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Short Review

# ANTI ANGIOGENIC NATURAL PRODUCTS IN CANCER THERAPY

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***Abstract: Angiogenesis, the formation of new capillaries from preexisting blood vessels, is a multistep, highly orchestrated process involving vessel sprouting, endothelial cell migration, proliferation, tube differentiation, and survival. The aim of this paper is to summarize putative biological actions of flavonoids, Eicosanoids, Lactic acid and insulin to further understanding of the beneficial health effects of these substances against cancer.***

**Key words-** Angiogenesis, Eicosanoids, flavonoids, Lactic acid

## INTRODUCTION

Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vesselsThus it not only occurs in benign and malignant tumors but also in wound healing, ovulation, menstruation, and pregnancy. Abnormal angiogenesis also takes place in other diseases including rheumatoid arthritis, psoriasis, and atherosclerosis.

### Types of Angiogenesis

**Sprouting angiogenesis:-**It was the first identified form of angiogenesis. It occurs in several well-characterized stages. First, biological signals known as angiogenic growth factors activate receptors present on endothelial cells present in pre-existing veins. Second, the activated endothelial cells begin to release enzymes called proteases that degrade the basement membrane in order to allow endothelial cells to escape from the original (parent) vessel walls.[1]

**Intussusceptive angiogenesis:-**Intussusception, also known as splitting angiogenesis, was first observed in neonatal rats. In this type of vessel formation, the capillary wall extends into the lumen to split a single vessel in two. There are four phases of intussusceptive angiogenesis. First, the two opposing capillary walls establish a zone of contact. Second, the endothelial cell junctions are reorganized and the vessel bilayer is perforated to allow growth factors and cells to penetrate into the lumen. Third, a core is formed between the two new vessels at the zone of contact that is filled with pericytes and myofibroblasts.. Finally, the core is fleshed out with no alterations to the basic structure. Intussusception is important because it is a reorganization of existing cells [1].

## ANGIOGENESIS AND CANCER

Angiogenesis plays an important role in the growth and spread of cancer. New blood vessels “feed” the cancer cells with oxygen and nutrients, allowing these cells to grow, invade nearby tissue, spread to other parts of the body, and form new colonies of cancer cells. Because tumors cannot grow or spread without the formation of new blood vessels, scientists are trying to find ways to stop angiogenesis. They are studying natural and synthetic angiogenesis inhibitors, also called antiangiogenic agents, in the hope that these chemicals will prevent or slow down the growth of cancer by blocking the formation of new blood vessels [2].

**Advantages of Angiogenesis Inhibitors :** Angiogenesis inhibitors usually have only mild side effects and are not toxic to most healthy cells. Tumors do not seem to develop a resistance to angiogenesis inhibitors, even when given over a long period of time, unlike the resistance seen when chemotherapy drugs are used.Angiogenesis inhibitors seem to help some chemotherapy drugs and radiation therapy work more effectively when given in combination.[2]

**Limitations of Angiogenesis Inhibitors:** Angiogenesis inhibitor therapy may not necessarily kill tumors, but instead may keep tumors stable. Therefore, this type of therapy may need to be administered over a long period. Because angiogenesis is important in wound healing and in reproduction, long-term treatment with antiangiogenic agents could cause problems with bleeding, blood clotting, heart function, the immune system, and the reproductive system

**Steps of angiogenesis in tumors or wounds**

1. Cancer cells (or adjacent tissues) secrete angiogenic factors.
2. The basement membrane surrounding a mature capillary vessel dissolves, and a bud begins to grow.
3. Vascular (endothelial) cells proliferate and migrate from the bud toward the angiogenic stimulus—often toward a low-oxygen (hypoxic) environment.
4. The sprout eventually forms a hollow tube (lumen) and joins its end with another sprout to form a new capillary vessel.

## ANGIOGENIC FACTORS AND ANGIOGENESIS INHIBITION

There are two possible therapeutic routes by which angiogenesis can be reduced.

1) Normalize the machinery that restrains angiogenesis.
2) Inhibit the factors that stimulate it. This route is the primary focus here.

**Machinery that restrains angiogenesis**

**1) Mechanical forces** - Generated through the tension that exists between the cell and the extra cellular matrix and are mediated by CAMs. Endothelial cells are resistant to growth factors and angiogenesis if they have no room to stretch or spread. For this reason, it is possible that vasodilation (like that occurs in inflammation) is necessary to make endothelial cells susceptible to growth factors.[3]

**2) Binding of Angiogenic substances to ECM-**

The ECM can bind various growth factors and make them inaccessible to endothelial cells.

**3) Angiogenesis suppressor genes-**

Tumor suppressor genes such as *p53* may inhibit angiogenesis. However, mutated genes would not fulfill this function.

**4) Antiangiogenic compounds. -** A number of negative regulators of angiogenesis exist within the body, including angiostatin and thrombospondin. In some human cells, thrombospondin is under the control of the *p53* tumor suppressor gene.

***Normalization of the machinery that restrains angiogenesis-*** Natural products that minimize the VEGF increased vascular permeability

- Anthocyanidins
- Butcher's broom
- Centella asiatica
- Horse chestnut
- Proanthocyanidins

## ROLE OF NATURAL PRODUCTS IN CANCER THERAPY

**Role of eicosanoids (Prostanoids and Leukotrienes) in angiogenesis and their inhibition -** Eicosanoids, arachidonic acid (AA)-derived metabolites, have potent biologic activities on vascular endothelial cells. Endothelial cells can synthesize various eicosanoids, including the 12-lipoxygenase (LOX) product 12(S)-hydroxyeicosatetraenoic acid (HETE). When produced in appropriate amounts and at appropriate times, eicosanoids play a positive role in the body; When they are produced inappropriately, however, they can play a variety of roles in the initiation, promotion,and progression of cancer.Many

natural products beneficially effect the synthesis of eicosanoids like Boswellic acids, CAPE and bee propolis, Curcumin, EPA and DHA, Flavonoids (including genistein, apigenin, luteolin, quercetin, and EGCG), Garlic, Glutathione-enhancing agents, Melatonin, NF-kB Inhibitors , Parthenolide, PTK inhibitors, Resveratrol, Vitamin E.[4]

**Histamine-Role of Mast Cells in angiogenesis-** Histamine is generated by mast cells in response to tissue injury and other factors. Mast cells migrate toward tumors in response to growth factor production, and once at the site, the histamine they release increases vascular permeability and stimulates angiogenesis. Natural products that inhibit mast cell granulation in vitro are extract of *Eleutherococcus senticosus*, Flavonoids (including apigenin, luteolin, genistein, quercetin,EGCG, and proanthocyanidins), Vitamin C.

**Role of lactic acid in angiogenesis and prevention using natural products -** Under hypoxic conditions lactic acid may stimulate production of angiogenic factors by macrophages.

Few natural compounds have been tested for their effects on lactic acid generation in cancer cells.

In one study, apigenin and luteolin inhibited both proliferation and lactic acid release from a human adenocarcinoma cell line in vitro.

In other studies, the flavonoid quercetin reduced the production of lactic acid in healthy rat cells, probably by blocking the transport of lactic acid out of the cell.

Antioxidants may also inhibit lactic acid production. For example, vitamin C

**Role of Insulin in angiogenesis and prevention using natural products-** One growth factor that is intimately involved in glycolysis is insulin. Insulin stimulates not only glycolysis but also proliferation of many cancer cell lines. It may facilitate angiogenesis by increasing lactic acid production in hypoxic tumor cells and by stimulating the proliferation of vascular cells. For example, insulin injection can increase angiogenesis in mice. High insulin levels are common in cancerous tissue and in the plasma of cancer patients. In addition, the high insulin levels found in the early stages of non-insulin-dependent diabetes mellitus type II (NIDDM) have been implicated as a risk factor for a variety of cancers.

Few natural compounds have been tested for their effects on insulin level and cancer[3-5].

**Flavonoids in cancer therapy -** It has been stated that flavonoids, as antioxidants, can inhibit carcinogenesis. Some flavonoids—such as fisetin, apigenin, and luteolin—are stated to be potent inhibitors of cell proliferation. A large clinical study suggested the presence of an inverse association between flavonoid intake and the subsequent incidence of lung cancer[6]. This effect was mainly ascribed to quercetin, which provided >95% of the total flavonoid intake in that particular study. Quercetin and apigenin inhibited melanoma growth and influenced the invasive and metastatic potential in mice. This finding may offer new insights about possible therapies for metastatic disease. Furthermore, it has been speculated that flavonoids can inhibit angiogenesis. Angiogenesis is normally a strictly controlled process in the human body.[7] The process of angiogenesis is regulated by a variety of endogenous angiogenic and angiostatic factors. It is switched on, for example, during wound healing. Pathologic, unregulated angiogenesis occurs in cancer. Angiogenesis inhibitors can interfere with various steps in angiogenesis, such as the proliferation and migration of endothelial cells and lumen formation. Among the known angiogenesis inhibitors, flavonoids seem to play an important role. A possible mechanism could be inhibition of protein kinases. These enzymes are implicated to play an important role in signal transduction and are known for their effects on angiogenesis.

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