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# Angiogenesis inhibition by antioxidants

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**Abstract:** Reducing cancer morbidity and mortality requires several synergic approaches target on tumoural cells and their environment. Angiogenesis is the development of new blood vessels from the pre-existing vasculature. This process is normally observed only transiently during embryogenesis, and in adulthood, during wound healing and uterus function. However, pathologic angiogenesis is involved in some diseases, including cancer. Tumoural angiogenesis favors cancer invasion and metastasis emission. Normally, endothelial cells are maintained in a latent state, but under determined stimulus they suffer activation, a process called “angiogenic switch”. Among stimulatory angiogenic factors are vascular endothelial growth factor (VEGF), angiopoietin-1 and 2, interleukin-8 (IL-8), fibroblast growth factor basic (bFGF), platelet-derived growth factor (PDGF) and angiotensin II. Furthermore, matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, play role in angiogenesis. Reactive oxygen species (ROS), as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), participates in angiogenesis signaling through VEGF receptors, mainly VEGFR2 (Flk-1/KDR), and angiopoietin-1/Tie-2 receptors. The major source of ROS in endothelial cells is the enzyme NAD(P)H oxidase, but the role of nitric oxide (NO<sup>•</sup>), from endothelial nitric oxide synthase (eNOS), should not be neglected. Moreover, oxidized phospholipids and products from arachidonic acid metabolism can participate in angiogenesis induction. Then, it would be likely that antioxidants could inhibit angiogenesis. Really, a number of studies demonstrated that several antioxidants found in natural products (catechins from teas, resveratrol, polyphenols, flavonoids, isoflavones, lycopene, pigment epithelium-derived factor, glutathione); nutritional components (vitamins C, D, E, β-carotene and selenium); and semi-synthetic and synthetic compounds (*N*-acetylcysteine, L-NAME, L-NIO, sodium piruvate, pyrrolidine dithiocarbamate, and organoselenium compounds) were able to inhibit angiogenesis. These compounds were tested in several *in vitro* assays and *in vivo* animal models and inhibited angiogenesis via redox-sensitive and insensitive mechanisms. Thus, the consumption of antioxidants from natural sources can be recommended in face to benefic effects related to angiogenesis inhibition, while high fat diet can be undesired. In addition, some semi-synthetic and synthetic compounds has potential as future drugs for inhibiting tumoural angiogenesis, but it needs more detailed studies in terms of efficacy and security.

**Keywords:** Cancer, Angiogenesis, Reactive Oxygen Species, Antioxidants, Selenium

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## 1. Introduction

Cancer is a disease that affects millions of people around the world. Strategies for reducing its morbidity and mortality include cancer prevention, cancer therapy and inhibition of cancer reappearance. To reach more success in chemoprevention and in cancer treatment, several approaches need to be applied targeting tumoural cells and tumour environment. Among them, it can be cited strategies for inhibiting DNA mutation, by improving the systems for DNA repair, counteracting toxins and chemical carcinogens, blocking reactive species, inducing apoptosis of neoplastic cells, inhibiting metastasis, and reducing blood supply to the

nucleus of tumour (De Flora and Ferguson, 2005).

Angiogenesis is, conceptually, the development of new blood vessels from the pre-existing vasculature (Folkman, 1971). This process is normally observed only transiently during embryogenesis, and in adulthood during wound healing and uterus function (Folkman and Klagsbrum, 1987; Folkman 1990; Carmeliet, 2005). However, pathologic angiogenesis is involved in some diseases as diabetic retinopathy; chronic inflammation including arthritis, atherosclerosis and psoriasis; ischemic heart and limb disease; and cancer (Folkman, 1995; Kumamoto *et al*, 1995; Armstrong *et al*, 2011; Kim *et al*, 2013).

In a normal tissue the oxygen diffusion can occur with

blood vessels up to 100-200  $\mu\text{m}$ ; however an oxygen pressure almost zero has been reported in blood vessels with 100  $\mu\text{m}$  (Folkman *et al*, 2000; Gatenby and Gillies, 2004). On the contrary, tumours possess an extensive region of hypoxia relative to corresponding normal tissue and diffusion of oxygen can occur in vessels less than 70  $\mu\text{m}$  (Vaupel, 2004).

A tumour requires angiogenesis to grow beyond 1 - 2  $\text{mm}^3$  in size and to give off metastasis (Folkman, 1990; Cherrington *et al*, 2000). It is possible to recognize two distinct phases of tumour progression: the pre-vascular phase and the vascular phase (Hanahan and Folkman, 1996). In the initial pre-vascular phase, tumour growth is sustained by nutrients and oxygen through passive diffusion from the host vasculature. Therefore, cell proliferation and cell death are balanced and the size of the tumour does not exceed a few cubic millimeters. Once neovascularization occurs, the tumour acquires a rapid growth rate and increases its metastatic potential (Hanahan and Folkman, 1996).

Since angiogenesis activation in cancer favors metastasis, the anti-angiogenic therapy seems to be an important co-adjuvant treatment against tumour growth and spread. Further, after surgical resection of a tumour, angiogenesis inhibition can help in avoiding cancer reappearance.

In normal vascular bed, endothelial cells remain in a latent state. However, under determined stimulatory signals they suffer activation and neoangiogenesis occurs, a process called "angiogenic switch". Angiogenesis is a process regulated by a thin balance between activators and inhibitors. There are about 30 activators of angiogenesis and the same number of inhibitors. Major pro-angiogenic factors are vascular endothelial growth factor (VEGF) (Coultas *et al*, 2005; Ho and Kuo, 2007; Roskoski, 2007), angiopoietin-1 (Kim *et al*, 2006), angiopoietin-2 (Oliner *et al*, 2004), interleukin-8 (IL-8) (Koch *et al*, 1992), fibroblast growth factor basic (bFGF) (Flamme and Risau, 1992; Szabenyi and Fallon, 1999), platelet-derived growth factor (PDGF) (Potapova *et al*, 1996) and angiotensin II (Bell and Madri, 1990; Otani *et al*, 1998; Sasaki *et al*, 2002; Emanuelli *et al*, 2002). Activation of matrix metalloproteinases (MMPs), mainly MMP-2 and MMP-9, also plays important role in new vessels invasion of poorly vascularized tissues (Pepper, 2001).

Angiogenesis involves degradation of basement membrane of endothelium and of extracellular matrix, disruption of cell-cell contacts, endothelial cells proliferation, migration, and capillary tube formation (Carmeliet *et al*, 2000; 2005). Taking account endothelial cells generally are genetically stable and angiogenesis is not important in adulthood, its inhibition is normally related to lesser possibilities of resistance development and it is thought has a few unfavorable effects (Longo *et al*, 2002). Actually it is recognized that reactive oxygen species (ROS) as hydrogen peroxide, at low concentrations, acts as signaling molecules in endothelial cells; at intermediary levels can induce angiogenesis; while higher concentrations (250 - 1,000  $\mu\text{M}$ ) can be cytotoxic, causing apoptosis (Shono *et al*, 1996; Lakshminarayanan *et al*, 2001; Maulik and Das, 2002; Stone and Collins, 2002; Cai, 2005; López-Lázaro, 2007). There

are many sources of ROS in mammalian cells, as chain electron mitochondrial, xantine oxidase, glucose oxidase, the cytochrome *p*450, nitric oxide synthase (NOS), and NADPH oxidase. At mitochondria and at catalytic site of enzyme NADPH oxidase it is generated superoxide ( $\text{O}_2^{\cdot-}$ ), which is quickly decomposed to hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) by the enzyme superoxide dismutase (SOD) and further detoxified to water by catalase. The major source of ROS in endothelial cells is the enzyme NADPH oxidase, which is involved in angiogenesis induction (Ushio-Fukai, 2006; Ushio-Fukai and Alexander, 2004; Ushio-Fukai and Nakamura, 2008), although participation of endothelial nitric oxide synthase (eNOS) should not be neglected (Ziche *et al*, 1994; Gallo *et al*, 1998; Lee *et al*, 2000; Murohara and Asahara, 2002). Then, it is plausible that free radical scavengers and/or antioxidants can act as inhibitors of angiogenesis. In this context, objectives of this review are: i) discuss the role of ROS in activation of angiogenesis and; ii) comment a number of studies in which antioxidants showed anti-angiogenic effect.

## 2. Role of ROS in Angiogenesis Activation

Generally, concentrations of  $\text{O}_2^{\cdot-}$  and  $\text{H}_2\text{O}_2$  are maintained in basal levels and do not impair cells. However, for long it has been described that tumoural cells produce higher levels of  $\text{H}_2\text{O}_2$  (Szatrowski and Nathan, 1991). Indeed, there are several reports that incriminated  $\text{H}_2\text{O}_2$  as an inducer of angiogenesis (Yasuda *et al*, 1999; Monte *et al*, 1997; Ushio-Fukai and Alexander, 2004), by mediating signal deflagrated by VEGFR2/KDR receptor (Colavitti *et al*, 2002) and angiopoietin-1/Tie2 receptor (Harfouche *et al*, 2005; Kim *et al*, 2006), up-regulating NADPH oxidase 1 (Nox1) via hypoxia inducible factor 1 (HIF-1) (Goyal *et al*, 2004) or through up-regulation of VEGF expression in rat heart endothelial cells (CHUA *et al*, 1998). Accordingly, it was demonstrated that  $\text{H}_2\text{O}_2$  induced expression of VEGF mRNA in human keratinocytes target on GC-rich sequence from bp - 194 to - 50 of VEGF gene promoter via transcription factor SP-1 (Sen *et al*, 2002); increased binding of transcription factors NF- $\kappa$ B and AP-1 to DNA of endothelial cells, elevated expression of VEGF mRNA and caused release of IL-8 (Shono *et al*, 1996). On the other hand, VEGF stimulated ROS production via activation of Rac1-dependent NADPH oxidase in endothelial cells (Yamaoka-Tojo *et al*, 2004; Ikeda *et al*, 2005) and ROS generated by Nox1-containing NADPH oxidase triggered the angiogenic switch in cultured cells (Arbiser *et al*, 2002). It was also demonstrated that VEGF induced eNOS mRNA and protein, and increased NO $^{\cdot}$  production by human endothelial cells (Hood *et al*, 1998).

Oxide nitric (NO $^{\cdot}$ ) is a product of NOS that plays a role in vascular tonus and permeability, but some works demonstrated its participation in angiogenesis activation (Murohara and Asahara, 2002). It is showed that NO $^{\cdot}$  inhibited lipopolysaccharide-induced apoptosis in culture of

transfected endothelial cells overexpressing iNOS (Tzeng *et al*, 1997). Shen and coworkers (1998) demonstrated that NO<sup>•</sup> inhibited apoptosis of endothelial cells at low concentration (100 - 300 μM of NO<sup>•</sup> donor S-nitroso-N-acetylpenicillamine - SNAP), but induced at higher levels (750 μM of SNAP). Lee and coworkers (2000) exposed human umbilical vein endothelial cells (HUVECs) in Matrigel to 100 μM of SNAP and observed induction of angiogenesis. This effect was blocked in presence of eNOS inhibitor N-iminoethyl-L-ornithine (L-NIO; 100 μM). Further, in a study with patients suffering head and neck cancer, it was demonstrated that levels of total NOS and iNOS were higher in tumours than in normal mucosa. Additionally, patients with lymph node metastasis presented a higher total NOS activity and tumours were more vascularized than specimens from patients with no lymph node involvement (Gallo *et al*, 1998).

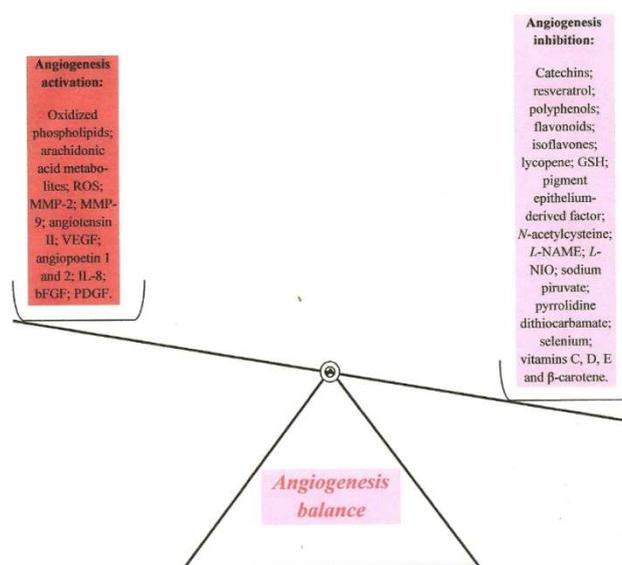
ROS oxidizes biomolecules as DNA, proteins and lipids. Membrane phospholipids are prone to fast action of ROS, which can deflagrate in cascade lipid peroxidation. Bochkov and coworkers (2006) elegantly demonstrated that, in atherosclerotic lesions, oxidized phospholipids induced angiogenesis via autocrine mechanism, while West and coworkers (2010) addressed toll-like receptor 2 (TLR2) mediating angiogenesis by end products of lipid oxidation (carboxyalkylpyrroles). Soon, it is possible that ROS can indirectly activate angiogenesis via generation of lipid peroxidation products. On the other hand, 12(R)-hydroxyeicosatrienoic acid [12(R)-HETrE], which is an arachidonic acid metabolite with potent stereospecific pro-inflammatory and pro-angiogenic properties, induced angiogenesis via activation of NFκβ and generation of ROS (Stoltz *et al*, 1996). Finally, it is known the relation between inflammation and oxidative stress with angiogenesis (Coussens and Werb, 2002; Kim *et al*, 2013). In this concern, there are studies showing that some anti-inflammatory compounds, chemical and natural antioxidants as well as nutritional components can ameliorate oxidative stress and inhibit angiogenesis. Furthermore, several antioxidants can inhibit angiogenesis and cancer invasion by redox-insensitive mechanisms.

### 3. Antioxidants as an Alternative for Tumoural Angiogenesis Inhibition

Several studies demonstrated that antioxidants were able to reduce or inhibit angiogenesis in both, *in vitro* and *in vivo* assays. These compounds include natural substances (catechins, resveratrol, polyphenols, flavonoids, isoflavones, lycopene, pigment epithelium-derived factor, glutathione); nutritional components (vitamins C, D, E; β-carotene; and selenium); and semi-synthetic and synthetic compounds (N-acetylcysteine, L-NAME, L-NIO, sodium pyruvate, pyrrolidine dithiocarbamate, and organoselenium compounds) (Figure 1).

Consumption of drinking tea, especially green tea and

black tea (*Camellia sinensis*), are the most popular beverage worldwide. Green tea is prepared by boiling leaves of *Camellia sinensis* in water. It causes release of a rich variety of catechins as polyphenolic substances that include epicatechin 3-gallate (ECG), epigallocatechin (EGC), epigallocatechin 3-gallate (EGCG) and epicatechin. Other less prominent polyphenols in green tea are quercetin, myricitrin and kaempferol. The most abundant polyphenol in green tea is EGCG (Johnson *et al*, 2010). A cup of green tea (2.5 g of dried green leaves brewed in 200 ml of water) may contain 90 mg of EGCG. In addition, it contains a similar or slightly smaller amount of (-)-epigallocatechin, about 20 mg each of (-)-epicatechin 3-gallate and (-)-epicatechin, and about 50 mg of caffeine. Black tea is prepared allowing the leaves undergo oxidation of polyphenols. In black tea, the above tea catechins are reduced to about one-tenth to one-third of those in green tea, and theaflavins account for 1 to 2% of the total dry matter (Yang and Wang, 1993). It has been demonstrated that EGCG and other catechins from green tea and black tea display anti-cancer and anti-angiogenic properties.



**Figure 1.** Angiogenesis balance. The dynamic equilibrium between the activated and the rest state of endothelial cells depends on the proportion of pro-angiogenic and anti-angiogenic factors. Several antioxidants, acting via redox-sensitive and insensitive mechanisms, can operate as inhibitors of angiogenesis activation.

Cao and Cao (1999) developed both assays *in vitro* and *in vivo* to tested potential of EGCG in inhibiting angiogenesis. *In vitro*, Cao and Cao (1999) demonstrated that EGCG was able to inhibit proliferation of endothelial cells from bovine capillaries in a dose-dependent manner (inhibition at 10 and 50 μg/ml). In chick chorioallantoic membrane assay it was also observed an in dose-dependent manner inhibition of angiogenesis (10 – 100 μg per disc). In another *in vivo* assay, Cao and Cao (1999) tested green tea in a model of corneal neovascularization in mice stimulated by VEGF (160 ng of VEGF per pellet put on cornea). Green tea was administrated as sole drinking fluid to animals, at 1.25% (4.69 ng/ml)

containing 708 µg/ml of EGCG. Concentration in the plasma was previously reported to be in range of 0.1 – 0.3 µM, which is similar to levels in human after drinking two or three cups of tea (Yang *et al*, 1998). It was observed that green tea consumption inhibited significantly angiogenesis in this *in vivo* model. Such observation is relevant because consumption by mice was at concentrations that can be reached in humans drinking regularly green tea.

Tang and Meydani (2001) showed that EGCG (0.5 – 1 µM) inhibited angiogenesis *in vitro* through suppression of IL-8 production by human microvascular endothelial cells. Additionally, it was postulated that EGCG reducing angiogenesis is related to inhibition of urokinase (Jankun *et al*, 1997) or MMPs activity (Maeda-Yamamoto, 1999; Garbisa *et al*, 2001), by removing ROS (Zhang *et al*, 2000) and inhibiting VEGF induction in human colon carcinoma cells (JUNG *et al*, 2001).

In athymic BALB/c nude mice that were inoculated subcutaneously with human colon cancer cells, treatment with EGCG (1.5 mg/day/mouse 20 days) reduced number of tumour microvessels in 30%, reduced cell proliferation in 27% and caused an increase in apoptosis of tumoural cells and endothelial cells near to 1,9 and 3 folds, respectively (Jung *et al*, 2001). Also, EGCG was capable to repress ROS production by neutrophil, to inhibit chemokine-induced neutrophil chemotaxis *in vitro* and to block neutrophil-mediated angiogenesis *in vivo* in an inflammatory angiogenesis model (Doná *et al*, 2003).

It has been associated regular consumption of polyphenols, particularly red wine and green tea, with lesser incidence of coronary heart disease and cancer (Stoclet *et al*, 2004). In this concern, red wine polyphenolic compounds strongly inhibit VEGF expression and H<sub>2</sub>O<sub>2</sub>-induced release of VEGF in vascular smooth muscle cells in concentrations that are likely to be achieved in blood after moderate consumption of red wine (Oak *et al*, 2003). Moreover, polyphenols showed ability to scavenge ROS such as hydroxyl radical and superoxide anion (Frankel *et al*, 1993; Hanasaki *et al*, 1994; Miyagi *et al*, 1997), to inhibit the expression of xanthine oxidase (Lin *et al*, 2000), to diminish adhesion and invasion of tumoural cells induced by ROS from hypoxanthine/xanthine oxidase system (Zhang *et al*, 2000), and to increase activity of catalase and glutathione peroxidase (Khan *et al*, 1992). Taking account role of MMPs in new vessel growth and invasion, it was demonstrated that polyphenols from red wine and green tea were able to inhibit thrombin-induced MMP-2 activation (El-Bedoui *et al*, 2004; Oak *et al*, 2004) by directly inhibiting the activity of membrane-bound MT1-MMP, that is the activator of MMP-2 precursor, the pro-MMP-2 (Oak *et al*, 2004). In according, catechins from green tea inhibited MT1-MMP-dependent activation of pro-MMP-2 in cancer cells (Annabi *et al*, 2002), and EGCG inhibited VEGF expression in several types of cancer cells by inhibiting epidermal growth factor receptor (EGF-R) signaling, such as the constitutive activation of Sta3 and NFκβ factors (Masuda *et al*, 2002; Sartippour *et al*, 2002).

Since transcription factor AP-1 up-regulates genes as MMP-1 and urokinase, two important proteases for both angiogenesis and invasive behavior of metastatic cancer (Crawford and Matrisian, 1996), it was demonstrated that polyphenols reduced angiogenesis and tumour invasion by inhibiting AP-1-dependent transcription (McCarty, 1998). Indeed, it was reported that EGCG and theaflavins from teas inhibited AP-1 binding to DNA at doses between 5 and 20 µM (Dong *et al*, 1997)

Catechins-derived from gallic acid, as epicatechin gallate and epigallocatechin gallate, were more effective in inhibiting invasion and MMP activity of human fibrosarcoma HT1080 cells (Maeda-Yamamoto *et al*, 1999). In line with this, black raspberry extracts (*Rubus occidentalis*) were discovered to be anti-angiogenic (0.1% w/v). At 0.075% (w/v), the active fraction completely inhibited angiogenic initiation and angiogenic vessel growth. Further subfractionation of this active fraction revealed the coexistence of multiple antiangiogenic compounds, one of which was identified as gallic acid (Liu *et al*, 2005).

Resveratrol is a polyphenolic compound found in grapes, juice grapes, red wine and other fruits. It has been reported to inhibit angiogenesis. In an assay to test effects of resveratrol on endothelial cell proliferation induced by fibroblast growth factor-2 (FGF-2), it was showed that resveratrol inhibited endothelial cell growth in a dose-dependent manner. Similar results were obtained when endothelial cell proliferation was stimulated by VEGF (Brakenhielm *et al*, 2001). In regarding to *in vivo* models, it was demonstrated that resveratrol (1 – 100 µg per disc) inhibited angiogenesis in the chick chorioallantoic membrane assay in a dose-dependent manner. In a study for testing angiogenesis in mammals, researchers prepared a drinking solution for mice containing a low amount of resveratrol equivalent to the amount approximately 3 glasses of red wine per day for humans. It was observed that resveratrol significantly inhibited corneal neovascularization induced by VEGF and FGF-2 (Brakenhielm *et al*, 2001). Additionally, it was demonstrated that resveratrol, administered by oral route at concentration of 5,7 µg/ml (25 µM), significantly inhibited the growth of T241 fibrosarcoma in mice. Researchers also tested anti-wound healing effect of resveratrol in a mouse skin model. Oral administration of resveratrol of the same dose as in the tumour experiment significantly delayed wound healing in mice as measured by the sizes of wounds and percentage of animals with healed wounds. Sizes of wounds measured in the resveratrol-drinking group were significantly larger from day 2 onward (Brakenhielm *et al*, 2001).

Mechanisms underlying anti-angiogenic activity of resveratrol seem to depend from disruption of VEGF signaling and from its antioxidant property. In this concern, it was demonstrated that exposure of HUVECs to 1 – 2.5 µM of resveratrol significantly blocked VEGF-mediated migration and tube formation but not proliferation. At the same dose, resveratrol effectively abrogated VEGF-mediated tyrosine phosphorylation of vascular endothelial-cadherin and its complex partner, β-catenin. Src kinase assay

demonstrated that VEGF-induced endogenous Src kinase activation was strongly inhibited by 1 and 2.5  $\mu\text{M}$  of resveratrol. Also, it was observed that resveratrol diminished VEGF-dependent ROS production. Then, Lin and coworkers (2003) concluded that resveratrol inhibition of VEGF-induced angiogenesis was mediated by disruption of ROS-dependent Src kinase activation and the subsequent vascular endothelial-cadherin tyrosine phosphorylation.

Flavonoids are natural second constituents of plants that possess a polyphenolic structure. They are found in seeds, citrus fruits, and vegetables. Some flavonoids are genistein (the major isoflavone of soy), acacetin (a constituent of citrus fruits), apigenin (apple skins, citrus fruits, celery roots), chrysin (berries), kaempferol (broccoli, leek), morin (fruits, Chinese herbs), naringin (citrus fruits), naringenin (citrus fruits), and rutin (cranberries). Curcumin or diferuloylmethane is extracted from the root of *Curcuma longa* L. and is a common spice in India and surrounding regions. It presents strong anti-oxidative, anti-inflammatory and anti-septic properties and is widely used in Indian medicine and culinary traditions. Vitamin E is a generic denomination for all 8 naturally occurring tocopherols and tocotrienols as well as derivatives. The most biologically active form of vitamin E is  $\alpha$ -tocopherol ( $\alpha$ -TOH). However,  $\alpha$ -tocopheryl succinate ( $\alpha$ -TOS) is often used as the vitamin E source in commercial supplements because  $\alpha$ -TOS is more stable in the presence of oxygen than free TOH. On this issue, Schindler and Mentlein (2006) tested if flavonoids and vitamin E regulates VEGF secretion by human tumour cells *in vitro* (a line of breast cancer cell and two lines of glioma cells). In this study, genistein was utilized as a positive control because it was previously showed that this isoflavonoid inhibited angiogenesis (Fotsis *et al*, 1993; 1995), and VEGF expression and release (Büchler *et al*, 2004). Of 21 compounds tested, 9 showed significant inhibitory activity at 0.1  $\mu\text{mol/L}$  in breast cancer cells. The rank order of inhibitory potency was naringin > rutin >  $\alpha$ -tocopheryl succinate > apigenin > genistein >  $\alpha$ -tocopherol  $\geq$  kaempferol >  $\gamma$ -tocopherol. Among the tocopherol derivatives,  $\alpha$ -TOS (0.1mmol/L) was the most effective in reducing VEGF release. Overall, the glycosylated flavonoids (naringin and rutin) induced the greatest response to treatment at the lowest concentration in breast cancer cells. Compounds as chrysin and curcumin were inactive except at a concentration of 100  $\mu\text{mol/L}$  (Schindler and Mentlein, 2006).

But, in another study it was demonstrated that curcumin had anti-angiogenic property. It was observed that curcumin inhibited HUVEC differentiation on matrigel and endothelial cell infiltration and vessel formation in matrigel plug (Thaloor *et al*, 1998). Also, curcumin inhibited bFGF-induced corneal neovascularization in the mouse cornea (Arbiser *et al*, 1998) and curcumin derivatives inhibited angiogenesis in chicken chorioallantoic membrane assay (Shim *et al*, 2002). These activities seems related to inhibition of VEGF and angiopoietin 1 and 2 signaling as observed in EAT cells, to VEGF and angiopoietin 1

inhibition as detected in NIH3T3 cells, and the inhibition of the tyrosine kinase Flk-1/KDR (VEGF receptor-2) as identified in HUVECs (Gururaj *et al*, 2002). Since confirmed role of inflammation in angiogenesis, it was demonstrated that curcumin inhibited cyclooxygenase 2 (COX-2) (Huang *et al*, 1994; Rao *et al*, 1995). Furthermore, curcumin at 15  $\mu\text{M}$  reduced expression of epidermal growth factor receptor (EGFR) in caco-2 and HT29 cells (Chen *et al*, 2006) and reduced levels of MMP-2 (Su *et al*, 2006) and expression of VEGF and MMP-9 (Hahm *et al*, 2004).

Lycopene is another natural compound that appears to down-regulate angiogenesis. It was demonstrated that lycopene inhibited angiogenesis in the rat aortic ring and in chorioallantoic membrane assays. Furthermore, the *in vivo* matrigel plug assay in mice demonstrated that lycopene implanted subcutaneously at the highest dose used (400  $\mu\text{g}/\text{plug}$ ) completely inhibited the formation of vascular endothelial cells induced by VEGF. Angiogenesis inhibition promoted by lycopene occurred through inhibiting tube formation, invasion, and migration in HUVECs. Such actions were accompanied by reduced activities of MMP-2, urokinase-type plasminogen activator, protein expression of Rac1, by enhancing protein expression of tissue inhibitors of metalloproteinase-2 and plasminogen activator inhibitor-1, and by attenuating VEGFR-2 signaling (Chen *et al*, 2012). Elgass and coworkers (2012) confirmed the anti-angiogenic potential of lycopene in demonstrating that it inhibited *in vitro* angiogenesis in HUVECs as well as in rat aortic rings at physiological concentrations (1 - 2  $\mu\text{mol/L}$ ). In a final concentration of 1 - 15  $\mu\text{mol/L}$ , it was observed a significant reduction in network branching, that is, junction numbers, the number of tubules and tubule length, in both HUVECs as well as in the rat aortic rings. The inhibitory effect of lycopene was independent of the presence of the pro-angiogenic agents, VEGF and TNF- $\alpha$ . Recently, in a study with 48,898 men for investigating prevalence of prostate cancer between 1986 and 2010, it was reported that lycopene intake was inversely associated with prostate cancer. Higher lycopene intake was associated with biomarkers in the cancer indicative of less angiogenic potential (Zu *et al*, 2014).

Pigment epithelium-derived factor (PEDF) has been shown as a natural inhibitor of angiogenesis. It was demonstrated that PEDF inhibited the leptin-induced ROS generation, VEGF mRNA up-regulation, and DNA synthesis in human cultured microvascular endothelial cells (Yamagishi *et al*, 2003). Abe and coworkers (2004) carried out both the *in vivo* and *in vitro* assays for evaluating growth characteristic of human malignant melanoma G361 cell line, stably transfected to overexpress human PEDF. Overexpression of PEDF was found to significantly inhibit tumour growth and vessel formation in G361 nude mice xenografts. Furthermore, *in vitro* proliferation rates of G361 cells were decreased in PEDF transfected cells.

Since NO $\cdot$  participate in angiogenesis activation (Murohara and Asahara, 2002), it would be likely that antioxidant or NOS inhibitors would repress angiogenesis. Polyarchou and Papadimitriou (2005) showed that catalase

and sodium pyruvate (an intracellular hydrogen peroxide scavenger) inhibited HUVEC proliferation, migration and eNOS activity. The non-selective inhibitor of NOS activity *N*<sup>ω</sup>-nitro-L-arginine methyl ester (L-NAME), but not its inactive analogue *N*<sup>ω</sup>-nitro-D-arginine methyl ester (D-NAME), decreased endothelial cell proliferation and migration. Also, the potent inhibitor of eNOS activity *N*<sub>5</sub>-(1-iminoethyl)-L-ornithine dihydrochloride (L-NIO), but not the specific inhibitor of iNOS activity *N*-[[3-(aminomethyl)phenyl]methyl]-ethanimidamide dihydrochloride (1400W), diminished endothelial cells proliferation and migration, addressing eNOS involvement and reactive species generation in angiogenesis activation.

Moreover, it was showed that vitamin D reduced significantly count of microvessels in a model of murine retinoblastoma (Shokravi *et al*, 1995). In another study, it was demonstrated that vitamin D<sub>3</sub> and a synthetic analogue, 25 oxa-1,25 dihydroxi vitamin D<sub>3</sub>, inhibited angiogenesis in chick allantoic membrane assay (Oikawa *et al*, 1990). Furthermore, Mantell and coworkers (2000) tested 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>] (1 x 10<sup>-9</sup> to 10 x 10<sup>-7</sup> mol/L) in some assays evaluating its potential to inhibit angiogenesis induced by VEGF. *In vitro*, it was demonstrated that [1,25(OH)<sub>2</sub>D<sub>3</sub>] significantly inhibited endothelial cell proliferation at 10 x 10<sup>-7</sup> mol/L. Accordingly, in another assay it was observed that [1,25(OH)<sub>2</sub>D<sub>3</sub>] (1 x 10<sup>-9</sup> to 10 x 10<sup>-7</sup> mol/L) inhibited the formation of elongated sprouting of endothelial cells. Also, the compound caused a dose-dependent regression of preformed endothelial cells networks and induced a significant increase of apoptotic endothelial cells (at 10 x 10<sup>-7</sup> mol/L). *In vivo* it was demonstrate that BALB/c nu/nu mice that were inoculated MCF- 7 breast cancer cells overexpressing VEGF<sub>121</sub> (VEGF transfectants) and that received [1,25(OH)<sub>2</sub>D<sub>3</sub>] showed reduction in count of microvessels and tumours were smaller than in control group. It should be advised that this result was observed at dose of 12.5 pmol/day administrated during 8 weeks, which does not induce hypercalcemia in mice, and is the dose generally utilized as therapeutic replacement in human.

Results from other studies indicated that in animals receiving vitamin E,  $\beta$ -carotene, or glutathione in addition to applications of carcinogen, the developing tumours were expectedly smaller, fewer in number, and the notable angiogenesis seen in the tumour control animals was not observed in the animals receiving the nutrients (Shklar and Schwartz, 1996; Schwartz and Shklar, 1996). Vitamin E and glutathione appears to repress angiogenesis by inhibiting tumoural growth factor alpha (TGF- $\alpha$ ) expression (Schwartz and Shklar, 1997). In addition, in an animal model built with apolipoprotein-E-deficient mice for atherosclerosis studying, it was demonstrated that treatment with vitamin C (120 mg/kg/day, during 4 weeks) and  $\alpha$ -tocopherol (210 mg/kg/day, during 4 weeks) significantly reduced aortic VEGF and VEGFR-2 expression, circulating VEGF and plasma lipid peroxidation (Nespereira *et al*, 2003). In another study, mice were injected with B16F10 melanoma cells in subcutaneously tissue on the right flank. Following, they

were treated with vitamin E succinate (VES) at 100 mg/kg/dia from day 1 to day 17 after inoculating and then killed, or from day 17 to day 25 after tumour cells injecting and sacrificed. Authors described that VES caused tumour dormancy and this effect was related to inhibition of tumoural angiogenesis. This effect was evident at both, early or late stage of tumour growth. It was observed that VES suppressed the expression of VEGF, VEGFR-1 and VEGFR-2 receptors in melanoma tumours. Also, in an *ex vivo* assay it was demonstrated that VES caused dose-dependent reduction on VEGF protein secretion by tumoural cells from mice. Further examination revealed that diminishing in VEGF secretion was related to inhibition of VEGF promoter activity in DNA of melanoma cells (Malafa *et al*, 2002).

Selenium is a micronutrient essential for animal growing and reproducing. A novel focus has emerged into role of selenium in plants. Additionally, selenium plays important function in human health, including cancer chemoprevention (Prauchner, 2014). It is generally assumed that selenium speciation is divided into two major categories of compounds: the inorganic and the organic ones. Among inorganic species, the most common source of selenium for supplementing foods is sodium selenite (Na<sub>2</sub>SeO<sub>3</sub>), while sodium selenate (Na<sub>2</sub>SeO<sub>4</sub>) is the major source in soil fertilizers. In relation to organic compounds, it should be cited the selenoaminoacids selenocysteine (SeCys) and selenomethionine (SeMet). Vegetables that belong to Brassica and Allium genders represent important sources of methylated species of selenium in human diet. It is thought that methylselenol (CH<sub>3</sub>SeH) and methylselenocysteine (MeSeCys or CH<sub>3</sub>SeCys) are the most important species of selenium playing role in cancer chemoprevention (Prauchner, 2014). Ebselen [pz 51 – 2-fenil-1,2-benzisosenazol-3(2H)-one] and diphenyl diselenide [(PhSe)<sub>2</sub>] are two synthetic organoselenium compounds that showed anticancer and anti-angiogenic properties (Khatri *et al*, 2004; Prauchner, 2009).

In regarding to anti-angiogenic potential of selenium-derived compounds, it was reported that sodium selenite inhibited invasion of HT1080 human fibrosarcoma cells. Adhesion of HT1080 cells to the collagen matrix was also inhibited by selenium, but cell-cell interaction and cell motility were not affected by selenite. In addition, selenium inhibited expression of MMP-2, MMP-9 and urokinase-type plasminogen activator, but increased a tissue inhibitor of metalloproteinase-1 (TIMP-1). This inhibitory effect of selenite on the protease expression was mediated by the suppression of transcription factors, NF- $\kappa$ B and AP-1. However, sodium selenate, that was tested in the same assays that selenite, showed no remarkable effect on all steps of cancer cell invasion (Yoon *et al*, 2001).

Selenium is known to interfere with the action of lipoxygenases, in particular 5-lipoxygenase (Schnurr *et al*, 1996; Weitzel and Wendel, 1993). It was demonstrated by Ghosh (2004) that sodium selenite (1 – 5  $\mu$ M) inhibited the growth of an androgen-responsive prostate cancer cell line (LNCaP cells) and caused apoptosis of this cells at 1,5  $\mu$ M through caspase-3 activation, but not interfered upon normal

epithelial prostatic cells. These effects were minimized by arachidonic acid and by the 5-lipoxygenase metabolites, namely 5(S)-HETE and its dehydrogenated derivative 5-oxoETE, but not by metabolites of 12-lipoxygenase, such as 12(S)-HETE or 15-lipoxygenase 15(S)-HETE. On the other hand, 5-lipoxygenase inhibitors potentiated apoptotic effect of selenium on LNCaP cells.

In another study, pro-angiogenesis effects and mechanisms of sodium arsenite were determined using the chick chorioallantoic membrane model over 3 days and compared with standard pro-angiogenesis effect of bFGF. Following, it was tested the potential of various selenium-derived compounds, namely dimethyl selenone, diphenyl selenone, sodium selenite or methylselenocysteine, in reversing the pro-angiogenic effect of arsenite or bFGF. Mousa and coworkers (2007) reported that the pro-angiogenic effect of arsenite or bFGF was significantly ( $P < 0.01$ ) blocked by dimethyl selenone, diphenyl selenone, sodium selenite or methylselenocysteine. Mechanistically, authors commented that the pro-angiogenic effect of arsenic is initiated at the plasma membrane integrin  $\alpha v \beta 3$ , involves activation of the ERK1/2 pathway and is effectively reversed by various selenium-derived compounds.

Moreover, Jiang and coworkers (1999) examined the effects of chemopreventive levels of selenium-derived compounds on the intra-tumoural microvessel density and the expression of VEGF in 1-methyl-1-nitrosourea-induced rat mammary carcinomas, on the proliferation and survival and MMP-2 activity of HUVECs. Increased selenium intake as selenium-enriched garlic, sodium selenite, or methylselenocysteine led to a significant reduction of intra-tumoural microvessel density in mammary carcinomas, irrespective of the manner by which selenium was provided: continuous exposure (7-week feeding) with a chemoprevention protocol or acute bolus exposure (3 days) after carcinomas had established. Compared with the untreated controls, significantly lower levels of VEGF expression were observed in a sizeable proportion of the selenium-treated carcinomas. In contrast to the mammary carcinomas, the microvessel density of the uninvolved mammary glands was not altered by selenium treatment. In cell culture, direct exposure of HUVECs to selenium compounds induced cell death predominantly through apoptosis, decreased the gelatinolytic activities MMP-2, or both.

Afterwards, Jiang and coworkers (2000) addressed the role of methylselenol in the anti-angiogenic effect played by selenium. They carried out a study in which described that exposition of HUVECs to methylseleninic acid (MSeA) and methylselenocyanate (MSeCN), two selenium compounds that likely react intracellularly with reduced glutathione to generate methylselenol, decreased MMP-2 gelatinolytic activity in a concentration-dependent manner. In contrast, researchers found that selenium species that enter the hydrogen selenide pool lacked any inhibitory effect. Immunoblot and enzyme linked immunosorbent assay analyses showed that a decrease of the MMP-2 level largely

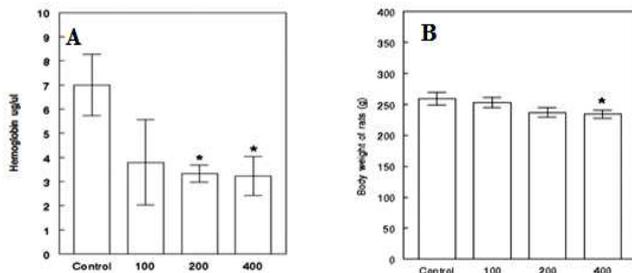
accounted for the methylated selenium-induced reduction of gelatinolytic activity. Additionally, in human prostate cancer (DU145) and breast cancer (MCF-7 and MDA-MB-468) cell lines, exposure to MSeA but not selenite led to a rapid and sustained decrease of cellular (lysate) and secreted (conditioned medium) VEGF protein. The concentration of MSeA required for suppressing VEGF expression was much lower than that needed for apoptosis induction.

Selenosemicarbazone are a class of organic compounds that have been investigated mainly for its anti-microbial, anti-malarial and anti-viral properties (Brucker *et al*, 1968; Mautner *et al*, 1956; Turk *et al*, 1986). More recently, Zec and coworkers (2012) investigated properties of the 2-formylpyridine selenosemicarbazone complex of zinc (II), cadmium (II) and nickel (II) and correspondent ligand in terms of modulation tumour metastasis and angiogenesis. It was reported that nickel (II) and zinc (II) complexes exhibited the strongest inhibitory potential towards MMP-2 and 9, while all investigated compounds significantly decreased proteolytic activity of MMP-2 and 9 in human breast cancer MDA-MB-361 cell line. In malignant cells, the complexes inhibited intracellular accumulation of ROS that are known for its pro-angiogenic properties via VEGF signaling. Furthermore, tubulogenesis test showed anti-angiogenic effect of the complexes in treated endothelial cells.

Khatri and coworkers (2004) developed transgenic mice that overexpress pp22phox, a component of the enzyme NAD(P)H oxidase in smooth muscle cells (SMC) for studying angiogenesis in atherosclerosis. Researchers found that SMC in arterial lesions of transgenic mice produced higher  $H_2O_2$  and VEGF levels than control animals likely due increased expression of hypoxia inducible factor (HIF-1 $\alpha$ ). In addition, lesions of transgenic mice were complicated by extensive neointimal angiogenesis. *In vitro*, it was demonstrated that treatment of SMC cells with ebselen (10 – 20  $\mu\text{mol/L}$ ), an organoselenium compound that acts a glutathione peroxidase-mimetic antioxidant, significantly diminished  $H_2O_2$  levels and decreased VEGF expression without affecting their viability. *In vivo*, it was observed that animals that underwent infusion of ebselen (10 mg/kg/day) during first 14 days after lesion initiation showed reduced arterial  $H_2O_2$  levels, lesion size and expansive remodeling of carotids arteries overexpressing NAD(P)H oxidase compared with vehicle-treated controls.

Moreover, *p*-phenylenebis(methylene)selenocyanate, that is another organoselenium compound, has been reported as cytotoxic to vascular endothelial cells and to inhibit neovascularization *in vivo* (Schumacher *et al*, 2001). Further, diphenyl diselenide [(PhSe) $_2$ ] is an organoselenium compound that acts as mimetic of glutathione peroxidase (Rossato *et al*, 2000; Nogueira *et al*, 2004) and is relatively non-toxic for animals (Prauchner *et al*, 2013). It has been shown to possess antioxidant (Rossato *et al*, 2000; Borges *et al*, 2006; Posser *et al*, 2006; Hort *et al*, 2011; Rupil *et al*, 2012), anti-inflammatory (Nogueira and Rocha, 2011), anti-sepsis (Prauchner *et al*, 2011), chemopreventive (Rosa *et al*, 2007; Barbosa *et al*, 2008) and pro-apoptotic activities

(Posser *et al.*, 2011). Taking account the participation of lipid peroxidation products in angiogenesis activation, it was demonstrated that [(PhSe)<sub>2</sub>] inhibited formation of thiobarbituric acid reactive species (TBARS) in both *in vitro* (Posser *et al.*, 2006) and *ex vivo* assays (Prauchner *et al.*, 2011), as well as reduced LDL oxidation *in vitro* (de Bem *et al.*, 2008). Accordingly, Prauchner (2009) tested [(PhSe)<sub>2</sub>] in an angiogenesis model built by implantation of sponges in subcutaneous pectoral or dorsal region in rats. The compound was injected with total doses of 100, 200 and 400 mg/kg body weight (i.p.), in four divided doses, every other day, during seven days. At eighth day, sponges were homogenized in distilled water for quantification of hemoglobin. It was observed that diphenyl diselenide, at intermediary dose, reduced hemoglobin content of sponges (Figure 2A), without affecting body weight gain (Figure 2B). Thus, it had potential to inhibit angiogenesis in this animal model. Finally, it was observed that oxidized phospholipids stimulated VEGF expression, up-regulated COX-2 and increased IL-8 synthesis, while COX-2 inhibitors (indometacin and NS-398) reduced oxidized phospholipids-induced endothelial cell sprouting (Bochkov *et al.*, 2006). The arachidonic acid metabolite [12(R)-HETrE] stimulated the formation of capillary-like cords of microvessels endothelial cells similarly to the effect promoted by bFGF. Antioxidants as *N*-acetylcysteine, butylated hydroxyanisole, and pyrrolidine dithiocarbamate inhibited [12(R)-HETrE]-dependent capillary endothelial cells cords formation via inhibiting NFκβ activation (Stoltz *et al.*, 1996).



**Figure 2.** Effects of diphenyl diselenide on (A) hemoglobin content in pectoral region and on (B) body weight gain of adult rats during treatment. Rats were anesthetized and a little sponge was implanted in subcutaneous tissue of the chest. After recovered, rats were injected with diphenyl diselenide at 100, 200 or 400 mg/kg body weight divided in four injections, every other day, during seven days. Control group received 5 ml/kg body weight of soya bean oil. At eighth day after surgery, animals were subjected to euthanasia and the sponge was withdrawn and homogenized in distilled water for hemoglobin quantification. Data are expressed as  $\pm$  S.E.M. \*Significantly different from control,  $p < 0.05$ ,  $n = 5$  per group.

Then, several antioxidants, acting via redox-sensitive or insensitive mechanisms, were able to inhibit angiogenesis activation. This potential was evident in various *in vitro* assays and *in vivo* animal models, including those for testing tumoural angiogenesis.

## 4. Conclusions

Angiogenesis inhibition can be thought as a co-adjutant

therapy for inhibiting cancer growth and metastasis emission. It is well recognized the role of ROS in angiogenesis activation, although other mechanisms have been reported. So, antioxidants have potential to interfere in this process and, in turn, are able to down-regulated angiogenesis in tumours. In this concern, consumption of antioxidants from diet, as vitamin C, D, E,  $\beta$ -carotene, selenium, polyphenols, flavonoids, isoflavones, lycopene, or drinking tea and red wine can be considered a healthy habit, while eating high fat diet can be not recommended. In addition, some semi-synthetic and synthetic compounds showed potential to inhibit angiogenesis. If these compounds are to be the new anti-angiogenic drugs in the future they need more intensive research in terms of efficacy and security.

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