

Angiogenesis In The Prevention and Management Of Cancer

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The following discussion primarily pertains to the ability of various natural health products to inhibit angiogenesis – the process by which cancer cells sprout new blood vessels to feed themselves the oxygen and nutrients they require to thrive and metastasize. However, it should be noted that many natural health products that inhibit angiogenesis also influence other molecular pathways associated with cancer, providing effects on multiple targets that help reduce the development and growth of cancer. A potential advantage of phytochemicals and other compounds derived from natural health products (when compared with drugs) is that they may act through multiple cell-signalling pathways and reduce the development of resistance by cancer cells. The primary molecular pathways affected by natural health products include:

- angiogenesis
- epidermal growth factor receptor
- HER2/neu gene
- cyclo-oxygenase-2 enzyme
- nuclear factor kappa-B transcription factor
- protein kinases
- Bcl-2 protein
- coagulation pathways

The Importance of Angiogenesis to Cancer Cells

Human tumours can remain dormant for years because of a balance between cell proliferation and apoptosis. To progress, cancers require a source of nutrition and oxygen. Tumours that outgrow their oxygen supply cannot form masses greater than 1–2 mm without developing central necrosis. A critical part of this process is the induction of local small blood vessels, termed “angiogenesis. Tumours do not grow progressively unless they induce a blood supply from the surrounding stroma. Cancers that lack angiogenesis remain dormant. The induction of new blood vessels provides tumours with a survival advantage. The survival and growth of cells depends on an adequate supply of oxygen and nutrients and on the removal of toxic products. Oxygen can diffuse radially from capillaries for only 150–200 µm. When distances exceed this maximum, cell death follows. Thus, the expansion of tumour masses beyond 1 mm in diameter depends on the development of a new blood supply—angiogenesis.

An increasing density of tumour vasculature raises the probability that the tumour will metastasize. Generally, increased microvascular density (“angiogenesis index”) is a significant indicator of poorer prognosis. Angiogenesis plays a central role in the progression of most solid tumours, including those of bladder, brain, breast, cervix, colon, lung, and prostate. Increased vascular density has also been found in the bone marrow of patients with acute myeloid leukemia and myeloma

The balance between factors that stimulate new blood vessel growth and those that inhibit it determines the vascular density. The inhibitory influence predominates in normal

tissues; in tumours, many neoplastic cells switch from an angiogenesis-inhibiting to an angiogenesis-stimulating phenotype. That switch coincides with the loss of the wild-type allele of the *TP53* tumour suppressor gene and is associated with reduced production of thrombospondin-1 (TSP-1), a controller of angiogenesis in fibroblasts.

The production of VEGF is considered essential for most cancer cell migration and for angiogenesis. Expression of VEGF messenger RNA is upregulated by many oncogenes (including *H-ras* and *K-ras*, *src*, *TP53*, and *c-jun*) and growth factors including epidermal growth factor, transforming growth factors alpha and beta, insulin-like growth factor-1, and platelet-derived growth factor. The list below outlines the number of endogenous angiogenic polypeptides that have angiogenesis-stimulating effects:

Endogenous Angiogenic Polypeptides

Activator protein 1 (AP-1)

Angiogenin (AG) and angiotropin (AT)

Angiopoietin (APN)

Basic fibroblast growth factor (bFGF)

Cyclooxygenase (COX) and lipoxygenase (LOX)

Granulocyte-colony stimulating factor (G-CSF)

Hepatocyte growth factor (HGF)

Insulin-like growth factors 1 and 2 (IGF-1 and -2)

Interleukin-8 (IL-8)

Nuclear factor kappa B (NF- κ B)

Placental growth factor (PGF)

Platelet-derived endothelial cell growth factor (PD-ECGF)

Pleiotrophin (PTN)

Proliferin Thrombospondin-1 (TSP-1)

Transforming growth factor alpha (TGF α)

Transforming growth factor beta (TGF β)

Tumour necrosis factor alpha (TNF α)

Vascular endothelial growth factor (VEGF)

Vascular permeability factor (VPF)

Neoplasms are able to synthesize or induce some of these polypeptides, an activity that is partly achieved by the secretion of vascular endothelial growth factor (VEGF) and angiopoietins (APNs). Hypoxia stimulates these peptides; the result is a sprouting of endothelial cords. This sprouting creates profuse but immature networks of thin endothelial-lined channels, essential for tumour oxygenation. Although these networks permit progressive tumour growth, they are less efficient than the vascular supply to

normal tissues. Tumours often secrete a relative excess of VEGF that results in disorganized and leaky vessels that cause local bleeding and edema.

The growth of many cancers is associated with an absence of the endogenous inhibitors of angiogenesis—for example, interferon beta (INFβ). A potent inhibitor of angiogenesis, INFβ works by blocking interleukin-8 (IL-8), basic fibroblast growth factor (bFGF), and collagenase type V, which are all potent angiogenic factors that aid tumour development and invasiveness. Thus, the importance of a strong immune system is highlighted in that immune cells secrete various anti-angiogenic interleukins and interferon.

Monoclonal Antibody Drugs That Inhibit Angiogenesis

Recently, targeted therapies using monoclonal antibodies that antagonize the formation of new blood vessels have been developed. One example is bevacizumab (Avastin: Genentech, San Francisco, CA, U.S.A.). Bevacizumab is a genetically engineered humanized monoclonal immunoglobulin G antibody that blocks the VEGF receptor in endothelial cells, thereby shutting off the tumour blood supply. Although bevacizumab increases survival for some patients, it increases the risk of adverse effects, including leucopenia, diarrhea, and hypertension.

Use of bevacizumab is also associated with major risks of thrombosis (resulting in stroke and myocardial infarction), fatal hemorrhage (such as gastrointestinal bleeding or hemoptysis), and visceral perforation. During a course of radiotherapy, some tumours increase their angiogenic activity.

Some anti-angiogenic agents also have anticoagulation activity that may also be associated with a reduction in metastasis. Heparin is a well-known example of a therapy with both anticoagulation and anti-angiogenic activities.

Natural Health Products That Inhibit Angiogenesis In Cancer Cells

Rather than develop multiple monoclonal antibodies to target the multiple peptides and their receptors, an alternative approach might be to evaluate phytochemicals and certain animal-derived chemicals that influence multiple pathways. The science of pharmacognosy evaluates natural drugs derived from herbal remedies or phytomedicines. Natural health products contain a cocktail of biologic chemicals that act on multiple pathways that initiate and maintain tumour angiogenesis. (A great deal of experimental and preclinical evidence suggests that some of these agents represent appropriate interventions in the complimentary management of cancer as well possibly serving a role in cancer prevention):

Curcumin - Curcumin inhibits the transcription of two major angiogenesis factors, VEGF and bFGF. It interacts with VEGF- and nitric oxide-mediated angiogenesis in tumours. Elevated levels of nitric oxide correlate with tumour growth. Curcumin reduces nitric oxide generation in endothelial cells. The membrane-bound enzyme CD13 (aminopeptidase N) is found in blood vessels undergoing active angiogenesis. Curcumin

binds to CD13 and blocks its activity, thereby inhibiting angiogenesis and invasion by tumour cell. Derivatives of curcumin are in development by the pharmaceutical industry for this purpose.

Curcumin downregulates the expression of the *VEGF* and *MMP9* genes that are associated with angiogenesis. Curcumin can interfere with the activity of both *MMP2* and *MMP9*, the basis of the angiogenic switch, thereby reducing degradation of the extracellular matrix (ECM). It also interferes with the release of angiogenic factors that are stored in the ECM. It inhibits growth factor receptors such as EGFR and VEGF receptor and the intracellular signalling tyrosine kinases. This cell signalling system can promote further angiogenesis through gene activation that increases levels of cyclooxygenase-2 (COX-2), VEGF, IL-8, and the MMPs,

Chinese Skullcap and the Baicalein Flavonoid - Baicalin and baicalein are the main derivatives of the Chinese skullcap herb. They are potent anti-angiogenic compounds that reduce VEGF, bFGF, 12-lipoxygenase activity, and MMP. *Scutellaria baicalensis* is one of the herbs found in PC-SPES, a complex of Chinese herbs that is clinically active against advanced prostate cancer.

Milk Thistle and the Silymarin flavonoids - Silibinin and silymarin are polyphenolic flavonoids isolated from the fruits or seeds of *Silybum marianum* (*milk thistle*). In the laboratory, silymarin demonstrates strong activity against a variety of tumours by downregulation of VEGF and EGFR. Silymarin suppresses VEGF when used as a single agent against human ovarian cancer.

Quercetin – Quercetin is a flavone found in apples, onions, raspberries, red grapes, citrus fruit, cherries, broccoli, and leafy greens. It inhibits angiogenesis through multiple mechanisms, including interaction with the COX-2 and lipoxygenase-5 enzymes, EGFR, the *HER2* intracellular signalling pathway, and the NF- κ B nuclear transcription protein. Quercetin may enhance the anticancer effects of tamoxifen through anti-angiogenesis **(1)**

Quercetin has also been shown to induce apoptosis of cancer cells by upregulating certain death receptors. Cytokines such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can induce apoptosis in colon cancer cells through engagement of death receptors. Nevertheless, evading apoptosis induced by anticancer drugs is common feature of many types of cancers. This results in the need for combination therapy. A study published in 2007 reported that quercetin, through its ability to redistribute death receptors at the cell surface, facilitates death-inducing signaling complex formation and activation of caspases in response to death receptor stimulation. **(2)**

Green Tea and its Polyphenols – Green tea is a rich source of polyphenols and catechins, mainly epigallocatechin-3 gallate (EGCG). These constituents inhibited proliferation of MDA-MB231 breast cancer cells and HUVECS and, in rodent studies, also suppressed breast cancer xenograft growth and reduced the density of tumour vessels. This activity was associated with a decrease in VEGF, regulated at the level of transcription. In addition, EGCG suppresses protein kinase C (PKC), another VEGF transcription modulator. **(1)**

Sartippour M and fellow researchers showed that EGCG decreased c-fos and c-jun RNA transcripts, suggesting that activator protein (AP)-1–responsive regions present in the human VEGF promoter may be involved in the inhibitory effect of EGCG. Furthermore, EGCG suppressed the expression of protein kinase C, another VEGF transcription modulator, in breast cancer cells. Inhibition of VEGF transcription appeared to be one of the molecular mechanism(s) involved in the antiangiogenic effects of green tea, which may contribute to its potential use for breast cancer treatment and/or prevention.

The inhibition of breast cancer angiogenesis by green tea likely involves multiple pathways other than VEGF transcription. It has been reported in other cell types that green tea inhibits other angiogenic molecules, i.e., urokinase, matrix metalloproteinases (MMP-2 and MMP-9), and platelet-derived growth factor. Tumor necrosis factor- α gene expression has also been shown to be inhibited by EGCG. Other studies suggest that another mechanism involves the suppression of interleukin-8 production by endothelial cells **(3)**

A dose of 1.0 g/m² three times daily [equivalent to 7–8 Japanese cups (120 mL)] has been recommended. In practice, lower total daily doses of 2–4 g standardized green tea extract (95% polyphenols and 60% catechins) are usually prescribed. Each gram of this extract provides 400–500 mg of EGCG. The dose-limiting adverse effects are the gastrointestinal and neurologic effects of caffeine. However, the caffeine may potentiate the anti-angiogenic effect of EGCG

Artemisinin (Chinese Worm Wood) - is the active constituent extracted from the plant *Artemisia annua*. Artemisinin has been used clinically as an anti-malaria drug. More recently, it was shown to be cytotoxic to cancer cells through induction of apoptosis. also lowered VEGF expression by tumour cells and KDR expression by endothelial cells. Artemisinin also has anticancer activity through other pathways. It inhibits the activation of nuclear factor kappa-B (NF- κ B), an important activator protein in cancer development and progression

Viscum album (European Mistletoe) - is also known as Iscador (Weleda, Palisades, NY, U.S.A.). It is often used as an anticancer agent in anthroposophic and homeopathic

medicine. Laboratory studies show that it is anti-angiogenic by downregulation of VEGF; it also induces apoptosis of cancer cells.

Shark Cartilage - The resistance of cartilage to tumour formation has been correlated with its capacity to inhibit the formation of new blood vessels. A number of *in vitro* and *in vivo* studies have suggested the existence of anti-angiogenic compounds in shark and bovine cartilage. The clinical effectiveness of whole cartilage for the treatment of cancer was not confirmed in a recent phase III randomized controlled trial. The main problem is lack of data correlating bioavailability with pharmacologic effects in the oral use of shark cartilage. Unsatisfactory outcomes in clinical trials may be secondary to inadequate bioavailability of the active constituents

Dogfish Shark and Squalamine - Squalamine is a steroid isolated from the liver of the dogfish shark. Squalamine significantly blocks VEGF-induced activation of mitogen-activated protein kinase and cell proliferation in human vascular endothelial cells. Squalamine is anti-angiogenic for ovarian cancer xenografts, and it appears to enhance the cytotoxic effects of cisplatin chemotherapy, independent of *HER2* status. Overexpression of *HER2* is normally associated with resistance to cisplatin and promotion of tumour angiogenesis. In a phase II trial of patients with advanced small-cell lung cancer, squalamine was administered at a dose of 300 mg/m² by continuous infusion for 5 days, with paclitaxel and carboplatin given on day 1. Patient survival data and a satisfactory safety profile indicated that the combination should be explored further. **(1)**

References:

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