′-dideoxyverticillin</td>
<td><em>Shiraia bambusicola</em></td>
<td><em>Mori Folium</em></td>
<td>Tumor angiogenesis</td>
<td>~1 µM</td>
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<td>Celastrol</td>
<td><em>Tripterygium wilfordii</em></td>
<td><em>Tripterygiumae Radix</em></td>
<td>Tumor angiogenesis</td>
<td>~100 nM</td>
<td>Huang, 2003; Tao, 2003; He, 2009</td>
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<td>Erinin</td>
<td><em>Dendrobium chrysotoxum</em></td>
<td><em>Dendrobia Stipes</em></td>
<td>Tumor angiogenesis</td>
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<td>Pediculariside G</td>
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<td><em>Pedicularis Herba</em></td>
<td>Tumor angiogenesis</td>
<td>~100 µM</td>
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<td>Shiraiachrome A</td>
<td><em>Shiraia bambusicola</em></td>
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<td>Tumor angiogenesis</td>
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<td>Thymoquinone</td>
<td><em>Nigella sativa</em></td>
<td><em>Nigellae Semen</em></td>
<td>Tumor angiogenesis</td>
<td>&lt;100 nM</td>
<td>Arbiser, 2007</td>
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FARNESIFEROL C (FC) REPRESENTS A NOVEL CLASS OF COMPOUNDS THAT TARGET BOTH VEGFR-1 AND VEGFR-2 SIGNALING

The hypothesis was examined that novel antiangiogenic activities of FC from *Ferula assafoetida* contribute to anticancer efficacy (Lee et al., 2010). In HUVECs, exposure to the 10–40 µmol/L concentration range of FC inhibited VEGF-induced cell proliferation, migration, invasion, tube formation and the expression of MMP-2. In addition, FC inhibited the angiogenic sprouting of VEGF-treated rat aorta in an ex vivo model. Furthermore, FC inhibited the in vivo growth of mouse Lewis lung cancer (LLC) allograft model by 60% ($p < 0.001$) at a daily i.p. dosage of 1 mg/kg body weight without any negative effect on the weight of the host mice. Immunohistochemistry staining showed decreased microvessel density (CD34) and proliferative index (Ki-67) without affecting the apoptotic (terminal deoxyadenosine-5′-triphosphate nick end labeling) index. Mechanistically, FC decreased the binding of VEGF to VEGFR-1/Fit-1, but not to VEGFR-2/KDR/Flk-1. In terms of early signaling, FC exerted a rapid inhibitory action (examined within 10 min) on VEGF-induced autophosphorylation of VEGFR-1 without affecting that of VEGFR-2. Nevertheless, FC decreased the phosphorylation of most of the kinases downstream of VEGFR-2: focal adhesion kinase (FAK), Src, ERK 1/2, p38 MAPK and JNK without affecting Akt. Computer simulation suggests that FC may inhibit Src or FAK protein activities directly through its docking to their ATP-binding sites. Taken together, the multitargeting actions of FC, particularly VEGFR-1 inhibition, suggest a novel drug candidate to complement current VEGF/VEGFR-2-targeting antiangiogenic modalities for cancer.

ANTIANGIOGENETIC ACTIVITIES OF MEDICINAL HERBS AND PHYTOCHEMICALS IN CANCER

Some medicinal herbs and various compounds have been evaluated for antiangiogenic as well as anticancer activities. Naturally occurring gallotannins, penta-1,2,3,4,6-O-gallloyl-beta-d-glucose (PGG) isolated from Gallnut of *Rhus chinensis* MILL was reported to inhibit the proliferation, migration and tube formation of endothelial cells (Huh et al., 2005; Zhang et al., 2009) and also induce apoptosis in prostate cancer cells (Hu et al., 2008; Hu et al., 2009). Antiangiogenic activities have been reported for paeconol (Kim et al., 2009c), shikonin (Lee et al., 2008), campesterol (Choi et al., 2007), heynanol A (Lee et al., 2006a), 6-(1-oxobutyl)-5,8-dimethoxy-1,4-naphthoquinone (Lee et al., 2007), Korean Angelica gigas (Lee et al., 2009a) and herbal formulations such as Kamkaekyuktang (Lee et al., 2006b), Shiquandabutangjiaweibang (Kim et al., 2005) and Bojungbangdoktang (Kim et al., 2009b). In addition, Wang and colleagues demonstrated that feiyannang decoction (FD), a traditional Chinese herbal mixture, has inhibitory effects on angiogenesis by down-regulating the transcription factor nuclear factor kappa B (NF-kB), survival protein Akt and hypoxia inducible factor 1-alpha (HIF-α) in A549 lung cancer cells (Zhang et al., 2008; Wang et al., 2009). Resveratrol, a natural polyphenol, has been reported to suppress angiogenesis in rat glioma and other cancers (Chen et al., 2006; Bishayee, 2009). Furthermore, the inhibitory effect of morelloflavone on tumor angiogenesis was found to occur through the targeting of Rho guanosine triphosphatases (GTPases) and extracellular signal-regulated kinase (ERK) (Pang et al., 2009). Yi and colleagues reported that thymoquinone and gambogic acid decreased cell proliferation, migration, invasion and tube formation by suppressing the Akt pathway in human HUVECs and human prostate cancer cells (PC-3) (Yi et al., 2008a, 2008b). Significantly, vascular endothelial growth factor (VEGF) and/or its receptor were down-regulated or inhibited by numerous phytochemicals, including sulforaphane (Yao et al., 2008), celastrol (Huang et al., 2008), aplidin (Straight et al., 2006), meisoinodig (Xiao et al., 2006), 4-O-methygallic acid (Jeon et al., 2005), ellagic acid (Labrecque et al., 2005), delphinidin (Lamy et al., 2008), curcumin (Ejaz et al., 2009) and philinopside A (Tong et al., 2005).

Although it has been well established that angiogenesis plays a significant role in the tumorigenesis of solid tumors, recent studies have shown the critical role of angiogenesis in suspension leukemic cells (Letilovic et al., 2006; Xu et al., 2006). There is growing evidence that angiogenic factors such as bFGF, VEGF and VEGF-R are increased in leukemic cell lines and patients (Leung et al., 1989; Kato et al., 1995; Perez-Atayde et al., 1997) and also are involved in hematopoietic regulation (Hattori et al., 2001). In this regard, He and his colleagues reported that antisense-VEGF decreased VEGF protein expression and inhibited the growth of chronic myelogenous leukemia (CML) K562 cells and injection of antisense-VEGF expressing K562 cells into nude mice decreased the microvessel density of the bone marrow compared with untreated control (He et al., 2003).

Several natural products were reported to exert antiangiogenic effects against leukemia cells. For instance, mastic oil from *Pistacia lentiscus* var. chia attenuated angiogenesis by inhibiting VEGF expression and inhibited the cell growth and survival via the downregulation of ERK1/2 in K562 cells (Loutrari et al., 2006). Meisindigo, a compound from the Indigo plant *Isatis* also showed an antileukemic effect on CML through decreasing VEGF secretion as well as inhibiting tube formation of HUVECs in an in vitro Matrigel model (Xiao et al., 2006). Similarly, artemesunate, a derivative of artemisinin extracted from *Artemisia annua*, inhibited angiogenesis and VEGF expression in K562 cells in vitro and in vivo (Zhou et al., 2007). Overall, many herbs and their compounds have the potential of antiangiogenic activity in leukemia cells.

ANGIOGENESIS AND INFLAMMATION

Inflammatory cytokines are closely linked to angiogenesis (Krupinski et al., 2008). Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, IL-8 and monocyte chemotactant protein (MCP)-1 strongly promote chronic inflammation of rheumatoid arthritis (RA) and inflam-
mation-related angiogenesis (Koch et al., 1992; Harris, 1994; Feghali and Wright, 1997; Maruotti et al., 2006). Specifically, RA is characterized by endothelial cell proliferation and angiogenesis, leukocyte activation and pannus formation (Feldmann, 1996; Firestein, 2003). Therefore, angiogenesis inhibitors could be indicated to treat inflammatory arthritis (Schöttler and Brahn, 2009). Indeed, scopolin isolated from the stems of herbal plants such as Scopolia japonica is one of several coumarin constituents used for the therapy of RA (Silvan et al., 1996). Recent studies support the antiangiogenic and antirheumatic effects of scopolin on adjuvant-induced arthritis in rats (Pan et al., 2009). Scopolin reduced the expression levels of IL-6, VEGF and basic fibroblast growth factor (bFGF)-2 in rat synovial tissue. Similarly, fisetin and paeoniflorin showed inhibitory effects on inflammation and angiogenesis (Zheng et al., 2007; Lee et al., 2009b), and decreased the levels of IL-1β-induced inflammatory cytokines (TNF-α, IL-6)/chemokines (IL-8, MCP-1) and VEGF during RA in fibroblast-like synovial cells (FLS). Fisetin also reduced the levels of phospho-ERK, c-jun N-terminal kinase (JNK) and activated p38 mitogen-activated protein kinase (MAPK) along with the incidence and severity of collagen-induced arthritis (Lee et al., 2009b). Additionally, paeoniflorin inhibited inflammation and decreased the expression of IL-1β, IL-6, VEGF and granulocyte macrophage colony stimulating factor (GM-CSF) (Zheng et al., 2007). Dell’Aica and colleagues reported that hyperforin, a polyphenol-derivative of St John’s wort (Hypericum perforatum) extract, reduced IL-8-induced angiogenesis and bleomycin-induced inflammation in a murine model (Dell’Aica et al., 2007). Similarly, epigallocatechin-3-gallate (EGCG), the most abundant catechin of green tea, blocked neutrophil-mediated angiogenesis in an in vivo inflammatory angiogenesis model (Dona et al., 2003). Shirayaichrome A from the Chinese bamboo fungus Shirayabambusicola, which has been used for the treatment of RA as well as cancer in traditional Chinese medicine, exerted antiangiogenic effects on human microvascular endothelial cells (Tong et al., 2004). Collectively, this evidence suggests that many herbs and their phytochemicals may exert both antiangiogenic effects and antiinflammatory activity.

ANGIOGENESIS AND DIABETIC RETINOPATHY

Proliferative diabetic retinopathy is a vision-related complication of diabetes mellitus caused by too much angiogenesis (Jardeleza and Miller, 2009). Recently, caffeic acid, a phenolic compound present in vegetables, fruits and coffee, was reported to inhibit VEGF-induced proliferation, migration and tube formation of retinal endothelial cells by suppressing reactive oxygen species (ROS)-induced VEGF expression (Kim et al., 2009a). Chen and colleagues reported that querceitin (3,5,7-pentahydroxy flavone), found in various fruits and vegetables, inhibits proliferation, migration and tube formation of rhesus choroids-retina endothelial cell line RF/6A (Chen et al., 2008). Similarly, hypericin, an active ingredient in St John’s Wort, inhibited retinal neovascularization through the down-regulation of ERK in a mouse model of oxygen-induced retinopathy (Higuchi et al., 2008). Collectively, these data support the potential therapeutic effects of diverse herbal compounds on diabetic retinopathy.

ANGIOGENESIS AND ENDOMETRIOSIS

Endometriosis, the outgrowth of endometrium-like tissue into the uterine cavity, is a common disease among women of reproductive age. It has recently become apparent that angiogenesis plays a pivotal role in its pathophysiology (Groothuis et al., 2005; Becker and D’Amato, 2007; Taylor et al., 2009). EGCG inhibited the estrogen-induced activation of endothelial cells (Laschke et al., 2008). It also increased apoptosis in an endometriosis mouse model by reducing the mRNA levels of VEGF and enhancing the mRNA levels of NF-κB and MAPK1 (Xu et al., 2009). Curcumin, a phe- nolic isolated from the rhizome of Curcuma longa (tur- meric), arrested endometriosis by down-regulating MMP-9 activity (Swarnakar and Paul, 2009). Recently, many reports have confirmed the association of NF-κB with angiogenesis in endometriosis and suggest the potential of medicinal herals and phytochemicals in targeting NF-κB to treat endometriosis (Gonzalez-Ramos et al., 2008; Liu et al., 2009).

ANGIOGENESIS AND OBESITY

Latest evidence suggests that obesity is associated with the substantial modulation of adipose tissue structure, a process which involves adipogenesis, angiogenesis and extracellular matrix remodeling. In the early stages of adipose tissue development, blood vessel formation and pre-adipocyte differentiation are triggered by adipose tissue explants and endothelial cells, respectively. Therefore, modulation of angiogenesis and of proteolysis may impair adipose tissue development (Liu and Meydani, 2003; Christiaens and Lijnen, 2006; Lijnen, 2008). Therefore, modulation of angiogenesis and of proteolysis may impair adipose tissue development (Liu and Meydani, 2003; Christiaens and Lijnen, 2006; Lijnen, 2008).

Based on this concept, curcumin with its antiangiogenic activity and inhibition of angiogenesis in 3T3-L1 pre-adipocytes has been suggested for the prevention of obesity (Ejaz et al., 2009). Since angiogenesis requires the recruitment of new blood vessels (Rupnick et al., 2002), mice fed a high-fat diet and treated with curcumin (500 mg/kg) had a lower body weight gain, adiposity and microvessel density in adipose tissue, which coincided with reduced expression of VEGF and its receptor. Guggulsterone isolated from Commiphora wightii (syn C. mukul) was reported to suppress obesity, cancer and cardiovascular disease via regulation of various transcription factors, including NF-κB, signal transducer and activator of transcription 3 (STAT3) and CCAAT-enhancer-binding protein-alpha (C/EBP-α), and of various steroid receptors, such as androgen and glucocorticoid receptors (Deng, 2007; Shishodia et al., 2008). Similarly, 2-(8-hydroxy-6-methoxy-1H-2-benzopyran-3-yi) propionic acid (NM-3), a small coumarin molecule with antiangiogenic activity, was shown to attenuate renal alterations in obese type 2 diabetic db/db mice. These examples suggest the potential of antiangiogenic compounds from herbal plants as
preventive or therapeutic agents for metabolic diseases including obesity and diabetes (Ichinose et al., 2006).

**MOLECULAR TARGETS OF ANTIANGIOGENIC HERBAL COMPOUNDS**

VEGF expression is often stimulated by other indirect angiogenic factors, such as platelet-derived growth factor (PDGF), bFGF, TGF-α (Glade Bender et al., 2004). Labrecque and colleagues reported that ellagic acid mediated the inhibition of VEGF-induced phosphorylation of VEGFR-2 in bovine aortic endothelial cell (BAEC) as well as the PDGF-induced phosphorylation of PDGF receptor (PDGFR) in pulmonary aortic smooth muscle cell (PASMC) (Labrecque et al., 2005). Delphinidin and philinopside A also showed inhibitory effects on PDGFR in smooth muscle cell (SMC) and human mammary epithelial cells, respectively (Tong et al., 2005; Lamy et al., 2008).

MMP is another major molecule that contributes to angiogenesis (Stetler-Stevenson, 1999). Hyperforin strongly inhibited MMP-2 in bovine aortic endothelial cells (Martinez-Poveda et al., 2005) as well as MMP-9 in polymorphonuclear neutrophils (PMNs) (Dell’Aica et al., 2007).

Increased levels of proteins associated with the cell survival pathway, including Akt, NF-κB and MAPKs are known to play a major role in angiogenesis (Barthomeuf, 2007). In addition, recent papers have demonstrated that HIF-1α is associated positively with angiogenesis in tumors (Tsuuzuki et al., 2000; Bos et al., 2005). Thymoquinone from *Eupatorium ayapana* inhibited Akt and extracellular signal-regulated kinase signaling pathways and suppressed tumor angiogenesis and tumor growth (Yi et al., 2008a). Likewise, apigenin from *Dendranthes indica* var. aromaticum or *Lobelia chinenisis* inhibited VEGF and angiogenesis through suppression of HIF-1α expression and Akt activation in human lung cancer cells, suggesting a possible mechanism to prevent lung cancer (Liu et al., 2005). Furthermore, a variety of natural compounds have been reported to inhibit angiogenesis via down-regulation of the MAPK signaling pathway: morelloflavone (Pang et al., 2009), thymoquinone (Yi et al., 2008a), sulforaphane (Yao et al., 2008), epoxysynol B (Kamiyama et al., 2008), delphinidin (Lamy et al., 2008), decursin (Jung et al., 2009; Lee et al., 2009a) and 11,11’-dideoxyverticillin (Chen et al., 2005) in cancer. Our group reported that PGG diminished p38 MAPK activation and increased p38 MAPK phosphorylation of VEGFR-2 in bFGF-stimulated HUVECs. This suggests that p38 MAPK plays a critical role in the inhibition of COX-2 and angiogenesis by PGG. Considering that p38 MAPK is generally activated by genotoxic agents or apoptosis, activation of p38 MAPK by PGG may mediate the apoptosis of endothelial cells during antiangiogenesis (Huh et al., 2005).

NF-κB promotes angiogenesis and metastasis by regulating VEGF and MMP expression in tumors. For instance, octacosanol isolated from *Tinospora cordifolia* down-regulated VEGF gene expression by inhibiting MMPs and translocation of transcription factor NF-κB to the nucleus (Thippeswamy et al., 2008). Likewise, several natural compounds such as scopolin, fisetin and paoniflorin reduced the pro-inflammatory cytokines IL-6, IL-8 and MCP-1 that are known to be closely associated with angiogenesis (Zheng et al., 2007; Lee et al., 2009b; Pan et al., 2009).

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Conflict of Interest

The authors have declared that there is no conflict of interest.


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