# A Novel Approach to Cancer Treatment

# Botanicals that Inhibit Angiogenesis and/or Enhance Nonspecific Biological Immune Response

**By Donald Yance**

## Introduction

Two of the most important targets of cancer therapy include (1) the inhibition of selective (cancer-driven) angiogenesis, and (2) the activation of the immune system to target cancer cells. I would also like to mention a 3rd target of the utmost importance: the non-specific enhancement of the "whole," by building the neuroendocrine system, vitality and vital energy of the person. It is amazing to ponder on the thought that many of the herbs I use in my protocols for people with cancer target all three of these areas simultaneously.

Emerging on the horizon in cancer therapy is an expansion of the scope of treatment beyond cytotoxic approaches to include molecular management of cancer physiopathology. The goal in these integrative approaches, which extends beyond eradicating the affected cells, is to control the cancer phenotype. One key new approach appears to be modulation of the inflammatory cascade, as research is expanding that links cancer initiation, promotion, progression, angiogenesis, and metastasis to inflammatory events.

## The Angiogenic-Metastatic Pathway

Angiogenesis refers to the formation of new blood vessel networks that permit sustained tumor growth, which is a prerequisite for tumor growth and metastases. It is one of the most rapidly growing fields in basic and applied cancer research. Clinical studies have shown that angiogenesis in solid tumors relates to a poor prognosis and, in premalignant lesions, indicates potential for cancerous transformation. The extent of angiogenesis is determined by the balance between positive- and negative- regulating molecules that are released by the tumor and host cells in the micro-environment. The growth of many cancers is associated with the absence of the endogenous inhibitors of angiogenesis, such as interferon beta (INF beta). Cancer treatment therapies with INF beta, or INF alpha, act in part, by inhibiting angiogenesis. INF-beta administered by subcutaneous injections has shown to be a potent inhibitor of angiogenesis by blocking Interlukin (IL)-8, bFGF, and collagenase type V, all potent angiogenic factors aiding in tumor development and invasiveness. [1]

Many chemotherapeutic agents, such as cytoxin, taxol, and thalidomide, are being used in low dosages to inhibit angiogenesis. This new strategy is permitting advanced cancer patients to live with cancer by managing it. With this approach, they fair much better in terms of quality of life as opposed to when very high and toxic doses are used to try and completely eradicate the cancer. The harshness of such treatment causes the patient to greatly weaken and the cancer, which may have seemed gone, often comes back with a vengeance. This new low dose therapy is refereed to as "metronomic" dosing. The advantages of low-dose metronomic or continuous dose delivery using a combination of phytoceuticals, together with whole-plant extracts that possess known cytotoxic compounds, is a therapy I utilize in patients with active or more aggressive cancer. For low grade, less aggressive cancers, and for the prevention of cancer reoccurrence, I employ gentle, nutritive vitalistic herbal formulations that consist of primary, secondary, and companion adaptogens. Many of these herbs include common spices and teas which, inhibit cancer angiogenesis through a host of mechanisms including the modulation of inflammation, a potent promoter of angiogenesis.

Control of the angiogenesis can be attempted at various points through the modulation of inflammatory processes, such as cyclo-oxygenase-2 (COX-2) inhibition and thromboxane A2 inhibition, or through copper-chelation, or at the growth factor level. The effectiveness of any given therapy will depend on the sensitivity of the particular cell line or through targeting specific characteristics, and by reducing various

stressors both of chronic and/or acute nature. The normalization of various hormones, cytokines, prostaglandins, and cellular energy transfer are all important for the prevention and treatment of cancer. Cancer possess an energy of its own and this energy, when intelligent enough, when determined enough, and when the patient is weak, will hijack and take control of all these areas within the body.

## Cancer and Immune Suppression

Oncogenesis and immune suppression are likely to be closely interlinked processes. It has been theorized that clearance of transformed neoplastic cells may be a routine physiological function of the normal, non-compromised immune system. This phenomenon, known as *immune surveillance,* is thought to be an evolutionary mechanism largely mediated by natural killer (NK) cells and to a lesser extent by cytotoxic T cells, that may serve to eliminate neoplastic cells that arise spontaneously due to genetic mutations or other oncogenic signals. [2,3]

Cancerous cells that successfully evade this initial immune killing are then able to subsequently propagate into established tumors. As they proliferate, these tumor cells accumulate additional mutations secondary to Darwinian selection, which may confer additional immuno-evasive survival advantages on the growing neoplasm. Consequently, by the time the tumor is clinically detectable, it has developed potent immunosuppressive qualities that enable it to depress host antitumor immunity. [4-10]

The importance of using adaptogens as immuno-enhancing agents cannot be overstated. It is one of the targeted objectives in non- toxic herbal treatment in oncology. It is by no means the only target of adaptogens or herbal therapy but it is critical to long-term success. There is equally an enormous amount of scientific data in recent medicinal journals confirming the importance of the immune system in oncology. Many herbs and specific compounds derived from herbs, act in a multitude of ways to suppress cancer while at the same time promote healthy cell activity.

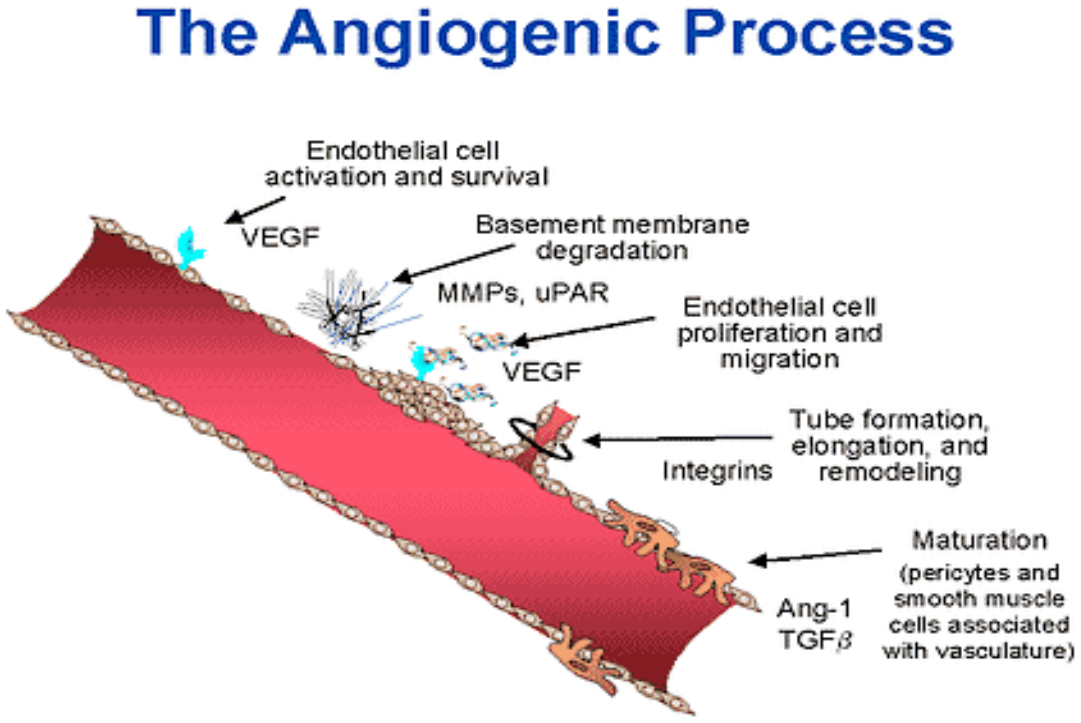
Medicinal mushroom extracts, rich in beta glucans, are some of the most researched agents in integrative cancer therapies. Beta glucans are natural carbohydrate molecules found in medicinal mushroom extracts, such as *Ganoderma lucidum* (Reishi) 15:1, *Poria cocos* 20:1, and *Coriolus versicolor* or *hirsutus* 20:1, that recruit immune cells to assist monoclonal antibodies (Mabs) in killing cancer cells. There are two other mechanisms by which Mabs can destroy tumors. One is to attract natural killer T cells to attack a tumor, and the other is to activate the complement system, a series of blood proteins that work together to puncture tumor cells. This third mechanism relies on orally administered Medicinal mushroom extracts to deliver beta glucan. Beta Glucan binds to specific receptors on neutrophils, which enable them to see the cancer as foreign. The antibodies and complement attract the primed neutrophils to the site of the cancer, where they join in the attack. Reishi extracts also contain another important, but often-overlooked compound called terpenes, or terpenoids, which actually act in a more direct way in fighting cancer. Research over the past decade has firmly established the efficacy of these Beta glucan-rich mushroom extracts as immune system enhancers and, more recently, as a highly promising complementary cancer immunotherapy. [11] Herceptin and other agents that target specific active transduction pathways will work better with an active and healthy immune system.

## What is Angiogenesis?

Angiogenesis, the regulated formation of new blood vessels from existing ones, is the basis of several physiological processes such as embryonic development, placenta formation and wound healing. It is one of the best examples of how a tumor can take control of these processes and deregulate them to its own advantage. The normal and orderly formation of new blood vessels consists of the endothelial cell receiving the stimulatory signal and secretion of Matrix Mettalloproteinase (MMP) and heparanase, which cause the dissolution of the extracellular matrix (ECM). The tight junction between the endothelial cells is then altered and the cells project through the newly created space where the newly formed endothelial cells organize into fresh capillary tubes, allowing the sprouting vessel to grow toward the source of fresh blood supply. [13]

The growth and survival of cells is dependent on an adequate supply of oxygen and nutrients and the removal of toxic products. Oxygen can diffuse radically from capillaries for only 150 to 200 m. When distances exceed this, cell death follows. Thus the expansion of tumor masses beyond 1 mm in diameter depends on the development of a new blood supply, or angiogenesis. [14-17]

Benign neoplasms are sparsely vascularized, whereas malignant neoplasms are highly vascular. The increase in vasculature also increases the probability that a tumor cell line will produce metastasis. Many but not all recent studies indicated that increased microvessel density in the areas of most intense neovascularization is a significant and independent prognostic indicator in early-stage breast cancer. Studies with other neoplasms such as prostate cancer, melanoma, ovarian carcinoma, gastric carcinoma, and colon carcinoma also support the conclusion that the vascular density, that is, the angiogenesis index, is a useful prognostic factor.




## The Process of Cancer Metastasis

The process of cancer metastasis consists of a series of sequential interrelated steps, each of which is rate-limiting, since a failure at any of the steps aborts the process. The outcome of the process is dependent on both the intrinsic properties of the tumor cells and the responses of the host; the balance of these interactions can vary among different patients. In principle, the steps or events in the pathogenesis of a metastasis are similar in all tumors.

The process of metastasis consists of sequential linked steps. Metastatic cells must complete all of these steps if a clinically relevant lesion is to develop. If a disseminating tumor cell fails to survive any of these steps, it will not produce a metastasis.

**The major steps in the formation of a metastasis are as follows:**

1) *Transformation of normal cells into tumor cells and their growth* after the initial transforming event. Growth of neoplastic cells must be progressive, with nutrients for the expanding tumor

mass initially supplied by simple diffusion.

2) *Extensive vascularization*, that is, angiogenesis, must occur if a tumor mass is to exceed 1 mm in diameter. The production and secretion of proangiogenic factors by tumor cells and host cells play a major role in establishing a capillary network from the surrounding host tissue.
3) *Local invasion* of the host stroma by some tumor cells occurs by several parallel mechanisms. Thin-walled venules, like lymphatic channels, offer very little resistance to penetration by tumor cells and provide the most common pathways for tumor cell entry into the circulation.
4) *Detachment and embolization* of single tumor cells or aggregates occurs next, with the vast majority of circulating tumor cells being rapidly destroyed. Once the tumor cells have *survived* the circulation, they must *arrest* in the capillary beds of distant organs, by *adhering* either to capillary endothelial cells or to subendothelial basement membrane, which may be exposed.
5) *Extravasation* occurs next, probably by mechanisms similar to those operative during invasion.
6) *Proliferation* within the organ completes the metastatic process. To continue growing beyond the size of 0.2 mm in diameter, the micrometastasis must develop a vascular network and evade destruction by host defenses. The cells can then invade blood vessels, enter the circulation, and produce additional metastases. [30-34]

Angiogenesis can occur by either sprouting or non-sprouting processes. Sprouting angiogenesis occurs by branching (true sprouting) of new capillaries from preexisting vessels. Non-sprouting angiogenesis results from the enlargement, splitting, and fusion of pre-existing vessels produced by the proliferation of endothelial cells within the wall of a vessel. Transcapillary pillars (or transluminal bridges) are sometimes observed in enlarged vessels produced by non-sprouting angiogenesis. This type of angiogenesis can occur concurrently with sprouting angiogenesis in the vascularization of organs or tissues such as the lungs and heart. The mechanism of non-sprouting angiogenesis in metastasis is not yet known, but VEGF, which plays a pivotal role in developmental, physiologic, and pathologic neovascularization, is a candidate effector molecule. VEGF stimulates the proliferation and migration of endothelial cells and induces the expression of metalloproteinases and plasminogen activity by these cells. Moreover, overexpression of VEGF in tumor cells enhances tumor growth and metastasis in several animal models by stimulating vascularization (increased microvessel density). [35--39]

## Important Targets Affecting Cancer Growth and Angiogenesis

Tumor growth and metastasis both depends upon angiogenesis, and cancer cells begin to promote this process early in tumorigenesis. This angiogenic impulse is characterized by oncogene-driven tumor expression of proangiogenic proteins. Some of these include:

1) vascular endothelial cell growth factor (VEGF), also known as vascular permeability factor (VPF),
2) basic fibroblast growth factor (bFGF)
3) transferring growth factor – _ (TGF- _),
4) platelet-derived growth factor (PDGF),
5) fibroblast growth factor (FGF),
6) epidermal growth factor (EGF),
7) transforming growth factor-_ (TGF-_), and TGF-_,
8) Insulin-like growth factor I and II (IGF-1 and II) and possible insulin
9) fibrin,
10) interleukin-8, (IL-8) and possible IL-6,
11) tumor necrosis factor-_,
12) COX-2, LOX-5/12, NF-kappa beta, AP-1
13) angiogenin, and angiotropin,

The formation of new vasculature consists of sequential steps: endothelial cells must proliferate, migrate, and penetrate host stroma and extracellular matrix (ECM). The endothelial cells must also undergo morphogenesis. The vasculature of many solid tumors is not identical to that in normal tissues. [40, 41]

There are differences in cellular composition, permeability, vessel stability, and regulation of growth. The extent of angiogenesis is determined by the balance between factors that stimulate and those that inhibit

new blood vessel growth and survival. Although in normal tissues the inhibitory influence predominates, in tumors many neoplastic cells switch from an angiogenesis-inhibiting to an angiogenesis-stimulating phenotype, which coincides with the loss of the wild-type allele of the p53 tumor suppressor gene and is the result of reduced production of the antiangiogenic factor thrombospondin. [42-43]

**IMPORTANT BLOOD TESTS FOR ASSESSING AND MONITORING ANGIOGENESIS/METASTATIC PROGRESSION**

- ❑ LDH (Lactate dehydrogenase)
- ❑ ESR (Erthrocyte Sedimentation Rate)
- ❑ Serum Insulin (fasting)
- ❑ Serum zinc
- ❑ Ceruloplasmin
- ❑ Serum copper
- ❑ Vitamin D (1,25 DI-OH & 25 OH-VIT D)
- ❑ PAI-1
- ❑ D-Dimer
- ❑ Leiden factor 5
- ❑ Fibrinogen
- ❑ Cardio C reactive protein (CRP)
- ❑ VEGF

## A Systematic Approach using Botanical Agents for Cancer Inhibition

Botanical and dietary chemopreventive strategies aimed at inhibiting angiogenesis are safe and effective for the prevention and treatment of neoplasms. While there is no one approach that will fit all cancers I am in the process of developing both a model and several formulations that can be effectively used in cancer therapies. It is crucial to see the whole picture, develop a sound plan to follow and not fall back on the next trendy product falsely promoted as a cure for cancer. Working with cancer patients is hard work and requires only the most dedicated of people.

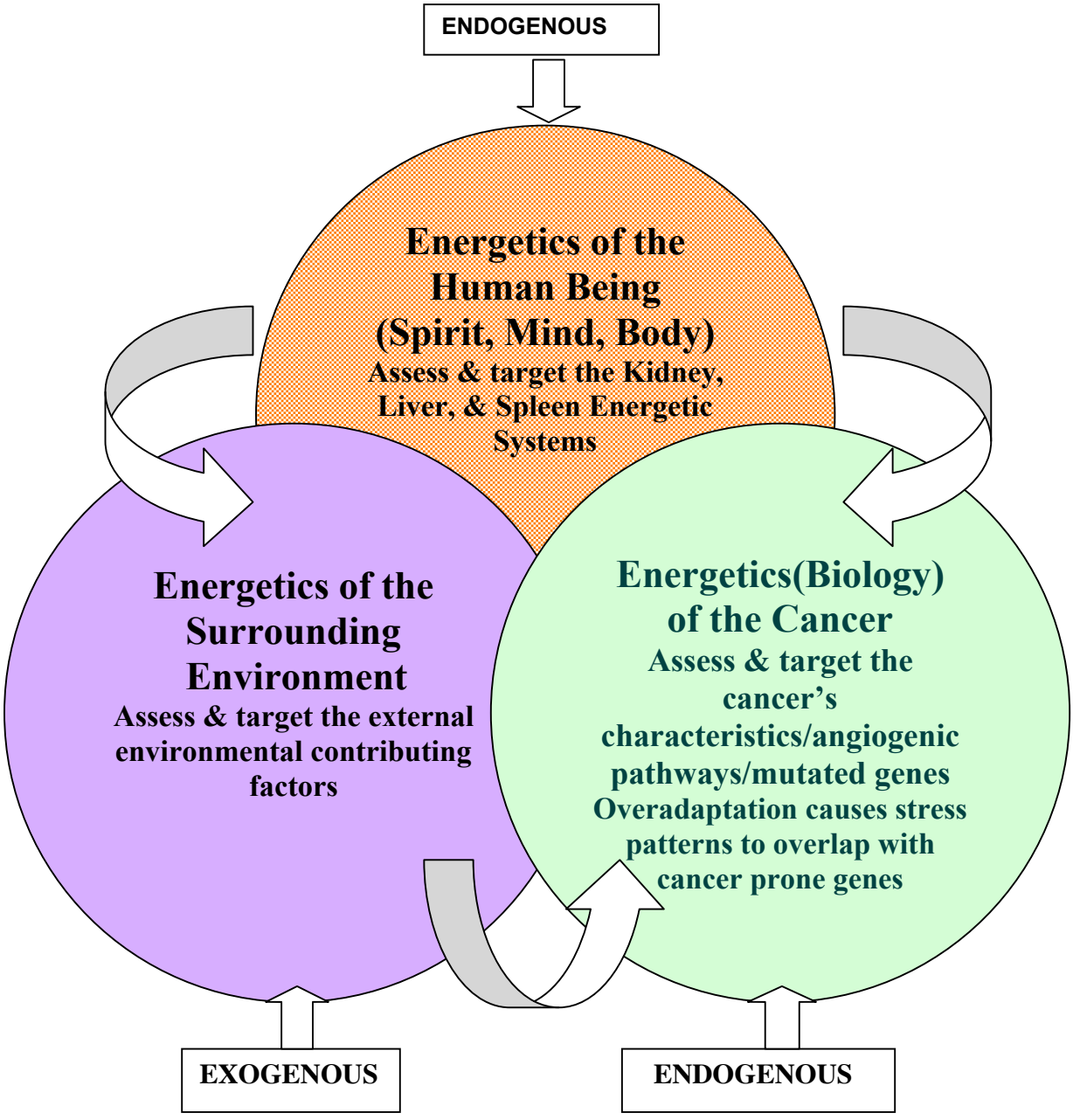
Botanicals act in multiple ways - constant study not only of the herbal literature (old and new), but also of the allopathic research is essential to the practitioner who works with persons with cancer. Herbs have healing powers because they are charged with light and are alive with life. Herbs, like humans and all living beings are positioned to adapt and respond, as opposed to drugs, which are solely functional. Even with all of our modern medical treatments for cancer (and all diseases), herbs and herbalists, in their humble way, have much to contribute to the health and healing of those inflicted with cancer.

When approaching a disease like cancer it is important to formulate a balanced protocol that addresses (1) the energetic weaknesses of the person (2) the biomechanics (characteristics) of the cancer, and (3) the external environment. This is the basis for the Trinitarian Model of healing. It is when the energy of cancer overrides the internal healing ability of the person that it can impede on one's health and do serious damage. These three dynamic aspects, namely "the cancer energy", and the person's own internal "healing energy", and the "exogenous energy" should been addressed with an understanding of the relationship, dynamics, and interplay that co-exist between them. Modern medicine is extremely direct and powerful (often too powerful), but yet so reductionistic, while traditional healing encompasses many factors contributing to disease, both exogenous and endogenous; the inner imbalances, such as organ weaknesses, including the presence of deficiencies and/or excesses; and of utmost importance, the human spirit. Exogenous factors include dietary factors, environmental factors, and lifestyle choices. Wholistic traditional healing seeks to bring about harmony and vitality through detoxification and tonification. It sees the "WHOLE", understanding cancer is part of self, created in part by self, rather than seeing the cancer cell as an isolated entity, that in the case of breast cancer, it is the breast to blame. Cancer usually involves a cascade of highly complex contributing factors that are, in part, hereditary genetic weaknesses; but more-often self induced by our poor internal self-care, and contributing exogenous factors, as well. It varies drastically from person to person. There are hundreds of different types of breast cancer, which are constantly undergoing change and mutation; and still underneath each type is a unique individual. It is our

commitment to understand and positively effect what is endogenous, while at the same time, understand what is exogenous and can be positively changed. This is imperative for long-term success regardless of whether or not cytotoxic agents are used.

## FORMING A TREATMENT PLAN BASED ON THE ENERGETIC RELATIONSHIPS OF THE FOLLOWING

### Understanding the Trinitarian (Triphasic) Model



## Gene Mutations: The p53 Protein

Mutation of the p53 tumor suppressor gene is the most common genetic alteration in human cancer. The p53 protein is often called the guardian of the genome, It prevents replication of damaged DNA in normal cells and promotes suicide or apoptosis of cells with abnormal DNA. [44] Faulty p53 molecules allow cells (carrying damaged DNA) to survive when they would normally die and to replicate when they would normally stop. Cell cycle constraints are when pass, repair, and apoptotic mechanisms falter and disturbed cells pass mutations down to offspring. Thus, a lack of p53 regulation promotes the spontaneous emergence of mutant cells, a cellular distortion that is an invitation to cancer. [45]

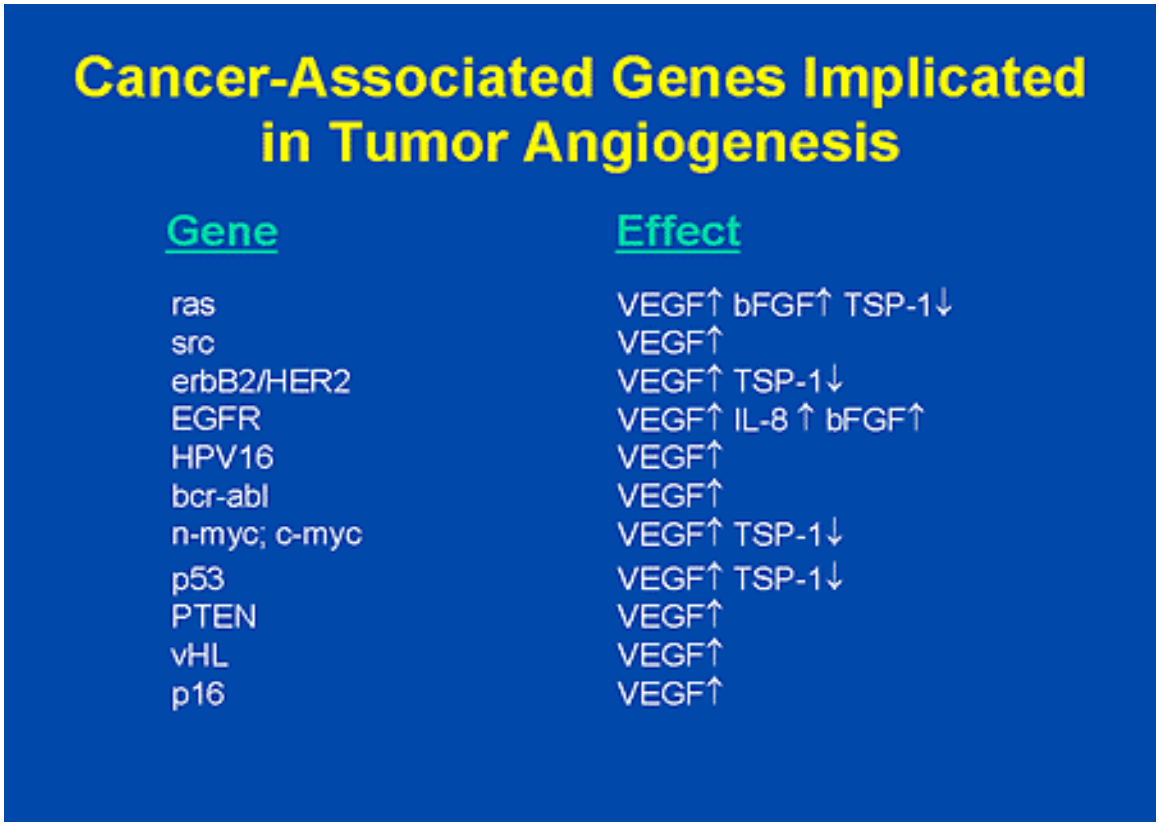
Normal p53 function has been demonstrated to be crucial in the induction of apoptosis in human and murine cells following DNA damage. This result was further supported by the findings that p53 is the most commonly mutated tumor suppressor gene. Lack of p53 expression or function is associated with an increased risk of tumor formation. [46-53]

**Quercetin inhibits p53:** A mechanism by which quercetin shows its antitumor effects is by inhibiting the expression of certain gene mutations. Quercetin inhibits the mutation of the tumor suppressor protein gene p53. The mutation, or defect of this suppressor is involved in more than half of all cancer cell lines including breast, ovarian and prostate cancers. [54] Quercetin strongly inhibited, in a time- and dose-dependent fashion, the expression of the mutated p53 protein, in breast cancer. [55]

**Resveratrol induces p53:** The anti-tumor activity of resveratrol occurs through p53-mediated apoptosis. Recent studies clarify the potential signaling components underlying resveratrol-induced p53 activation and induction of apoptosis. [56, 57]

**Diet, Activity, and Lifestyle Associations with p53 Mutations**: The association between the p53 tumor suppression gene mutation, which is a common event in the development of colon cancer (as well as many other cancers), and dietary and lifestyle factors was evaluated as part of a multi-center case-control study. Subjects with a p53 mutation were more likely to consume a Western-style diet compared with controls than were cases who were p53 wild type. Specific components of the diet were also found to be most strongly associated with p53 mutations, including a diet with a high glycemic load as well as foods high in red meat, fast food, and trans-fatty acids (mutation vs control, odds ratio = 1.92 95% CI = 1.47-2.50). These diets, relative to the lowest intake were found to be significantly associated with missense mutations (OR = 1.69; 95% CI = 1.23-2.33, comparing p53+ to controls, and OR = 1.72; 95% CI = 1.19-2.50, comparing cases p53+ to cases of p53 wild type). **The authors conclude that components of the Western diet -- namely, red meat and foods that increase glycemic load -- may play an important role in the process of the p53 mutation that then causes cancer.**

This important study shows a clear association between specific features of the Western diet and the p53 tumor suppressor gene. The strength of this study lies in the number of subjects studied and the case-control study design, although little information is provided on the dietary methodology used and the quality of the dietary data collected (eg, what was the extent of under-reporting. This is a useful 'hypothesis-generating' study, and further research is certainly warranted in this area, particularly the role of fruit and vegetables (and other food components) as possible protective factors. [58]



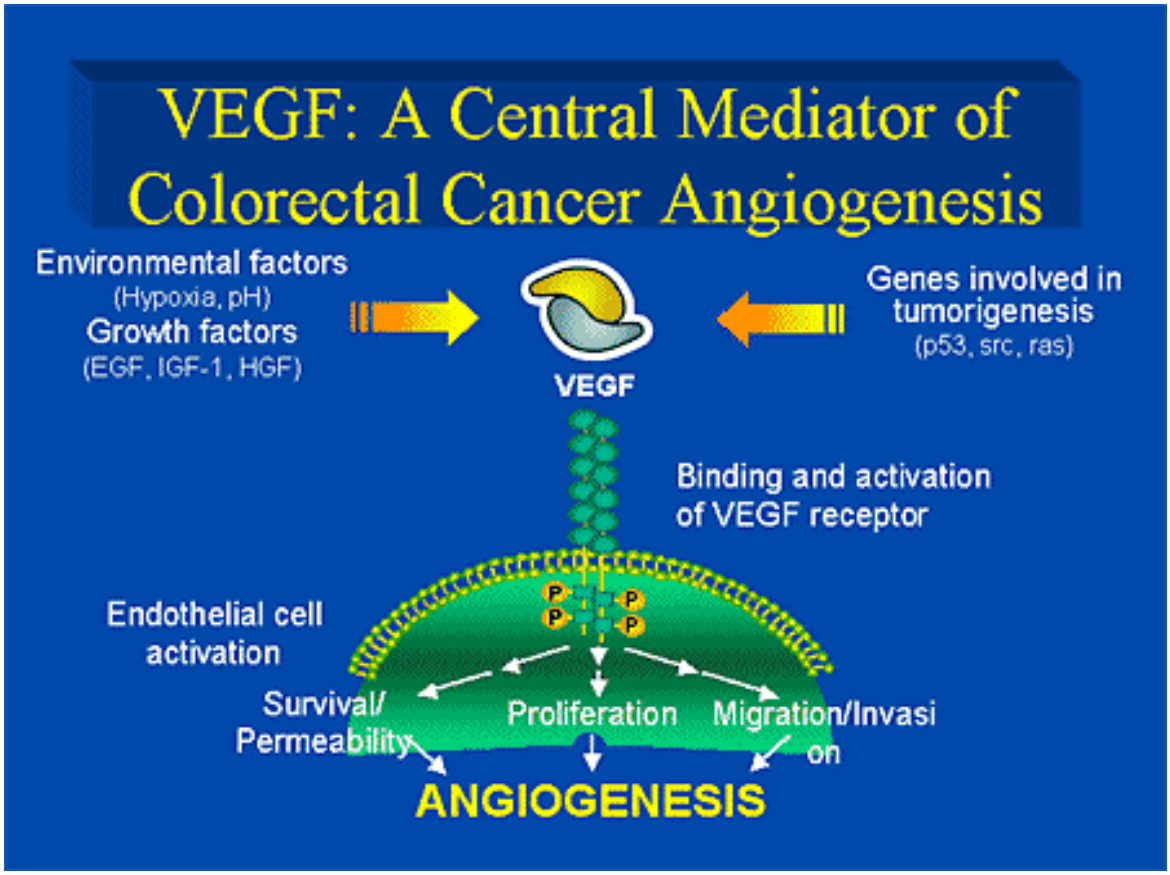

## Vascular Endothelial Growth Factor (VEGF)

The production of VEGF is considered essential for most cancer cell migration and for angiogenesis. A high VEGF expression level is associated with a worse outcome in a wide array of malignancies. VEGF mRNA expression is upregulated by a wide array of oncogenes (including H-*ras* and K-*ras*, v-*raf*, *src*, *PTEN*, *p53*, *Wnt*, and c-*jun*, among others) and growth factors (including EGF, TGF-alpha, TGF-beta, insulin-like growth factor-1, and PDGF). [59-65]

Considering the critical role of VEGF in tumor development, and the recently reported positive impact of VEGF-targeted therapy, this is one of the most exciting fields of cancer investigation today. Several herbs and herbal compounds have been found to dramatically inhibit VEGF.

**Herbs that inhibit VEGF:**

1. *Curcuma longa* (Turmeric) - 95% Curcumin
2. Magnolia seed cones - 90% Honokiol
3. *Camellia sinensis* (Green tea extract)- 50%EGCG, plus other compounds
4. *Vitis vinifera* (Grape seed extract) - 95% OPC's
5. *Angelica sinensis* (Dong quai) - 4-hydroxyderricin
6. *Taxus breviflora* (Pacific yew)- taxol and other related taxans
7. *Scutellaria baicalensis* (Chinese Baical skullcap) - 95% baicalin and other compounds, mostly flavonoids
8. *Polygonum cuspidatum* (Foti, Japanese knotweed) - 20% Resveratrol
9. *Artemisia annua* (Chinese wormwood) - 95% Artemisinin, and other related terpenes and flavonoids
10. *Silybum marianum* (Milk thistle) – 80% Silymarin




**Curcumin**, found in Turmeric, and its derivatives demonstrated significant inhibition of VEGF and bFGF-mediated corneal neovascularization and directly inhibited angiogenesis in vivo and in vitro. [66]

**Baicalin**, a main compound in Chinese skullcap, is a potent anti-angiogenic compound that reduces VEGF, bFGF, 12 lipoxygenase activity and MMP, all of which contribute to angiogenesis. [67]

In a recent study **Grape seed extract** inhibited VEGF expression, reducing tumor growth and formation. [68]

**Resveratrol,** a naturally occurring phytoalexin found in grapes and wine, possesses cancer-preventive activity. Angiogenesis is a crucial step in the growth and metastasis of cancers. We have investigated the effect of resveratrol on angiogenesis in vitro and ex vivo, and found that resveratrol directly inhibited human umbilical vein endothelial cell growth and decreased the gelatinolytic activities of matrix metalloproteinase-2. Tube formation was inhibited by treatment with resveratrol after plating endothelial cells on Matrigel. Resveratrol treatment also inhibited endothelial cell attachment to basement membrane components fibronectin and laminin, and displays similar behavior on cell chemotaxis. In addition, resveratrol has been found to be an angiogenesis inhibitor. Therefore, inhibition of angiogenesis associated with cancer may be a novel mechanism for the anticancer activity of resveratrol. [243]
Resveratrol reduces a wide range of angiogenic growth factors including VEGF expression. [246]

The seed cones from **Magnolia trees** contain substances that inhibit the growth of new blood vessels. Honokiol, the active ingredient in the magnolia cones inhibited the growth of blood vessel endothelial cells more than other kinds of cells and cut tumor growth in half in experiments in mice.[69]

**Silybin**, a Sliymarin compound in Milk thistle, bound to phosphatidylcholine, was shown to inhibit VEGF when used as a single agent against human ovarian cancer. [160]

**Greater support from friends and neighbors of presurgical patients with ovarian carcinoma appears to be associated with reduced level of vascular endothelial growth factor (VEGF) and possibly less disease progression, according to researchers at the University of Iowa, Iowa City.** The women with carcinoma who reported higher levels of social well-being had lower levels of VEGF. Woman who reported greater helplessness or worthlessness had higher VEGF levels, but, say the researchers, "depression as a whole...was not related to VEGF levels. [70]

## Targeting EGFR (HER1)

The Epidermal growth factor receptor (EGFR) is over-expressed in many different solid human tumors; this over-expression has been associated with advanced stages of disease, resistance to conventional treatments, and poor prognosis. Blockade of the EGFR was shown to stop cell proliferation in cancer models both in vitro and in vivo. Numerous conventional drugs, as well as safe non-conventional herbal compounds, targeting EGFR are under development, but 2 strategies have been more extensively explored in clinical trials: the use of monoclonal antibodies (MAbs) directed against the external domain of the receptor, and the use of small molecules that compete with adenosine triphosphate for binding to the receptor's kinase pocket, thus blocking receptor activation, also known as TK inhibitors (TKIs). [71-77]

EGF stimulates urokinase-type plasminogen activator expression, which in turn promotes angiogenesis. The isoflavone estrogen-like compound genistein, which is found in traditional soy foods, has shown the ability to suppress EGF. [77] Curcumin and genestein inhibit EGF. Human gingival fibroblasts expressed a basal uPA activity, which was inhibited by genistein, but not by curcumin. After treatment with 10 ng/ml EGF, uPA production was strongly stimulated. Exposure to genistein and curcumin inhibited EGF-stimulated urokinase production. Using more specific inhibitors, we found that the mitogen-activated extracellular kinase and c-Jun N-terminal kinase (JNK) inhibitors PD98059 and SP600125 also blocked the EGF-dependent stimulatory effect. On the other hand, SB203580, inhibitor of the p38 member of mitogen-activated protein kinase family, did not alter this response. In accordance to these findings, EGF stimulated a potent activation of JNK and a mild activation of extracellular signal-regulated kinases 1/2. Finally, EGF stimulated the phosphorylation of its receptor and tyrphostin (AG1478), curcumin and genistein were able to inhibit this stimulatory effect. [79]

Genistein and curcumin inhibited protein tyrosine kinases that could stimulate the enhancement of u-PA levels induced by TGF-beta(1). Genistein and curcumin also blocked the expression TGF-beta(1)-induced synthesis of fibronectin, an early responsive gene to the growth factor. These results show that genistein and curcumin could play an important role in inhibiting tumor progression. [80]

**Natural compounds that have shown to block EGF receptor activation and its downstream effectors**:

1. Resveratrol [81]
2. Vitamin D-3 [82]
3. Licorice [159]
4. Quercetin (inhibits both EGF and her2-neu expression) [83, 84]

## Targeting HER2 neu

The HER2 neu gene (also known as c-erbB-2, or *neu*) has shown to be amplified in over one-fifth of patients suffering from breast cancer and is linked to highly aggressive tumors with a poor prognosis. HER2 is dramatically amplified (from 2-fold to greater than 20-fold) in 30% of breast cancer tumors, and amplification of the HER2 gene is an independent predictor of a shorter overall survival and time to relapse in patients with breast cancer. HER2 is over-expressed in a significant proportion of patients (10% to 45%) in other malignancies as well, including NSCLC, ovarian cancer, prostate and gastric cancer. In addition, HER2 status predicts poor outcome in patients with ovarian and gastric cancer. [85-89]

Chemotherapy, which suppresses the immune system, is commonly given in conjunction with herceptin (a drug that inhibits HER-2 neu). [90, 91] Using botanical agents to enhance the immune system has been shown to improve the effectiveness of monoclonal antibodies including herceptin against HER-2 neu.

Studies show the key ingredient found in olive oil, known as **oleic acid**, assisted in cancer protection by significantly cutting activity levels of Her-2/neu.[12]

Emodin, a natural constituent of Foti (**Japanese knotweed**), *Hippohae rhamnoides,* (**Sea buckthorn**) and other medicinal herbs, significantly inhibited the growth of cancer, in part by inhibiting HER-2 neu expression. Emodin has been reported to be nontoxic for normal cells but to possess specific toxicity for neuroectodermal tumor cells. [93]

**Insulin resistance, adipocytokines and angiogenesis**

The adipocytokines are biologically active polypeptides that are produced either exclusively or substantially by the adipocytes, and act by endocrine, paracrine, and autocrine mechanisms. Most have been associated with obesity, hyperinsulinemia, type 2 diabetes, and chronic vascular disease; in addition, six adipocytokines--vascular endothelial growth factor, hepatocyte growth factor, leptin, tumor necrosis factor-alpha, heparin-binding epidermal growth factor, insulin-like growth factor, and interleukin-6--promote angiogenesis while one, adiponectin, is inhibitory. Obesity and insulin resistance have both been identified as risk factors for breast cancer and are associated with late-stage disease and poor prognosis. [94]

Recent findings showed that curcumin, from turmeric and EGCG, in green tea, can inhibit a member of the MMP family, aminopeptidase N (APN) which is implicated in the angiogenic switch process. Most notably, curcumin and EGCG can also interfere with the expression of VEGF by processes other than hypoxia, such as transforming growth factor (TGF)-b release, COX-2 over-expression, hydrogen peroxide release from bone cells, constitutive and aberrant EGFR and Src signaling and most importantly, by aberrant NF-kB signaling in established cancers. Companion adaptogens such as curcumin, grape seed extract and green tea components are also known to interfere with the endothelial cell function by inhibiting specific integrin engagement and usage. They do not however interfere with normal cell function. This is the beauty of these safe compounds.

**These companion adaptogenic agents are believed to suppress the transformative, hyperproliferative and inflammatory processes that initiate carcinogenesis.** These inhibitory influences may ultimately suppress the final steps of carcinogenesis, namely angiogenesis and metastasis. Companion adaptogens can also be classified as chemopreventive agents since their ability to delay the onset of the carcinogenic process has been studied extensively. Because these chemopreventive agents are derived from natural sources, they are considered pharmacologically safe. [95]

**Herbs as inhibitors of the NF-kB and COX-2 activation pathway**

NF-kB is a family of closely related protein dimers that bind to a common sequence motif in the DNA called the kB site. Research over the past decade has revealed that NF-kBisan inducible transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation and growth and cancer metastasis. Several natural compounds found in many companion adaptogens are potent inhibitors of NK-kB. These include resveratrol, piceatannol, curcumin, EGCG, and ursolic acid.

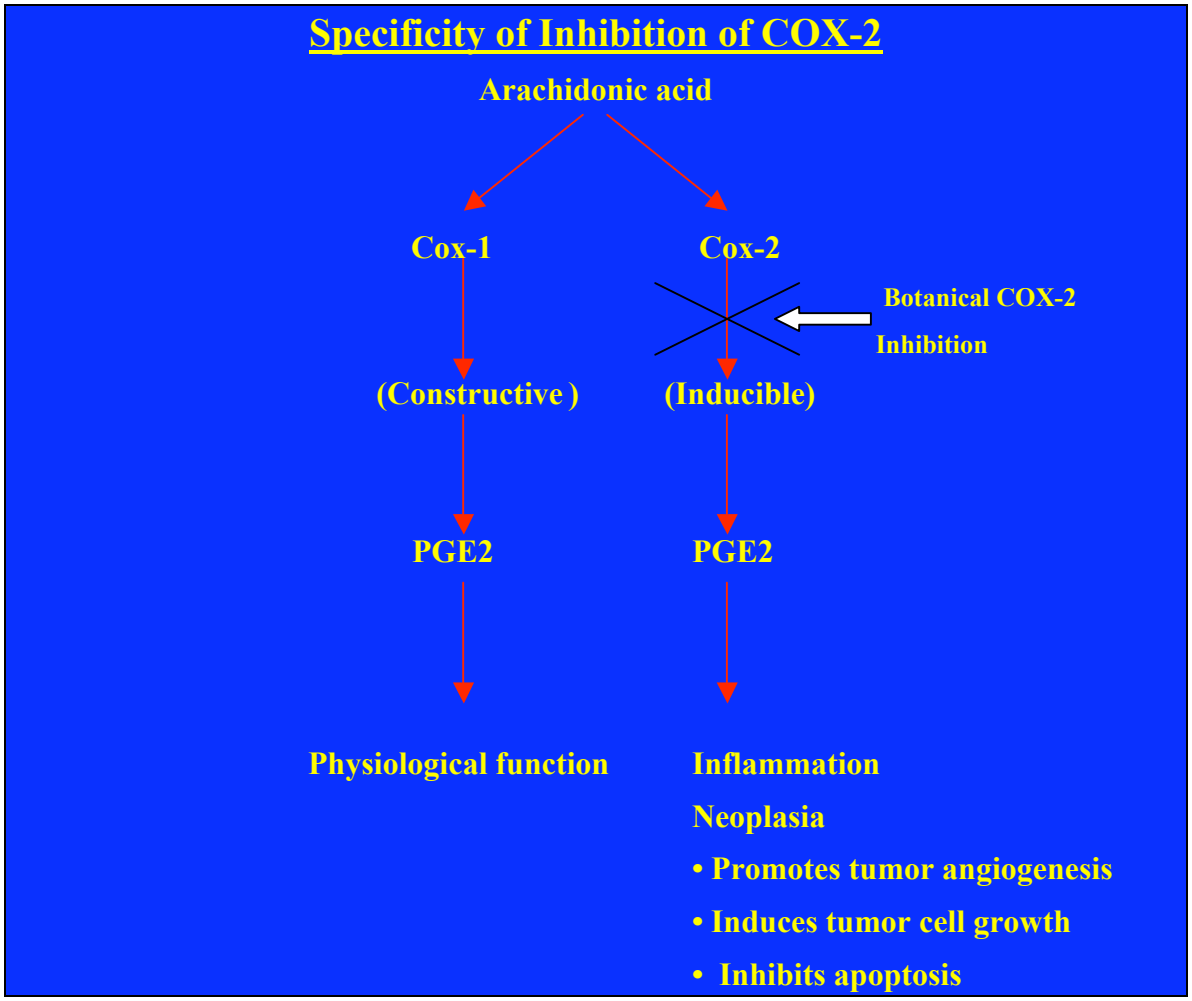
NK-kB induces the over-activation of cyclo-oxygenase (COX) proteins. COX-1, which is expressed in most normal tissues, is responsible for the synthesis of healthy prostaglandins (PGs) required for essential physiological functions. In contrast, COX-2 is not detectable in most normal tissues; it is induced by phorbol esters, cytokines, and growth factors, including TGF-β and bFGF, and has been associated with carcinogenesis.

Recent animal studies have suggested colorectal tumors expressing Ras mutation produces significant amounts of COX-2. This is of note since Ras mutations are involved in the production of late stage adenomas and eventual loss of chromosome 18.

**What we know so far of the cancer COX-2 over-expression relationship:**

1) COX-2 expression is up-regulated during intestinal tumorigenesis and by tumor promoters
2) Modulation of COX-2 expression affects tumor growth
3) Treatment with COX-2 inhibitors reduces tumor growth
4) COX-2 may be a relevant target for prevention and/or treatment of many types of cancer
5) Expression of COX-2 is increased in HER2/neu expressing carcinomas

Depending upon the stimulus and the cell type, different transcription factors including AP-1, NF-IL-6, NF-kB can stimulate COX-2 transcription. The balance between the activation of the oncogenes and the inactivation of the tumor suppressor genes, and expression of several proinflammatory cytokines can modulate the expression of COX-2 in tumors. Complicating matters further is that conventional cancer therapies such as radiation, surgery and chemotherapy can induce COX-2 and prostaglandin biosynthesis. [96]




**Botanical agents, which exhibit COX-2 inhibition through a mechanism different than that of pharmaceutical agents, offer several advantages over pharmaceutical agents. The main advantages of botanical COX-2 inhibitors over pharmaceutical agents are:**

1. Botanical COX-2 inhibiting agents are far safer. Most prescription drugs that block COX, including even aspirin, and some of the new so-called selective COX-2 inhibitors, such as celebrex, also block prostacycline. This is, in part, what makes them still hard on the digestive track, leading to GI pain and even a potential bleeding ulcer. Botanicals that exert a COX-2 effect on controlling inflammation do not interfere with prostacycline production and therefore do not carry the same risk. As a matter of fact,

many of the herbs with COX-2 inhibiting activity promote a healthy GI tract and inhibit ulcer formation, most notably ginger.

Pharmaceutical COX-2 inhibitors interfere with beneficial short-term inflammation. This has been noted to inhibit wound healing and ligament healing after sprains. [97, 98]

Pharmaceutical COX-2 inhibitors substantially increase the risk for heart disease and a hear attack. On the other hand the botanical agents are protective against heart disease.

2. Many botanical agents, because of the synergy within many of their natural occurring compounds, also inhibit cancer by acting as powerful modulators of oxidative stress, quenching and deactivating dangerous free radicals before they can do damage. Herbs, particularly those in the oregano family, have even higher antioxidant activity than vegetables, fruits, and/or vitamins or minerals. By binding to and removing the free radicals, antioxidants may help prevent cancer, heart disease, and other diseases.

   Many botanical COX-2 inhibiting agents block the activation of the transcription factor NF-[kappa]Beta without affecting basal NF-[kappa]Beta activity. The latter result suggests that many botanical agents inhibit abnormal cell proliferation, cell-mediated cytotoxicity, and cytokine production, at least in part through the inhibition of NF-[kappa]B activation. [99]

In addition to its involvement in cancer progression, COX-2-mediated angiogenesis most likely has a critical role in the progression of preneoplastic lesions to the invasive phenotype. [229-232]

## Adaptogens: Modulators of Inflammatory Pathways

There is an emerging relationship between neoplasia and inflammatory eicosanoids (PGE2 and related prostaglandins), with a focus on how inhibition of their synthesizing oxidases, particularly COX, offers anticancer actions. Although a majority of this research emphasizes the pharmaceutical applications of non-steroidal anti-inflammatory drugs and selective COX-2 inhibitors, these agents fail to address alternate pathways available for the synthesis of pro-inflammatory eicosanoids. Evidence is presented that suggests the inhibition of lipoxygenase and its by-products-LTB4, 5-HETE, and 12-HETE-represents an overlooked but crucial component in complementary cancer therapies. Based on research natural agents capable of modulating both lipoxygenase and COX may advance the efficacy of cancer therapy. Selected nutritional and botanical agents (notably, omega-3 fatty acids, bromelain, curcumin, grape skin & seed (resveratrol), green tea (EGCG), quercetin, boswellia, etc.) favorably influence eicosanoid production. [100]

**Adaptogens also modulate inflammatory cytokines: They down-regulate the tumor promoter IL-6 and TNF-α, up regulate IL-2, 10 & 12, and α and β-interferon. Many cancers, such as Multiple Myeloma, prostate, and kidney cancer all over-express IL-6. Stress and inflammation increase IL-6 production. Many adaptogens and n-3 fatty acids have demonstrated an ability to reduce IL-6 and/or TNF-α.**

Companion adaptogens, such as curcumin have shown to possess significant COX-2 inhibiting activity through the suppression of NF-kB. Thus, non-toxic compounds such as curcumin will be useful in the treatment of several cancers targeting angiogenesis since COX-2 expression stimulates angiogenesis. Since COX-2 derived prostaglandins stimulate aromatase activity in an organ specific manner, an independent source of estradiol generation in breast cancer patients undergoing anti-estrogen therapies can be blocked by curcumin and other chemopreventives that have significant COX-2 inhibitory activity. COX-2 inhibitors will be particularly useful in the treatment of advanced breast cancers through inhibition not only of HER-2/neu activity but also of aromatase activity. Many companion adaptogens, including curcumin achieve this effect by inhibiting the upstream activator complex consisting of NF-kB-inducing kinase (NIK) and IkBa kinase (IKK) enzymes. [101-102]

Many primary adaptogens including Panax ginseng have profound anti-angiogenic actions, involving multiple mechanisms including COX-2 and NF-kB inhibition. [103-105] The aqueous extract of Atractylodes japonica suppressed PGE(2) synthesis by inhibition of cyclooxygenase-2 (COX-2). [106]

**Activator Protein-1 (AP-1)**

Activator Protein -1 (AP-1) can also promote the transition of tumor cells from an epithelial to mesenchymal morphology which is one of the early steps in tumor metastasis. These oncogenic properties of AP-1 are primarily dictated by the dimer composition of the AP-1 family proteins and their post-transcriptional and translational modifications.

While several inhibitors of angiogenesis are in clinical trials, it is very important to note that the herbal extracts and phyto-nutrients I employ here are completely safe and are already known to target these pathways. [109, 110] **Several agents that are known to inhibit the NF-kB or the AP-1 activation process, most notably curcumin, green tea, 6-gingerol (ginger) and resveratrol can cause a significant suppression of cell proliferation and sensitize cells for apoptosis.** Most notably, these compounds are also known to down regulate the expression of apoptosis suppressor proteins, such as Bcl-2 and Bcl-XL in several cancer cell lines. Ginger also down-regulates EGF expression. [107, 108]

Curcumin can interfere with the activity of MMP-2 and 9, reducing the degradation of ECM, which forms the basis of angiogenic switch. [111] Thus, it can also interfere with the release of angiogenic and other growth factors that are stored in the ECM. By inhibiting several growth factor receptors such as EGFR and VEGFR, it can also significantly impact upon the mechanisms of angiogenic switch and vessel cooption that are necessary for the sprouting growth of new blood vessels in the tumor. By interfering with the non-receptor tyrosine kinases such as Src and FAK, agents such as curcumin, resveratrol, and green tea components can interfere with the downstream PI-3 Kinase signaling responsible for the induction of the angiogenic target genes such as COX-2, VEGF, IL-8 and the MMPs. By inhibiting another member of the MMP family, namely MMP-2, curcumin may have a negative impact upon the MMP-2 mediated degradation of the lamin-5 isoform which is implicated in the formation of loose and primitive looking meshwork formed by aggressive cancers such as melanoma and prostate cancers. [112-114]

**Lipoxygenase Products shown to promote tumor angiogenesis**

The 12-LOX product of arachidonic acid metabolism, 12-hydroxyeicosatetraenoic acid (12-HETE), like COX-2, has been shown to promote tumor angiogenesis. In experiments it has been demonstrated that enhanced angiogenesis in nude mouse solid tumors formed from 12-LOX cDNA-transfected MCF-7 human breast cancer and PC-3 human prostate cancer cell lines, respectively. 12-HETE also possesses mitogenic activity for fetal bovine aortic endothelial cells and microvascular endothelial cells. As in the case of the PGs, the effect of products of LOX activity on angiogenesis occurs in collaboration with the angiogenic protein growth factors. Our knowledge of the mechanisms involved is incomplete, but it has been shown that interaction occurs with bFGF. Using selective LOX inhibitors, including those with high specificity for 12-LOX, bFGF-stimulated bovine capillary endothelial cell growth was suppressed without causing cytotoxicity. [115]

**Green tea and its main catechin epigallocatechin-3 gallate (EGCG) may decrease the risk of cancer.** This study showed that green tea extract (GTE) as well as its individual catechin components inhibited MDA-MB231 breast cancer cell and human umbilical vein endothelial cell (HUVEC) proliferation. Further, GTE suppressed breast cancer xenograft size and decreased the tumor vessel density in vivo. In the current study, we investigated the effect of GTE on the major angiogenic factor vascular endothelial growth factor (VEGF) in an in vitro experiment. GTE or EGCG (40 mg/L) significantly decreased the levels of the VEGF peptide secreted into conditioned media. This occurred in both HUVEC and human breast cancer cells and the effect was dose dependent. Furthermore, GTE and EGCG decreased the RNA levels of VEGF in MDA-MB231 cells. This inhibition occurred at the transcriptional regulation level and was accompanied by a significant decrease in VEGF promoter activity. We also showed that GTE 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 GTE. Furthermore, GTE 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. [116]

The primary action of green tea is through its catechin, EGCG, which blocks the induction of vascular endothelial growth factor (VEGF), considered essential in angiogenesis. In vivo studies have shown the following actions on cancer cells: a 58% inhibition of tumor growth, a 30% inhibition of microvessel density, an increase in tumor cell apoptosis 1.9-fold, and a threefold increase in endothelial cell apoptosis.

**Note:** It may be more efficacious to take powdered green tea extract rather than tea as a cancer adjuvant therapy. An appropriate dose for VEGF blockade would be 2-4 grams of standardized green tea extract (95% polyphenols/60% catechins)) Each gram of this extract provides 400-500 mg of the critical anticancer polyphenol called epigallocatechin gallate (EGCG). Caffeine has been shown to potentiate tea polyphenols, such as EGCG, so it is preferable not to decaffeinate the tea.

**Ginko biloba:** Recent studies conducted have revealed that Ginkgo biloba extract has anticancer (chemopreventive) properties that are related to their antioxidant, anti-angiogenic and gene-regulatory actions. The Ginkgo biloba extract used in most of the research is EGb 761, which contains 22-27% flavonoids (ginkgo-flavone glycosides) and 5-7% terpenoids (ginkgolides and bilobalides) inhibits angiogenesis involving the down-regulation of VEGF. [117, 118, 223]

**Anti-angiogenic mechanisms of polyphenols**
Accumulating evidence demonstrates that polyphenols in natural products are beneficial against human lethal diseases such as cancer and metastasis. The underlying mechanisms of anti-cancer effects are complex. Recent studies show that several polyphenols, including epigallocatechin-3-gallate (EGCG) in green tea and resveratrol in red wine, inhibit angiogenesis when administrated orally. These polyphenols have direct effects on suppression of angiogenesis in several standard animal angiogenesis models. Perhaps the greatest therapeutic advantage of these small natural molecules over large protein compounds is that they can be administrated orally without causing severe side effects. It is anticipated that more polyphenols in natural products will be discovered as angiogenesis inhibitors and that these natural polyphenols could serve as leading structures in the discovery of more potent, synthetic angiogenesis inhibitors. [220]

**Curcumin (Turmeric):** The anti-invasive effects of curcumin appear to be mediated through the downregulation of MMP-2 (matrix metalloproteinase) and the upregulation of TIMP-1 (tissue inhibitor of metalloproteinase), 2 common effector molecules that have been implicated in regulating tumor cell invasion. This study also demonstrates that curcumin inhibits the transcript levels of 2 major angiogenesis factors VEGF (vascular endothelial growth factor) and b-FGF (basic fibroblast growth factor) mainly in ER-negative MDA-MB-231 cells. [221]

**Grape seed extract (GSE)** feeding strongly inhibited tumor growth in animal studies that accounted for 59-73% ($p < 0.001$) inhibition in tumor volume and 37-47% ($p < 0.05$) decrease in tumor weight at the end of the experiment. It did not show any significant change in body weight gain profile and diet consumption. Immunohistochemical analysis of tumors showed that GSE decreases proliferation index by 51-66% ($p < 0.001$) and increases apoptotic index by 3-4-fold ($p < 0.001$). CD31 staining for endothelial cells, showed decrease in intratumoral microvasculature in GSE-fed group of mice. Control tumors showed 64.0 +/- 1.6 CD31 positive cells/400x field compared to 23.2 +/- 0.9 and 15.7 +/- 0.08 ($p < 0.001$) CD31 positive cells in 100 and 200 mg/kg doses of GSE-treated tumors, respectively. GSE strongly inhibited (47-70%, $p < 0.05$) vascular endothelial growth factor (VEGF) secretion. Recently, the circulating level of insulin-like growth factor binding protein (IGFBP)-3 is shown to be inversely related with PCA risk, growth and prognosis. Consistent with this, a 6-7-fold ($p < 0.001$) increase in tumor-secreted levels of IGFBP-3 was observed after GSE feeding. These findings suggest that GSE possesses in vivo anticancer efficacy against hormone-refractory human prostate cancer, which is associated with its antiproliferative, proapoptotic and antiangiogenic activities together with upregulation of IGFBP-3. [223]

Recent studies show that edible berries may have potent chemopreventive properties. Multiple berry extracts were tested on inducible VEGF expression. Six berry extracts (wild blueberry, bilberry, cranberry,

elderberry, raspberry seed, and strawberry) and a grape seed proanthocyanidin extract (GSPE) were studied. Antioxidant activity of the extracts was determined by ORAC. Cranberry, elderberry and raspberry seed samples were observed to possess comparable ORAC values. Each of the berry samples studied significantly inhibited both H2O2 as well as TNF alpha induced VEGF expression. [219]

## Prostaglandins, Fatty Acids as Angiogenic Factors

Prostaglandins are autacoids derived from arachidonic acid via COX-mediated metabolism and include the PGs prostacyclin (PGI2) and thromboxane (Tx). A role for arachidonic acid-derived prostaglandins (PG)s in the process of angiogenesis was proposed by Ben Ezra in 1978 and later established directly by angiogenic bioassays. Ziche and colleagues used a rabbit corneal assay to demonstrate the angiogenic activity of PGE2 and that stimulation of neovascularization by mouse fibroblasts was blocked by a nonselective COX inhibitor. [221-223]

The COX and LOX products of n-6 fatty acid metabolism may exert stimulatory effects on cancer progression at several levels. This following review presents published data in support of a role in tumor-mediated angiogenesis. In addition, these eicosanoids can modulate tumor cell growth and invasion directly and promote the intra-vascular steps of the metastatic cascade. Thus the multiple events contributing to aggressive tumor behavior may be enhanced indirectly by n-6 fatty acids and directly by the eicosanoids derived from them and suppressed by the n-3 fatty acids and pharmacological inhibitors of eicosanoid biosynthesis. [224, 225]

Dietary fatty acids have been shown to inhibit the growth of preexisting breast cancer micrometastases when used as adjuvant nutritional therapy after excision of the primary tumor, and most likely the suppression of angiogenesis contributes to this therapeutic effect. [226] This study suggests that dietary n-3 fatty acid supplementation should be implemented as an adjunct to surgery and conventional combination chemotherapy and for cancer prevention. [228, 235] **Overall, a review of the published experimental studies indicates that selective herbal-based pharmacological inhibitors of COX and LOX activity and dietary n-3 fatty acid supplementation should be included in future clinical trials and that the biological rationale rests, in part, on their antiangiogenic effects.**

There is now a substantial amount of research showing that omega-3 fatty acids enhance immune function and reduce cancer growth. Diets high in omega-3 fatty acids exert suppressive effects on cancer growth and are associated with impaired angiogenesis. Both EPA and DHA have shown to inhibit metastasis of several cancer cell lines including breast, prostate and colon cancer. [233-241]

**The most common dietary fatty acids I use in my practice are EPA/DHA n-3 derived from fish oil concentrates and GLA-rich Pine seed, Evening Primrose, and Borage oils.**

EPA and DHA intake are both related to lower total prostate cancer risk and advanced prostate cancer risk. Men with the highest quintiles of EPA and DHA combined had an 11 per cent lower total prostate cancer risk and advanced prostate cancer risk was 26 per cent lower, according to the risk analysis. [241]

## Protein Kinase Inhibitors

According to the Laboratory of Molecular Biophysics, of the hundreds of protein kinases in the human genome, only about 27 protein kinase structures have been solved to date. Yet, so important are the family of kinases, oncogenes that encode (program) protein kinases are under ongoing study for their participation in cancer. In normal cells, protein kinases are involved in signals sent between the cell membrane and the nucleus, regulating progression through the cell cycle. Protein kinases control these processes by activating other proteins in response to stimuli. Mutated kinase genes have been found in a number of malignancies, including chronic myelogenous leukemia and breast and bladder cancers.

Kinases can lead to cancer though various pathways including overproduction, an event caused by mutations in the control regions of their genes. Compared to normal cells, tumor cells often overproduce

kinases, encouraging the cell to divide. A commonly overproduced kinase in cancerous tissue is the receptor for epidermal growth factor (EGF), an upregulation strongly favoring the cancer.

Numerous compounds derived from edible plants have been reported to interfere with a specific stage of the carcinogenic process. Some anti-inflammatory botanicals and/or phyto-agents with cyclooxygenase-2 inhibitory activity have been found to exert chemopreventive properties by targeting intracellular signaling molecules. These include mitogen-activated protein kinases and transcription factors, such as NF-kappaB and AP-1. [124]

Kinases can also contribute to cancer if their structure is abnormal. Many tumor cells possess protein kinases that (because of a structural defect) are permanently turned on, goading the cell into division. Examples of kinases that behave abnormally in certain human cancers are the Abl, Src, and cyclin-dependent kinases. [125]

Carnosol, as well as ursolic acid, compounds found in *Rosmarinus off.* **(Rosemary)**, have been shown to inhibit tumor promotion by inhibiting the Tyrosine kinases and Ornithine decarboxylase activity. Other compounds found in Rosemary called diterpenoids, also have antioxidant activity. [126] Carnosol has also shown to reduce nuclear factor-kappaB (NF-kappaB) [127] and the anti-apoptotic protein Bcl-2. [128]

Obviously, an inhibitor of dysfunctional kinases is a worthy cancer therapy research objective. The challenge is finding a substance that can distinguish one kinase from another. Many of the protein kinases in mammalian cells have similar structures, particularly in biochemically active regions. Hence, an inhibitor of any single protein kinase might disrupt the activity of others, that is, an unrelated kinase crucial to normal cell function. **Herbal agents have the advantage of normalizing several pathways, regulating gene expression rather than completely shutting down a particular target site or kinase. Several have been found to inhibit the growth of cancer cells possessing mutated kinase genes.**

Genistein and daidzein, isoflavones found in soy, are specific inhibitors of protein tyrosine kinase (PTK). By modulating pathways involved in signal transduction, isoflavones acting upon PTK put the brakes on rapidly dividing cells. [129] Oxidants and free radicals selectively react with the regulatory center of protein kinase C (PKC), signaling tumor promotion and cell growth. In contrast, antioxidants (selenium and polyphenolic agents, such as curcumin; and vitamin E analogues) inhibit cellular PKC activity and thus interfere with the action of tumor promoters. Other polyphenolic phytochemicals, that is, the constituents of green tea and resveratrol, respond similarly, displaying significant PKC inhibition. [130]

Ursolic acid, present in *Ocimum sanctum l.* (**Holy Basil**) and Rosemary, is a well-known antitumor agent that suppresses protein kinase C (PKC) activity, down regulates MMP-9, and induces apoptosis), is hepatoprotective, anti-inflammatory (COX-2 inhibition), anti-ulcer, anti-microbial, anti-hyperlipidemic, and antiviral. [131]

Enhanced activity of tyrosine kinase receptors (RTKs) has been implicated as a contributing factor in the development of malignant and nonmalignant proliferative diseases such as cancer and atherosclerosis. Several growth factors transducing mitogenic signals through RTKs are implicated in the development of tumor and cardiovascular diseases. Therefore, in recent years many efforts have been made to develop RTK small molecule inhibitors for the treatment of tumor and cardiovascular diseases.

Recently, catechins, the main compounds of green tea leaves, have been identified as potent natural inhibitors of several RTKs. Furthermore, there is increasing evidence that catechins possess antiangiogenic properties. In summary, several animal and cell culture studies suggest that catechins are potential candidates for the clinical therapy of cancer and cardiovascular diseases. [132]

These growing bodies of knowledge about the effect of kinases on cell regulatory genes helps explain why soy extracts (genistein and daidzein), curcumin, several caroteniods, and certain types of vitamin E have anticancer effects. There are findings from related studies indicating that the following phytonutrients might be beneficial in suppressing protein kinase C that is involved in controlling cancer cell propagation:

**A few natural compounds that inhibit PTK and/or PKC include the following:**

- CAPE (caffeic acid phenethyl ester) found in propolis and echinacea
- Curcuminoids from Turmeric
- Flavonoids, including apigenin, found in propolis, *Chamomilla recutita* (Chamomile), and *Passifloras* (Passion-flower), luteolin, quercetin, found in onions, broccoli and *Glycyrrhiza glabra* (Licorice)
- Corosolic acid isolated from the fruit of *Crataegus pinnatifida var. psilosa* (Hawthorn)
- Resveratrol, a phytoalexin found in the grape skin and leaf
- Catechins from in green tea, including EGCG
- Silymarin from milk thistle
- Hyperforin from *Hypericum* (St. John's Wort)
- Forskolin from *Coleus forskohlii*
- Ursolic acid from Holy basil and rosemary
- EPA and DHA from Omega-3 fatty acids (Fish Oil)
- Vitamin E, as vitamin E succinate, and as the isomer gamma-tocopherol
- Tocotrienols (analogs of vitamin E)
- Genistein and Daidzein (isoflavones found abundantly in soy foods)
- Spingolipids, lipid substances found abundantly in soy foods and eggs

## Bcl-2 Protein

Bcl-2 is a normal human protein. Bcl-2 and its family members play a pivotal role in the normal process of cell death known as **apoptosis**. In mature individuals, apoptosis is necessary to accommodate the billions of new cells produced daily and to eliminate aged or damaged cells. The regulation of this process i.e. the decision to initiate the process of cell death—is mediated primarily by the Bcl-2 protein family.
Bcl-2 is normally found in the mitochondrial membrane where it regulates the release of a substance known as cytochrome C. Once released from the mitochondria, cytochrome C triggers the activation of a number of enzymes (known as caspases), which ultimately result in cell death.

**Apoptotic Signaling Pathway**

Apoptotic signaling is broadly characterized as occurring by either a mitochondrial pathway, resulting in cytochrome induced activation of the initiator caspase 9, or by extra-mitochondrial pathways, frequently involving the initiator caspase 8. Both pro and anti-apoptotic Bcl-2 family members regulate the release of cytochrome c from mitochondria. Recent studies suggest that activation of the mitochondrial pathway is controlled by activation of BH3-only Bcl-2 family members such as BAD, BIM, BMF, and NOXA. The ability of such BH3-only Bcl-2 family members to induce apoptosis is in turn dependent upon the function of Bax and Bak. Consistent with this, BAX oligomers have been demonstrated to allow transport of cytochrome c in pure liposomes. BH3-only family members such as BAD bind to anti-apoptotic molecules such as Bcl-2 and Bcl-XL, and augmented mitochondrial levels of BAD ultimately facilitate the formation of higher order oligomers of BAX and BAK. The intracellular localization of BH3 family members is tightly regulated and appears to serve as a trigger for the mitochondrial apoptotic cascade described above. [199-201]

**Bcl-2 Link to Cancer**
High levels of Bcl-2 are associated with most types of human cancer. In these diseases, Bcl-2 blocks the release of cytochrome C, which would ordinarily be triggered by cancer therapy. Bcl-2 also appears to be a major contributor to both inherent and acquired resistance to current anticancer treatments.

**Bcl-2 is known to:**

- Prevent programmed cell death
- Enhance metastatic potential
- Promote resistance to anticancer therapy
- Indicate poor prognosis in many cancers

**Natural compounds that reduce BCL-2 expression**

High levels of Bcl-2 are associated with most types of human cancer. [202] **Curcumin and Green tea extract** inhibit Bcl-2 expression. [203-205] **Scutellaria baicalensis extract**, rich in many phenolic compounds, including **baicalin, baicalein, wogenin oroxylin,** was found to inhibit Bcl-2-overexpression, prostaglandin E (2) synthesis, COX-2 gene expression, and block nuclear factor-kappaB (NF-kappaB) binding and transcriptional activation. [206, 207] Hibiscus protocatechuic acid (PCA), a phenolic compound isolated from the dried flower of **Hibiscus sabdariffa L**. (Malvaceae), demonstrated antioxidant and antitumor promotion effects in part through Bcl-2 inhibition mechanism. [208, 209] **Carnosol** may be useful as a novel chemotherapeutic agent against B-lineage leukemias, and possibly other types of cancers that express high levels of the protective protein, Bcl-2. [210] 3,3'-**Diindolylmethane (DIM)** is a major in vivo derivative of the putative anticancer agent indole-3-carbinol (I3C), which is present in vegetables of the Brassica genus. In a recent study DIM treatment decreased total transcript and protein levels of the apoptosis inhibitory protein Bcl-2, and the amount of Bcl-2 bound to the pro-apoptotic protein Bax. DIM treatment also caused an increase in Bax protein levels, but did not affect the level of Bax that was bound to Bcl-2. As a functional test of the role of Bcl-2 down-regulation in the DIM-induced apoptotic response, ectopic expression of Bcl-2 in MCF-7 cells was shown to attenuate the apoptotic effect of DIM. These results demonstrate that DIM can induce apoptosis in breast cancer cells independent of estrogen receptor status by a process that is mediated by the modulated expression of the Bax/Bcl-2 family of apoptotic regulatory factors. [211]

Other reducers of Bcl-2 include **beta-sitosterol**, a main dietary phytosterol found in adaptogenic herbs, [212] and **EPA** from fish oil. [213]A lectin extract of *Viscum album* **(Mistletoe)** has demonstrated an ability to induce apoptosis, by effecting Bcl-2. [214] **Theophylline**, a phosphodiesterase inhibitor, resulted in downregulation of bcl-2 concomitant with induction of apoptosis. **Theophylline** works through an indirect increase in cAMP, the role of several molecules on **B-CLL** cells. Direct cAMP inducers such as dibutyryl-cAMP (db-cAMP) and **forskolin** induced moderate apoptosis. [215] **6-Gingerol,** a naturally occurring plant phenol, is one of the major components of fresh ginger induced cell death in promyelocytic leukemia HL-60 cells, caused DNA fragmentation and inhibited Bcl-2 expression in HL-60 cells. These results suggested that the inhibition of Bcl-2 expression in HL-60 cells might account for the mechanism of 6-gingerol-induced apoptosis. [216] Grape seed extract, was also shown to **regulate bcl-2 gene and downregulate the oncogene c-myc.** [217]

**Echinocystic acid (EA),** a natural triterpene enriched in various herbs, including **ginseng**, has been showed to have cytotoxic activity in some cancer cells, and is used for medicinal purpose in many Asian countries. Molecular data showed that EA induced the truncation of Bid protein and reduced Bcl-2 protein. EA also caused the loss of mitochondrial membrane potential (DeltaPsi(m)) and cytochrome c release from mitochondria to cytosol. Moreover, EA could activate c-Jun NH(2)-terminal kinase (JNK) and p38 kinase, and JNK-specific inhibitor SP600125 and p38 kinase-specific inhibitor SB200235 could block serial molecular events of EA-induced apoptosis such as Bid truncation, Bcl-2 reduction, cytochrome c release, caspase activation, and DNA fragmentation in HepG2 cells. These findings indicate that JNK- and p38 kinase-mediated mitochondrial pathways might be involved in EA-induced apoptosis and enhance our understanding of the anticancer function of EA in herbal medicine. [218, 219]

Parthenolide is a sesquiterpene lactone responsible for the bioactivities of **Feverfew**. Besides its potent anti-inflammatory effect, this compound has recently been reported to induce apoptosis in cancer cells, possibly through mitochondrial dysfunction. The parthenolide-mediated cell death signaling pathway was examined by focusing on the involvement of Bcl-2 family members. Using a human colorectal cancer cell line COLO205, researchers first demonstrated that parthenolide acted through the cell death receptor pathway to activate caspase 8. Following caspase 8 activation, Bid, a proapoptotic Bcl-2 member, was cleaved and this cleavage then triggered Bax conformational changes and Bax translocation from cytosol to mitochondrial membrane. Meanwhile, another proapoptotic protein, Bak, was up-regulated and oligomerized on the mitochondrial membrane. All these alterations were found to be prerequisites for the subsequent release of proapopototic mitochondrial proteins, including cytochrome c and Samc, in parthenolide-treated cells. Moreover, selective inhibition of caspase 8 activity by a synthetic caspase inhibitor (IETD-FMK) or overexpression of a viral protein (CrmA) suppressed the cleavage of Bid, conformational changes of Bax, cytochrome c release, and apoptosis. Therefore, the proapoptotic Bcl-2 family members are important mediators relaying the cell death signaling elicited by parthenolide from

caspase 8 to downstream effector caspases such as caspase 3, and eventually to cell death. [220]

## Hyper-coagulation, Fibrin, and other Clot-forming Pathways Associated with Angiogenesis: Another Important Target Relative to Botanical Compounds

Active residual cancer, of any extent, and active anticancer therapy of any form represent persistent hypercoagulable states. The magnitude of the prothrombotic stimulus may actually intensify with time as disease burden and metastases mount. As in other persistent hypercoagulable states, including congenital deficiencies of natural anticoagulants and chronic antiphospholipid antibodies, active malignancy and ongoing therapy should prompt an extended duration of anticoagulant therapy.

Despite overwhelming evidence, the role of anticoagulation in the tumor and metastatic processes has not, as of yet, been fully explained and treatment possibilities have not been explored in conventional medicine. According to laboratory experiments on animals and to initial clinical trials, anticoagulation drugs, as well as herbs that inhibit abnormal coagulation, are effective in the prevention and treatment of metastasis, and in the prolongation of survival. Botanical agents are able to influence the development of primary tumors, metastases and to diminish the occurrence of thromboembolic diseases. These agents also prolong the survival of cancer patients.

The growth of a primary tumor depends on its proliferation potential, its hijacking of the immune system, and ability of tumor angiogenesis. Agents that maintain normal hemo-dynamic balance, inhibiting coagulation can influence all of these aspects. [133, 134, 227]

The usefulness of blood moving herbs, such as *Salvia miltiorrhizae* and *Angelica sinensis*, was demonstrated in a randomized, controlled clinical trial evaluating the combined modality treatment of a Chinese herbal formula and radiotherapy in patients with nasopharyngeal carcinoma. In this trial, 90 patients received combined herbal and radiation treatment compared with 98 patients who were randomized to receive radiation treatment alone. [135]

Using specific botanicals and botanical compounds, together with selective enzymes, such as lumbrokinase, bromelain, and nattokinase, you can interfere and inhibit tumor angiogenesis, cancer cell motility and adhesion.

The aqueous extracts of 24 herbs traditionally used for curing ischemic heart disease in a clinic in China were screened for their in vitro angiogenic activity, another twenty-four traditionally used as anti-tumor or anti-inflammatory remedies in China were screened for their anti-angiogenic activity. Among the herbal extracts examined, *Epimedium sagittatum, Catharanthus roseus, Taxus chinensis, Scutellaria baicalensis,* and *Polygonum cuspidatum* elicited significant inhibition at a concentration of 1g dry herb /ml. [135]

*Salvia miltiorrhiza*, inhibits tumor growth, perfusion, oxygenation and increases response to chemotherapy and radiotherapy. [137] Salvia miltiorrhizae treatment results in decreased lipid peroxidation in reperfusion injury. [138]

Ginseng saponins (ginsenosides) have been regarded as principal components responsible for the majority of pharmacological activities exerted by ginseng. Panax ginseng extract possess anti-tumor effects, including inhibition of invasion, metastasis and angiogenesis and induction of tumor cell apoptosis. Tumor promotion often accompanies elevated ornithine decarboxylase (ODC) activity, inflammation, and induction of cyclooxygenase-2 (COX-2), IL-6, and LOX 5 and 12 activity. [139-144]

Publications on Panax ginseng and its relation to cancer on the Medline database (1983-2004) cover experimental models and human studies on cancer-preventive activity, cancer-treatment potential and other beneficial effects. [140]

**Panax ginseng and its constituents have been tested for their inhibiting effect on putative carcinogenesis mechanisms, including:**

1) Inhibition of cell proliferation,
2) Induction of apoptosis, induction of differentiation in cancer cells,
3) DNA repair,
4) Enhancement of immunosurveillance, including antibody response, natural killer (NK) cell activity, interferon production and the proliferation and phagocytic ability of leukocytes,
5) Anti-inflammatory,
6) Inhibition of angiogenesis,
7) Anti-oxidative and antimutagenic,
8) Endocrine system enhancement – normalizing the HPA axis, insulin, cortisol etc. [139-144]

Research has confirmed that *Astragalus membranaceous* restores immune function in patients undergoing chemotherapy. Astragalus can modulate the imbalance state of Th1/Th2 in cancer patients, improve their immune function disturbance, which is critically important in treating cancer patients. [145-151]

Medicinal mushrooms have several compounds including polysaccharides, polysaccharide peptides, nucleosides, triterpenoids, alkaloids, and compound structures yet identified, all contributing an immunomodulating effect referred to as Host Defense Potentiators (HDP).

Polysaccharides, isolated from Reishi and *Coriolus*, have also been shown to promote anti-tumor activity. Other active cancer-fighting compounds found in reishi include triterpenes. This action occurs not from direct tumor cell destruction, but by stimulating T-cell and macrophage activity and inducing interferon release. Adenosine, also found in Reishi, and Cordyceps inhibits platelet aggregation and thrombocyte formation, increasing blood flow through vasodilation. Adrenaline release is countered by adenosine, which helps to explain Reishi's adaptogenic ability to modulate over-stimulation and reduce stress. [152-155]

In recent years, it has been extensively demonstrated both pre-clinically and clinically that aqueous extracts obtained from *Coriolus versicolor* (20:1) display a wide array of biological activities, including stimulatory effects on different immune cells and inhibition of cancer growth. A polysaccharide preparation from the mushroom *Coriolus versicolor*, called PSK, has been the focus of much cancer therapy research in Asia and Europe. It is the subject of over 200 cancer-related articles indexed on Medline, including 60 clinical studies, several of which were multiyear, randomized, double-blind trials involving hundreds of patients. [156-158]

*Poria cocos*, another important mushroom extract, is traditionally classified as a spleen and stomach tonic. Poria extract (12:1) possesses anti-cancer and anti-angiogenic activity through the following mechanisms: Inhibits Topo II- Of the triterpene acids found in Poria cocos, one of the nine, dehydroebriconic acid, could potently inhibit DNA topoisomerase II (topo II) activity, a known cancer promoting mechanism; a potent COX-2 inhibitor – down regulates NFKB, immune-modulating and biological response modifier (BRM) - possesses antiproliferation and differentiation of human leukemic cells, and antitumor activities against Sarcoma 180 in vivo. [168-172]

Medicinal mushroom extracts possess extremely high tolerability, have proven benefits to survival and quality of life, and compatibility with chemotherapy and radiation therapy. This makes them well suited for cancer management regimens.

Licorice polyphenols induce apoptosis in cancer cells. Glycyrrhizic acid, present in licorice, inhibits lipoxygenase and cyclooxygenase, inhibits protein kinase C, down-regulates the epidermal growth factor receptor (EGF), and normalizes TH1 to TH2 immune response. These and other activities of licorice suggest that a combination of agents work synergistically, and any clinical trials should be done using whole plant concentrates of licorice. [159]

*Rabdosia rubescens Hora* (Rabdosia) is used traditionally to treat many forms of cancer especially breast and esophageal cancers. The diterpenoids ponicidin and oridonin, possess significant antiangiogenic activity. Oridonin effectively inhibited the proliferation of a wide variety of cancer cells. Oridonin induced apoptosis and G0/G1 cell cycle arrest and inhibited the proliferation of cancer cells via apoptosis and cell cycle arrest

with p53 playing a central role in several cancer types, which express the wild-type p53 gene. Oridonin may be a novel, adjunctive therapy for a large variety of malignancies. [161-163]

*Epimedium grandiflorum/brevicornum* has demonstrated immune-enhancing, anti-tumor and anti-angiogenic activity. It also possesses profound adaptogenic qualities as well. [92, 242]

Gotu kola (*Centella asiatica*), extract (10% triterpenoids) was effective in destroying 100 percent of the cultured tumor cells and was completely nontoxic to healthy cells, thereby displaying its selective toxicity to tumor cells only. In follow-up studies on animals, centella extract more than doubled the life span of mice with tumors and displayed a remarkable lack of toxicity. [6] Oral administration of Centella extract to tumor bearing mice retarded the development of solid and ascites tumors and increased their life span.

Centella extract increases the formation of connective tissue components, in particular hyaluronan (also called hyaluronic acid), a natural substance produced by cells. When large amounts of hyaluronan are produced, it inhibits hydrolaronidase and can block the signals of ras, a cancer-causing gene, which can stop the growth of tumor cells. It can also stimulate the production of tissue plasminogen activator (tPA), which is associated with the ability to break down fibrin. [164-167]

## Copper Antagonists Inhibit Angiogenesis

High serum levels of copper correlate with certain cancers and high copper appears to play a role in cancer promotion. The role of copper in cancer promotion through inflammation and angiogenesis is now well known. We are learning that copper status is critical to the function of many angiogenic growth factors. The concept of tumor growth driven by angiogenesis is well accepted, but what drives angiogenesis? Based on several lines of evidence, it is reasonable to hypothesize that angiogenesis is dependent on copper status. Copper is incorporated in the extra-cellular matrix that forms the very structure of blood vessels. Copper acts as a co-factor to molecules known as bFGF, VEGF, and angiogenin. Without it, they cannot function, and growth of new blood vessels stops.

The angiogenic activity of bFGF, VEGF, TNF-alpha, and IL-1 were found to be copper dependent. Furthermore, copper repletion switches angiogenesis back "on" when a copper-sufficient diet is restored, providing evidence for a novel, physiologic, and metabolic control pathway of angiogenesis. Copper, but not other trace metals, stimulated the directional migration of endothelial cells. Using a low copper diet and penicillamine therapy, prostaglandin E-stimulated angiogenesis was suppressed. Diverse angiogenic molecules show high affinity for copper.

Copper metabolism is profoundly altered in neoplastic development in human cancer and in tumor-bearing animals. Serum copper levels correlate with tumor incidence, tumor burden, malignant progression, and recurrence in a variety of human cancers (Hodgkin's and non-Hodgkin's lymphoma, sarcomas, leukemias, and cancer of the cervix, breast, liver, and lung as well as brain tumors). [173]

A hypothetical scheme is one of a proposed "copper switch" that turns angiogenesis "on" (copper-sufficient) or "off" (copper deficient). Copper acts as an obligatory cofactor and is permissive to the angiogenic activator. Copper reduction blocks angiogenesis by "switching" endothelial cells into the apoptosis pathway.

Copper reduction, using specific supplements can help to inhibit the angiogenic activity of four structurally diverse angiogenic factors and cytokines. The specific supplements used to lower copper include zinc, molybdenum, lipoic acid, N-acetylcysteine, selenium, cilantro, and phenolic-rich herbal compounds.

## The Role of Adaptogens in Cancer Treatment and Prevention

In the field of cancer, adaptogens can play a pivotal role in prevention and treatment through multifaceted mechanisms such as inhibiting carcinogenesis, or by stabilizing or reversing pre-malignant conditions. It has been reported that these herbs possess anti-tumor effects, including inhibition of invasion, metastasis

and angiogenesis and induction of tumor cell apoptosis. Adaptogenic formulas will strengthen and harmonize the endocrine system, build vitality & adaptation; enhance the HPA axis, combat and control stress, making the effects of stress less damaging; improve energy transfer and reduce oxidative stress. Herbs that fall under the category of adaptogens tend to be diverse in their actions and require time to invoke their therapeutic effects. Adaptogens are important during active cancer, assisting the body in coping, and increasing the body's ability to withstand many of the negative effects of conventional cancer therapies such as surgery, chemotherapy, and radiation therapies. There is more research validating the use of adaptogenic herbs in cancer prevention and treatment than any other natural or even conventional medicine. Just the fact that adaptogens increase our capacity to withstand stress alone makes them immensely valuable, being that stress is a major causative factor and that having cancer just furthers ones stress. Also, when you combine the primary, secondary, and companion adaptogens into formulations, their cancer inhibiting effects are much greater than the effects of any one individual plant. Besides the direct actions adaptogens have against cancer they can be of great value in weakened conditions so often seen in cancer patients. They may reverse the fatigue often seen in people with cancer, as well as many of the other common symptoms including depression, low blood counts, sleep difficulties, poor appetite, and irritability. They may also inhibit many of the common and potentially life-threatening complications of cancer, such as blood clots and infections.

The foundation of my protocols are based on adaptogens (all categories) and immunomodulating mushroom extracts, which build nonspecific vitality, are safe, economical and proven effective agents for integrative oncology. They should always be given to cancer patients within a multiphase treatment strategy.

Many herbs have demonstrated an ability to inhibit angiogenesis. These include many common spices and teas as well as very potent herbs with cytotoxic compounds. When dealing with advanced cancer patients it is important to layer and possibly pulse dose various herb formulas in order to see that patient return to good health. When working with a person with cancer herbal formulas should include the following:
(1) Adaptogens including primary, secondary, and companion adaptogens;
(2) Immune enhancing/gentle alteratives/lymphatics/hepatics; and one with
(3) Cytotoxic plants including potent alterative/lymphatics.

I combine these formulas with specific enzymes such as lumbrokinase (an potent fibrin-dissolving enzyme derived from the earthworm) and/or bromelain; as well as certain targeting nutritional formulations, and a smoothie drink.

Adaptogens are able to activate the protective properties of the body, to protect it from extreme exposures and to stimulate regenerative processes. Stimulus-response coupling systems responsible for defense and adaptation of an organism to stressors are multi-targeted and very complicated pharmacological systems, including the neuroendocrine (stress) and immune system. The mode of action of adaptogens is basically associated with the stress-system (neuroendocrine-immune complex) and can be directed on the various targets of the system involved in regulation (activation and inhibition) of stimulus-response coupling. They can be both activating (catecholamines, LT-s, cytokines, NO, etc.--"switch on" system--which activates energetic and other resources of the organism), and deactivating (corticosteroids and PGE2-endogenous mediators of cellular communications, which protect cells and the whole organism from overreacting to the activating messengers--"switch off" system) stress-messengers. The balance between the activities of the "switch on" and "switch off" systems reflects the well being of the organism. Generally speaking, adaptogens can be defined as "smooth" pro-stressors, which reduce reactivity of host defense systems and decrease the damaging effects of various stressors due to increased basal level of mediators involved in the stress-response.

The antitumor effect of adaptogens is associated with immunomodulation - they can activate macrophages, natural killer cells, antigen-dependent T lymphocytes, and interferonogenic actions. They also have the ability to suppress experimental tumor growth, to enhance tissue differentiation, to improve intercellular adhesion, and to reduce the likelihood of metastasis spreading. Most of the synthetic chemotherapeutic agents available today are immuno-suppressants, cytotoxic, and exert variety of side effects that are particularly evident in cancer chemotherapy. Botanical based immunomodulators are often employed as supportive or adjuvant therapy to overcome the undesired effects of cytotoxic chemotherapeutic agents and to restore normal health. Furthermore, the use of adaptogens decreases the toxic effects of chemotherapy

and radiation therapy, and improves drug tolerance. Each monograph provides extensive research on adaptogens in oncology. Extensive studies in animal and human models with tumors using various cytotoxic therapies demonstrated that adaptogens in combination with cytotoxic agents reduces chemotherapeutic drug toxicity, particularly with regards to bone marrow restoration and enhances anti-tumor and anti-metastatic effects. Eleuthero possesses profound interferon enhancing activity when the body requires it otherwise it remains in a ready-and-wait mood. Important adaptogens to consider in oncology include *Eleutherococcus senticosus, Panax ginseng, Rhodiola rosea, Schisandra chinensis, Rhaponticum carthamoides, Aralia manchurica,* and *Ashwagandha*. Primary, secondary, and companion adaptogens are fundamental to any cancer treatment/preventive protocol nourishing the root system of the body. [174, 175]

## Stress and the Immune System

Overwhelming evidence has demonstrated that any type of stress has a detrimental effect on the ability to maintain optimal levels of important immunological response activities, including the ability of Natural Killer (NK) cells to destroy viral and cancer cells. A high degree of stress also significantly predicts a poorer response to interventions aimed at improving NK cell activity. This means that adaptogens are more important than immune-enhancing agents at assisting in immune response, particularly during times of stress. Experiments with mice showed that the tumor metastatic process increased while under stress, especially post surgery, which is a stressful event. The metastatic process can be inhibited by adaptogens, such as Eleuthero when given prior, during and after surgery. [176] Anyone undergoing surgery for cancer, or for any other reason should take adaptogenic formulas prior and after surgery.

Adaptogens are important remedies because they have been shown to ameliorate immune dysfunction by altering corticosterone levels in situations when the elevation of corticosterone is harmful. Some (secondary) adaptogen remedies act directly by stimulating macrophages and lymphocytes, reversing immunosuppression caused by stress. Thus, it is not always clear how a plant remedy is ameliorating immune dysregulation. In further studies of adaptogens it seems important to view them as working to enhance the HPA axis, which is what separates them from many other herbal remedies. [177-179]

Some plant remedies, such as *astragalus,* are not primary adaptogens, yet have immunotonic, immunostimulant, and/or immunomodulating properties. Astragalus, a secondary adaptogen that is considered a primary spleen tonic in TCM, for example, can stimulate many aspects of immune response, but does not increase resistance to a wide variety of stressors (e.g., psychological stress). In Russia, adaptogens have been used to the prevention of respiratory ailments with great success, reducing the incidence by 50%. These studies usually involve thousands of people, using a single adaptogen, such as Eleuthero, daily for several years. [181, 182]

**The Benefits of Adaptogens in Integrative Oncology Include:**

- Enhance and nourish the body's immune response against the cancer: As biological response modifiers, restoring immune surveillance, increasing non-specific human resistance, which aids both in the prevention and treatment of cancer by helping the body to fight existing cancer.
- Improve the overall health of the patient – reducing fatigue, enhancing the health of all the vital organs, increases nutrient utilization and protein synthesis (anti-catabolic); improves lipid and glucose energy efficiency.
- General antitoxic/antioxidant, scavenging free radicals before they reach target sites and initiate carcinogenesis. Many of these compounds also active enzymes that breakdown carcinogenesns, reducing them to harmless compounds.
- Systemic protection - kidney, liver, heart, bone marrow, adrenal gland. Steroids are often used in cancer treatments and cause a host of negative effects. Adaptogens potentiate steroids while reducing both short and long-term side effects.
- Retard the development of cancer and cancer metastases.
- Increases tolerability of radiation treatment, preventing radiation sickness; protects and enhances effectiness of radiation.

- Build up the bone marrow and blood counts, while reducing infections
- Increases tolerability and effectiness of chemotherapy and biological therapy, improves immune system recovery; protects vital organs and enhances the general condition (appetite, sleep, etc.).
- Inhibit multi-drug resistance (Pgp inhibition, reduces the expression of NF-kB, AP-1, p53, and Bcl-2. [183-187]

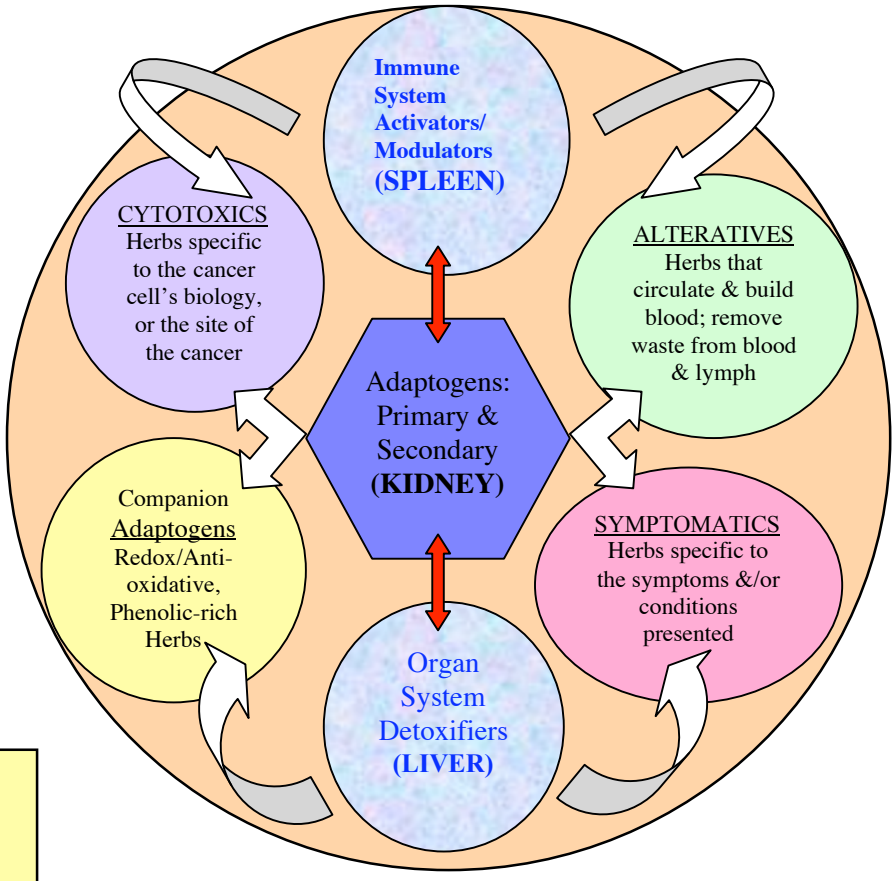
**SEVEN TARGET STRATEGIES TO ASSESS & TREAT THE PERSON WITH CANCER UTILIZING HERBAL MEDICINE**

#1 is to Build & Sustain the "Vital Force" & "Adaptive Energy"

Tonification Stimulation and/or Relaxation

- Immune System Response Modifiers (ISRMs)
- Immune-cell activators:
- Cytokines - IL-2 & IL-12, INF-α, INF-β, T-cells (Th1/TH2), NK cell, etc.
- Gut associated Lymphoid Tissue (GALT),
- B-cell-antibody response
- Antiseptic/Antimicrobial

1. Alkaloids possessing cytotoxic effects against certain cancer cell lines and/or biological characteristics
2. Other active compounds possessing direct anti-cancer effects (ex.terpenes)
3. Target specific sites of cancer




1. Move stagnant blood
2. Build blood using blood invigorating herbs
3. Improve the exchange of nutrients into the cell and waste material from cell for lymphatic drainage and removal (Lymphatics)

Cellular:

- Antitoxins
- Oxygenators
- Modulators of cell growth, induce apoptosis
- Repair mutations

- General Hepatics – Bitters/Detoxifiers
- Cholagogues
- Stomachics/Carminatives
- Laxatives (relaxing/ gentle stimulating /strong- cathartic)
- Diuretic/diaphoretic

- Pain (Anodyne, Antispasmodic)
- Hemorrhaging
- Anemia
- Blood clotting
- Appetite
- Nausea
- Cachexia (wasting)
- Sleep
- Depression
- Ulcerations
- Mouth sores
- Edema
- Fatigue
- Bone loss
- Diarrhea
- High uric acid
- Specific herbs to treat specific areas of the body – heart, kidney, lungs

## Botanicals and Phytoceuticals Clinically Used for Inhibition of Cancer Angiogenesis and Activation of the Immune Response

**Classifications:**

**I. Adaptogens (Primary and Secondary)**
**II. Companion Adaptogens**
**III. Alteratives, Lymphatics, Hepatics, Immune-tonics, and Cyto-Toxics**
**IV. Specific regulators of inflammation**
**V. Others**

**THE MOST RESEARCHED ADAPTOGENS IN ONCOLOGY INCLUDE:**

**PRIMARY ADAPTOGENS**

***Eleutherococcus senticosus* (Russian) root and leaf 2:1 ratio**
***Panax ginseng* and *Panax quinquefolius* root (Wisconsin, woods grown & 50:1, 80% ginsenosides)**
***Rhodiola rosea* root (Artic root)**
***Schisandra chinensis* seed**
***Withania somnifera* (Ashwagandha) root**
***Rhaponticum* (Leuzea) carthamoides root**

**SECONDARY ADAPTOGENS**

**Astragalus (*Astragalus membranceous)* 15:1**
***Cordyceps sinensis* 4:1, 40% Polysaccharides**
**Reishi (*Ganoderma lucidum*) 15:1,10% Polysaccharides, 4% Triterpenes**
**China root (*Poria cocos*) (20:1, 40% Polyphenols)**
**Panax Notoginseng (Tienchi ginseng), 10% Notoginsenosides**
**Atractylodes (*Atractylodes macrocephala)* 15:1 (red)**
**Licorice (*Glycyrrhiza glabra*), 26% Glycyrrhizic acid**
**Holy Basil (*Ocium sanctum*) 2.5% Ursolic acid**
**Goat weed (Epimedium grandiflorum)**

**COMPANION ADAPTOGENS**

To broaden the scope of what an adaptogen is, a theory has developed of using plants, berries, and various seeds that we choose to classify as companion adaptogen, which alone are not adaptogenic, in the traditional sense, but when combined with other herbs create a compounded remedy that serve as total and complete adaptogenic compounds. They have been shown to have enormous general health benefits, tonifing and balancing the entire body, protecting vital organs, assisting in the body's ability to protect against or withstand many forms of stress, particularly oxidative stress and inflammation. Their general actions enhance or synergize the effects of both primary and secondary adaptogens.

Flavonoids are a group of compounds found extensively in the plant kingdom, occurring universally in vascular plants. They're actually the largest group of several thousand compounds belonging to the antioxidant-rich polyphenol family. Flavonoids are further broken down into subclasses that you have likely heard of such as anthocyanins, flavonols, flavones, flavanones and flavanols. These terms, along with flavonoid and polyphenols (also called phytochemicals), are often used interchangeably in the literature, but they broken into these different groups because they have varying chemical structures. Flavonoid molecules have a distinctive structure consisting of multiple phenolic rings that are usually substituted by hydroxyl groups. While all flavonoids are antioxidants, some have stronger antioxidant properties than others, depending on their chemical structure. Beyond their antioxidant capabilities, they are known to exhibit antiinflammatory, anti-allergic, antimicrobial, hepatoprotective, antiviral, anti-cancer, anti-angiogenic, and anti-metastatic abilities. [188]

**Turmeric (*Curcuma longa)* extract, 95% Curcuminoids**
**Green tea (*Camellia sinensis*) extract 95% phenols, 40%EGCG (no chemical solvents)**
**Japanese Knotweed (*Polygonnum cuspidatum)* 20% Resveratrol**
**Grape seed (*Vitis vinifera*) extract 95% OPCs**
**Grape skin (*Vitis vinifera*) extract 30% Polyphenols**
**Amla / Indian Gooseberry (*Emblica off.)* extract**
**Ginger (*Zingiber off.*) extract, 5% Gingerols**
**Rosemary (*Rosemarinus off.*) extract, 6% Carnosic acid, 1% Rosmaric acid, 1.5 Ursolic acid**
**Hibiscus extract, protocatechuic acid**
**Quercetin**

**Dosage ranges of some companion adaptogens and phytoceuticals for angiogenesis inhibition**

| Herb/Phytoceutical | Preventive Dose | Cancer Adjuvant Dose |
|---|---|---|
| Green Tea 30:1 95% phenols (50% EGCG) | 200-500 mg/day | 1000-1200 mg/day 3 times/day |
| Grape Seed Extract: 95% OPCs with grape skin extract | 100 –200 mg/day | 400-800 mg/day |
| Resveratrol (Knoteweed 20%) | 30-50 mg/day | 300-500 mg/day |
| Quercetin with Bromelain | 500-1500 mg/day | 500-1000 mg 3 times/day |
| Ursolic acid (Holy basil & rosemary) | 10-20 mg. | 10-20 mg. 3 times /day |
| Limonene | 500 mg/day | 1000-2000 mg 3 times/day |
| Silibinin (standardized milk thistle) | 200 mg/day | Up to 2000 mg/day |

**ALTERATIVES, LYMPHATICS, AND HEPATICS**

**Echinacea (*Echinacea spp.*) 4% Phenolic compounds**
**Cat's claw (*Uncaria tomentosa*), 3% Pentacyclic alkaloids**
**Chinese salvia (*Salvia miltiorrhizae*) 10:1**
**Chinese Peony (*Paeonia lactiflora*)**
**Dong quai (*Angelica sinensis*) 1% Ligustilide**
**Ho Shou Wu, (*Polygonum multiflorum*) 10:1**
**Poke root (*Phytolacca decandra*) 1:3**
**May Apple (*Podophyllum peltatum*) 1:3**
**Burdock seed (*Articum lappa*) 40% Lignans - Arctiin & Arctigenin**
**Celandine (*Chelidonium majus*) Chelidonine**
**Red Clover (*Trifolium pratense*) 30% Isoflavones (genistein, daidzein, formononetin, & biochanin A)**
**Wolfberry (*Lycium chinese*) 10% Polysaccharides**
**Milk thistle (*Silybum marianum)* 80% Silymarin**
**Chinese Baikal skullcap (*Scutellaria baicalensis*) 95% baicalien and 8:1**
**Wild turmeric (*Curcuma aromatica*) 12:1**
**Bupleurum, Saikosaponin D**
***Thuja occidentalis***
**Yellow dock (*Rumex crispus*)**

**DIAPHORETICS**

**Yarrow (*Achillea millefolium*)**
**Boneset (*Eupatorium perfoliatum*)**

**CYTO-TOXICS**

These herbs either increase the innate immunity and cytotoxicity of one's immune system, or have direct antitumor/antineoplastic activity. The most common antitumor active principles found in plants are terpenes and alkaloids. Gene-repairing is a mechanism in which some plant compounds genetically alter cancerous cells to revert back to normal cells --- possibly by inhibiting cell division through means of a DNA repair mechanism, or by extinguishing the malignant information which can eventually kill the cancerous cell.

Many of the anti-cancer drugs currently being used or currently being developed were originally derived from nature, mostly from plants. For some other anticancer drugs, nature provided the initial lead from which the analogs were prepared and developed into drugs.

Knowledge of traditional medicine affords a valuable approach to the understanding and direction of anticancer drugs. A number of anticancer drugs currently on the market today were based on their use in traditional medicine, while others were discovered accidentally.

Various active compounds (or their semi-synthetic derivatives) derived from medicinal plants have been assessed for their efficacy and tolerability in the treatment of cancer. Some of these plant species, including Taxus baccata (paclitaxel, docetaxel), Podophyllum peltatum (etoposide), Camptotheca acuminata (camptothecin) and Vinca rosea (vinblastine, vinorelbine) have well recognized antitumour activity in cancer, and have been evaluated in clinical trials. [1]

Microtubules (MTs) play important and diverse roles in cell formation. Interfering with normal MT dynamics, for example, by the addition of tubulin ligands, can cause the cell great distress and affect MT stability and functions, including mitosis, cell motion and intracellular transport. It has been shown in the literature that tubulin is an important target molecule for developing anticancer drugs. Tubulin binding molecules have generated considerable interest after the successful introduction of the taxanes into clinical oncology and the widespread use of the vinca alkaloids vincristine and vinblastine. These compounds inhibit cell mitosis by binding to the protein tubulin in the mitotic spindle and preventing polymerization into the MTs. This mode of action is also shared with other natural agents eg podophyllotoxin. However various tubulin isotypes have shown resistance to individual taxanes and other commonly used MT agents. Therefore, there is a strong need to design and develop natural analogs that inhibit multi-drug resistance of these antimitotic agents and also interact with tubulin at sites different from those agents. [2] By using the whole plant extracts of the herbs in which these compounds have been developed from, offers a novel new approach to multi-drug resistance and drug poteniation.

**Metronimic dose using whole-plant extracts**

A phenomenon that may limit the advantages of low-dose metronomic or continuous dose delivery is a threshold effect for drug activity. The general utility of the maximum tolerated dose (MTD) paradigm, a strategy aimed at optimizing the chance of total tumor cell eradication, is here questioned. Evidence to date suggests that for many tumors the potential for eradication is in fact remote, with patients consistently demonstrating tumor cell presence subsequent to MTD treatments having eradicative intent. The failure to eradicate is attributed largely to the heterogeneous nature of the tumor. Heterogeneous cell populations demonstrate short-term refractoriness to up-front dose delivery, but ‘‘resensitize’’ as part of dose recovery, showing increased overall susceptibility to a given series of doses when delivered more evenly spaced. It is demonstrated: (1) that the minimization of total tumor burden, rather than complete eradication, may often be the more practical objective; and (2) that regularly spaced, ‘‘**metronomic**’’ dosing is the best way to achieve it. As a corollary, it is found that the more efficient ability of the tumor endothelial cells to resensitize following dosing predicts a targeting bias towards the endothelial compartment of a tumor when metronomic dosing is employed. This lends theoretical support to recent empirical studies showing that regularly spaced dosing schedules with no extended rest periods act more antiangiogenically, thereby delaying or avoiding the onset of acquired resistance.

Many of these plants contain a vast array of complimenting compounds that support and potentiate their actions. Some of the actions of these unique plant compounds include:

1) selective inhibition of complex I in the electron transport system in mitochondria,
2) inhibition of multi-drug resistance - P-glycoprotein (P-gp) inhibition,
3) inhibition of tubulin binding molecules,
4) telomerase inhibition,
5) induction of apoptosis,
6) selective inhibition of angiogenesis,
7) selective inhibition of insulin-like growth factor receptor binding,
8) "biological response modifying" actions (increasing host defense), enhancing cytotoxic T lymphocytes, natural killer cells etc.

**CYTOTOXIC HERBS**

**Artemisia annua (Chinese wormwood) - nine terpenoids including Artemisinin and flavonoids**
**Paw Paw (*Asimina triloba*, Annonaceae) seed, bark and twigs - acetogenins**
**Pacific Yew (*Taxus brevifolia*) bark and stem – taxanes (27)**
**Mistletoe (*Viscum album*) – lectins (viscumin, and viscotoxins), polysaccharides**
**Vinca rosea (*Catharanthus rosea*), Madagascar periwinkle – vinca alkaloids**
**Colchicum autumnale - colchicine**

**IV. SPECIFIC ANTI-INFLAMMATORIES AS ANTI-ANGIOGENIC AGENTS**

**Boswellia serrata (Indian frankincense), 75% boswellic acids**
**Feverfew (*Tanacetum parthenium L*) parthenolide**
**White willow (*Salix alba*), 30% salacin**

**V. OTHER HERBS THAT POSSESS ANTI-CANCER AND ANTI-ANGIOGENIC ACTIVITY**

***Coriolus* 20:1, 25% Polysaccharides**
**Gotu kola (*Centella asiatica*) 10:1, 10% Terpenes**
**Ginko (*Ginkgo biloba*)**
**Magnolia bark and cones (*Magnolia officinalis* ) Honokiol**

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