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Review article

Nutraceuticals and their role in tumor angiogenesis

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ABSTRACT

Angiogenesis plays a pivotal role in cancer initiation, maintenance, and progression. Diet may inhibit, retard or reverse these processes affecting angiogenesis (angioprevention). Nutraceuticals, such as omega-3 fatty acids, amino acids, proteins, vitamins, minerals, fibers, and phenolic compounds, improve health benefits as they are a source of bioactive compounds that, among other effects, can regulate angiogenesis. The literature concerning the pro-angiogenic and/or anti-angiogenic nutraceuticals and the possible activated pathways in cancer and other non-neoplastic diseases by *in vivo* and *in vitro* experiments are reviewed.

1. Introduction

Cancer chemoprevention was first defined by Sporn in the 1970's as the use of natural or synthetic compounds to inhibit, retard or reverse the process of carcinogenesis [1]. Diet is one of the major sources for identifying chemopreventive agents. Tosetti et al. [2] termed the concept that effective chemoprevention targets angiogenesis as "angioprevention".

Activation of the angiogenic switch in the course of tumor progression has been attributed to the synthesis or release of angiogenic factors (Table 1) [3]. The balance hypothesis assumes that the level of angiogenesis inducers and inhibitors governs cell differentiation states of quiescence or angiogenesis. This balance is altered by increasing activator gene expression, changing the bioavailability or activity of the inducer proteins, or reducing the concentrations of endogenous angiogenesis inhibitors (Table 2).

The classical definition of nutraceuticals is oral dietary components that provides health benefit in addition to its basic nutritional value [4]. Sources of nutraceuticals are represented by plants, animals, and microorganisms, including bacteria, yeasts, and fungi. The different classes of nutraceuticals are reported in Table 3. In the past years, dietary components have become a source of natural bioactive compounds exerting modulatory effects on angiogenesis. The aim of this article is to discuss the literature data concerning the activity of both pro-angiogenic (stimulator) factors and anti-angiogenic (inhibitor) factors contained in dietary nutraceuticals and providing evidence about the molecular mechanisms mediating the impact of nutraceuticals on cell biology in neoplastic processes. Moreover, in order to provide further evidence of a possible role of nutraceuticals in modulating cell proliferation via angiogenesis, we discussed literature regarding the modulatory effects of such nutrients on other pathological non-neoplastic proliferative processes biologically supported by angiogenesis, both in *in vitro* and *in vivo* experimental models.

1.1. Omega-3 polyunsaturated fatty acids (PUFAs) and angiogenesis

Omega-3 PUFAs inhibit angiogenesis by downregulating angiopoietin-2 (Ang-2) and may competitively inhibit the bioconversion of omega-6 PUFA's into their angiogenesis-promoting derivatives such as prostaglandins and arachidonic acid [5]. In contrast, omega-6 PUFAs, present at high levels in sunflower oil, peanut oil, and corn oils, stimulates endothelial migration and tube formation. Omega-3 fatty acids suppress a variety of tumors and to prevent osteolytic metastastic lesions in bone from breast cancer [6].

1.2. Phenolic acid compounds and angiogenesis

Phenolic acids and flavonoids are the most common form of phenolic compounds present in whole wheat grains. They have strong antioxidant, anti-inflammatory, and anti-carcinogenic activity.

Among phenolic acid compounds, wheat grains mainly contain ferulic and p-coumaric acid [7]. The grains of some wheat varieties contain various coumarins, among which coumarin and its hydroxylated derivatives [8].

Curcumin is an anti-cancer and anti-inflammatory molecule [9], that prevents the expression of vascular endothelial growth factor receptors

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Table 1
Angiogenic factors.

Angiogenin
Angiopoietin-1 (Ang-1)
Adrenomedullin
Fibroblast growth factor-1 (acidic FGF, FGF1)
Fibroblast growth factor-2 (basic FGF, FGF2)
Granulocyte-colony-stimulating factor (G-CSF)
Hepatocyte growth factor/scatter factor (HGF/SF)
Interleukin-6 (IL-6)
Interleukin-8 (IL-8)
Leptin
Placental growth factor (PlGF)
Platelet-derived growth factor (PDGF)
Pleiotrophin
Transforming growth factor-β (TGFβ)
Tumor necrosis factor-α (TNFα)
Vascular endothelial growth factor/vascular permeability factor (VEGF/VPF)

Table 2
Endogenous inhibitors of angiogenesis.

Angiopoietin-2 (Ang-2)
Angiostatin
Arresten
Canstatin
Decorin
Endorepellin
Endostatin
Interferons-α, β, and γ
Interleukin-4 (IL-4)
Interleukin-10 (IL-10)
Interleukin-12 (IL-12)
Interferon-inducible protein-10 (IP-10)
2-Methoxyestradiol
Osteopontin
Pigment epithelium-derived factor (PEDF)
Plasminogen activator inhibitor (PAI)
Platelet factor-4
Prolactin 16-KDa fragment
Proliferin-related protein
Prothrombin kringle 2
Maspin
Restin
SPARC cleavage product
Tissue inhibitors of matrix metalloproteinases (TIMPs)
Thrombospondin-1 and -2
Tumstatin
Vasostatin

(VEGFRs), and the activity of Src and focal adhesion kinases, involved in endothelial cell biosynthetic activity, polarity, and migration [10]. Curcumin inhibits matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9) expression in prostate tumor cells [11], inhibits angiogenesis, cyclooxygenase-2 (COX-2) and VEGF expression in hepatocellular carcinoma cells implanted in nude mice [12]. Curcumin inhibits tumor growth and angiogenesis in an orthotopic mouse model of human pancreatic cancer [13] and inhibits angiogenesis in liver fibrosis [14]. Moreover, curcumin inhibits oral squamous cell carcinoma proliferation and invasion via epidermal growth factor receptor (EGFR) signaling pathways [15]. Curcumin anti-angiogenic effects correspond to combined phosphodiesterase 1 and 4 (PDE2 and PDE4) inhibition [16]. Inulin based micelles loaded with curcumin exert an anti-angiogenic activity *in vivo* in the chick embryo chorioallantoic membrane (CAM) assay (Fig. 1) [17].

1.3. Polyphenols

Polyphenols are the most studied nutraceuticals. They are natural compounds which consists of one or more than one benzene rings blaring one or several hydroxyl functions. Natural polyphenols are found in high quantities in fruits, vegetables, cereals, and beverages [18]. They include catechins present in the tea, quercetin present in fruits and vegetables, and resveratrol, present in grapes and berries [19].

Table 3
Different types of nutraceuticals.

Omega-3 fatty acids	
Amino acids	
Proteins	
Vitamins	
Minerals	
Fibers	
Phenolic compounds	• Simple phenols • Polyphenols
Simple phenols	• Phenolic acids (curcumin, p-coumaric acid, caffeic acid, ferulic acid) • Coumarins • Phenolic alcohols
Polyphenols	• Stilbenes (resveratrol) • Flavonoids (flavonols, flavones, isoflavones, flavanones, flavanols, anthocyanins, chalcones) • Flavonols (kaempferol, quercetin, myricetin, fisetin, rutin) • Flavones (luteolin, apigenin, tangeritin) • Isoflavones (daidzein, genistein) • Flavanones (naringenin, hesperetin) • Flavanols (catechin, epicatechin, epigallocatechin, gallocatechin) • Anthocyanins (cyaniding, delphinidin, malvidin) • Chalcones (phloretin, phlorizin, arbutin)
Lignanes	
Tannins	
Secondary metabolites	

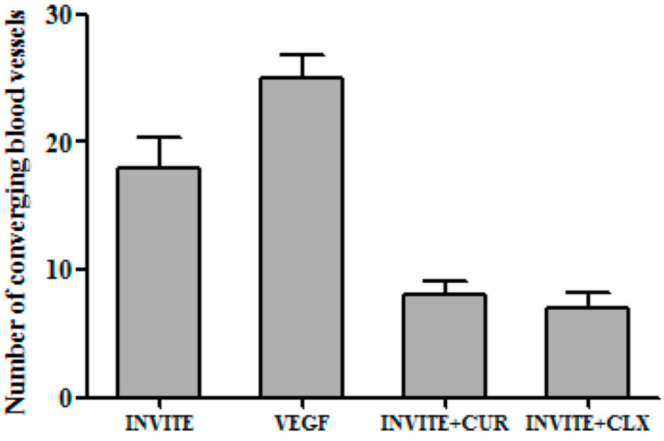

Fig. 1. Both inulin (INVITE)-curcumin (CUR) and INVITE-celexoximib (CLX) micelles possess remarkable anti-angiogenic activity, while the INVITE micelles alone resulted intrinsically pro-angiogenic, when tested in the *in vivo* CAM assay (Modified from Ref. [17]).

Long duration consumption of plants rich in polyphenols reduces the risk of cancer, hypertension, asthma, cardiovascular diseases, diabetes, osteoporosis, and neurodegenerative disorders [20].

Polyphenols have anti-proliferative effects on both tumor and endothelial cells, thereby suppressing tumorigenesis through their anti-angiogenic, anti-oxidant and anti-proliferative properties [21]. The effects of some polyphenols on angiogenesis have been investigated [22–26].

Among the stilbenes, resveratrol has been isolated from grapes, berries, peanuts and other plant sources. Red wine is a major source of resveratrol in the Mediterranean diet, as grape (*Vitis vinifera*) is a rich source of resveratrol. Resveratrol is found in seeds, skin, woody parts, and petioles. Therefore, red wine generally has a higher content of resveratrol than white wine. Resveratrol exerts anti-oxidant, anti-aging,

anti-inflammatory, and anti-angiogenic activities. It inhibits endothelial cell migration, tube formation as well as VEGF production [27]. *Trans*-resveratrol inhibits endothelial cell proliferation and repair of wounded endothelial cells [28]. Moreover, it prevents endothelial cell sprouting in fibrin gel, collagen gel invasion and morphogenesis on Matrigel *in vitro*, inhibits neovascularization of the chick embryo *area vasculosa* and murine melanoma B16 growth *in vivo* (Fig. 2) [28]. Resveratrol inhibits proliferation of human ovarian cancer cell and of human osteosarcoma cells by inducing hypoxia inducible factor 1 alpha (HIF-1α) degradation and reducing VEGF expression [29,30].

Resveratrol inhibits chemically induced mammary carcinogenesis, skin cancer tumorigenesis, and tumor growth and metastasis in mice bearing Lewis lung carcinoma [31,32]. In multiple myeloma cells, resveratrol inhibits VEGF-induced angiogenesis [33], and inhibits tumor necrosis factor alpha (TNF-α) mediated MMP-9 expression and invasion of human hepatocellular carcinoma cells [34].

Flavonoids are found in foods of plant source, being plant and flower pigment. Several dietary flavonoids including epigallocatechin-3 gallate (EGCG), a component of green tea, demonstrate their anti-angiogenenic and metastatic activities. Consumption of green tea has been advocated for several health benefits, such as ameliorating cardiovascular risk and prevention of cancer. EGCG specifically inhibits endothelial cell proliferation stimulated by fibroblast growth factor-2 (FGF-2) and induces avascular zones in CAM assay [35]. Mice that consume green tea show inhibition of VEGF-stimulated corneal neovascularization by as much as 70% and reduction of tumor cell invasion by 50% [36]. Both FGF-2 and VEGF induced angiogenesis in three-dimensional collagen gels are inhibited by several flavonoids [37]. Woganin, a flavonoid-like chemical compound, inhibits lipopolysaccharide (LPS)-induced angiogenesis both *in vitro* and *in vivo* [38].

Quercetin is the more representative of the flavonoids present in fruits and vegetables. It inhibits endothelial cell growth and migration [27,39], suppresses COX-2 expression and angiogenesis through inactivation of P300 signaling [40], decreases the expression and activity of MMP-2 and inhibits endothelial nitric oxide synthase (eNOS) [39,41,42]. Moreover, quercetin inhibits VEGF-induced angiogenesis [43], and upregulates the anti-angiogenic molecule thrombospondin-1 (TSP-1) [44].

Citrus flavones found in dietary sources extensively studied are luteolin, apigenin, nobiletin. Nobiletin interferes with endothelial cells functions including cell viability, migration and tubular structure formation [45,46]. Nobiletin inhibits angiogenesis in the CAM assay as well as in zebrafish embryo [45,46], and its anti-angiogenic and anti-invasive activity has been demonstrated in mouse sarcoma cells [47]. Luteolin inhibits cell migration and tubular structure formation by interfering with enzymatic activities and protein expression of MMP-2 and MMP-9 and the activation of JNK/STAT3, mTOR/AKT/ERK and VEGFR-2 pathways [48–51]. Luteolin inhibits blood vessel formation in CAM assay, rat aortic ring assay, rabbit cornea assay, retinal neovascularization and Matrigel plug model [48,51–53]. Apigenin interferes with hypoxia inducible factor-1 alpha (HIF-1α) and VEGF interaction and the stability of HIF-1α in ovarian cancer cell lines [54]. Apigenin decrease the vascularization in CAM assay, choroidal neovascularization in rats, and hemoglobin content as well as tumor vascularization in Matrigel plug models [55–58]. In lung cancer xenograft model, apigenins decrease tumor growth and downregulates VEGF, HIF-1α and proliferating cell nuclear antigen (PCNA) expression in the tumor tissue [57].

Inhibition of EGFR activation in the presence of quercetin [59] and high doses of red wine polyphenols [60] and luteolin [61] inhibit angiogenesis.

Genistein is a isoflavone that inhibits the proliferation and migration of endothelial cells [62,63] by blocking tyrosine phosphorylation [64] and *in vitro* angiogenic and metastatic potential of different tumor cell lines [65]. Moreover, genistein inhibits angiogenesis by modulating the expression of VEGF, MMPs and EGFR [66]. The anti-angiogenic activity of genistein has been detected in a study of healthy Japanese individuals who consumed a traditional soy-rich Japanese diet [67]. Urine from these subjects was examined for activity to inhibit FGF-2-stimulated endothelial cell proliferation.

Different effects of catechin on angiogenesis and inflammation depend on VEGF levels [24]. Green tea EGCG angiogenesis and suppresses VEGF-C/VEGFR-2 expression and signaling in experimental endometriosis *in vivo* [68]. Green tea polyphenol decreases mesenteric angiogenesis in rats with liver cirrhosis [69]. Green tea catechin inhibits ephrin-A1-mediated endothelial cell migration and angiogenesis [26].

1.4. Copper, selenium and iron

Gullino's studies demonstrated that the concentration of copper ions was more elevated in corneas treated with the pro-angiogenic prostaglandin E−1(PGE-1) than in untreated corneas [70]. On this basis, angiogenesis was tested in copper-deficient rabbits, which were unable to mount an angiogenic response to effectors active in rabbits with normal levels of plasma copper [70]. Then, Gullino hypothesized that copper-carrying molecules, such as ceruloplasmin, might be endowed with angiogenic activity. Native ceruloplasmin was angiogenic when implanted in the rabbit cornea, whereas copper-free apocerulosplasmin was not [71]. Moreover, Gullino and coworkers showed that heparin/-copper complex stimulated the motility of capillary endothelial cells *in vitro* [72]. Since then, several studies have confirmed the role of copper in angiogenesis and led to the hypothesis that copper chelating agent represent the basis for the development of anti-angiogenic therapies [73].

Administration of a copper chelator, tetrathiomolybdate (TM), to inflammatory breast cancer cell lines, revealed reduction of pro-angiogenic molecules VEGF, FGF-2, interleukin-1, -6 and -8 (IL-1a, IL-6 and IL-8) [74]. In a murine model of oral squamous cell carcinoma cells after TM administration, a 79% reduction of tumor volume and a 50% reduction in microvessel density was appreciable [75].

Selenium impacted both endothelial and cancer cells and led to the reduction of major regulatory molecules in angiogenesis. Methylseleninic acid (MSA) and selenite induced apoptosis in endothelial cells [76]. Methylated selenium affects endothelial cells, reduces MMP-2 production, abd inhibits VEGF expression un breast cancer cells [77].

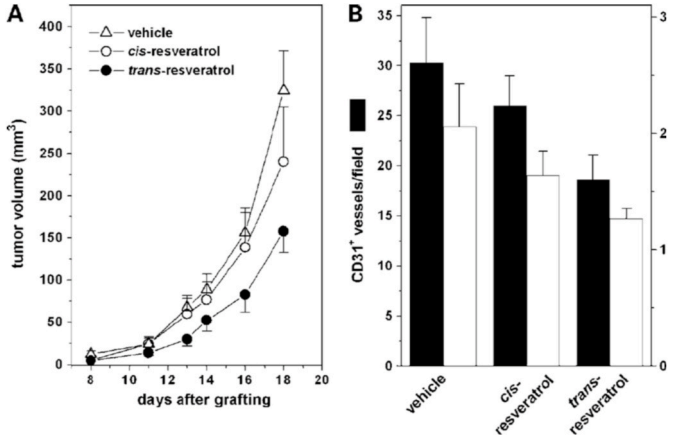

Fig. 2. Effect of resveratrol stereoisomers on tumor growth and neovascularization. A) female C57BL/6 N mice were transplanted s.c. with murine B16 melanoma cells. Animals were given *trans*-resveratrol or *cis*-resveratrol in the drinking water. Control animals received the same concentration of ethanol. Points, mean of 16 tumors; bars, SE. B) animals were sacrificed 18 d after grafting and tumor vascularization was assessed by counting the number of $CD31^+$ blood vessels per field in the most vascularized areas of five sections per each tumor (black columns) and by evaluating the levels of CD31/beta-actin mRNA ratio by quantitative real-time PCR analysis of total tumor RNA (open columns). Points, mean of 5 tumors; bars, SE. (Reproduced from Ref. [28]).

Microvessel density in mammary carcinoma was significantly reduced in rats supplemented with selenium-garlic compared to controls [78]. In a prostate cancer cell xenograft model, MSA reduced tumor growth and intratumoral microvessel density [79]. In melanoma, HIF-1α and VEGF were all decreased by selenite treatment and were thought to regulate tumor cell migration [80]. In a H69 human small cell lung cancer xenograft model, selenium-methyl-selenocysteine treatment reduced the microvessel density [81]. More recently, it has been demonstrated that MSA provided at nutrinional selenium levels inhibits angiogenesis by down-regulating integrin beta 3 signaling [82].

While iron supplementation inhibited VEGF signaling in endothelial cells *in vitro* and reduced lung carcinoma vascularization *in vivo* [83], lipocalin 2 supplementation resulted in reactive oxygen species (ROS) accumulation and increased brain endothelial cell migration which was reversible upon iron chelation [84]. Low dose of iron can inhibit angiogenesis, whereas high dose promotes oxidative stress promotes angiogenesis [85].

1.5. *In vitro and in vivo experiments on the effects of nutraceuticals on tumors and other angiogenesis-related disorders*

Many studies have explored the molecular mechanisms subtending the beneficial effects of nutraceuticals in the therapy of tumors, using both *in vitro* and *in vivo* experiments. Furthermore, since neoplastic processes are mostly angiogenesis-related disorders [86], studies have also investigated the role of angiogenesis as a mediator of these effects.

In vitro studies exploring the direct effect of nutraceutical nutrients on cell biology have clarified the molecular mechanisms, underling the potential role of nutraceuticals in tumors.

For example, studies focusing on Kaempferol, a phytochemical flavonoid found in many fruits and vegetables, in human umbilical vein endothelial cells (HUVECs) have indicated that the direct exposure of endothelial cells to such a nutrient, results in an increased VEGF-stimulated HUVEC viability, inhibition of cell migration, invasion, and tube formation. Furthermore, western blot experiments demonstrated that cell exposure to Kaempferol induced reduction of VEGFR-2, and elements of its downstream signalling cascades (such as AKT, mTOR and MEK1/2-ERK1/2) in VEGF-stimulated HUVECs [87].

Additionally, studies on breast cancer cells demonstrated the role of another flavonoid,luteolin (8-C-beta-D-glucopyranoside), a glycosyl dietary element, in modulation of tumorigenesis. In particular, Kikuchi and co-workers [88] reported that this nutrient can reduce tumor tissue invasion, a process importantly related to angiogenesis, by blocking expression of MMP-9 and IL-8. Within such a framework, the beneficial effect of luteolin on tumorigenesis could be related to the downregulated activity of IL-8, a chemokine that normally affects tumor microenvironment by promoting angiogenic responses in endothelial cells and increasing both neoplastic and endothelial cell proliferation [89].

Importantly, the potential anti-cancer role of luteolin has been confirmed by *in vivo* studies indicating a possible involvement of such a nutrient on angiogenesis regulation. In particular, a xenograft tumor mouse model of melanoma was used to evaluate the effect of Luteolin on the growth of A375 cells, a human melanoma cell line with an epithelial morphology that experimentally form tumors following implantation into immunocompromised mice. Results of this study indicated that luteolin significantly inhibits the tumor growth of A375 cells by suppressing MMP-2 and MMP-9, possibly via regulating the PI3K/AKT pathway signaling [90]. Importantly, MMP-2 and MMP-9 are critical elements in the formation of vasculogenic-like networks in several types of aggressive tumors, thus confirming the possibility that the beneficial effects of luteolin on cancer onset and development may be mediated by a reduction of neo-angiogenesis processes commonly supporting tumor tissue progression [91].

Further investigation has also indicated quercetin, a natural constituent present in vegetables, fruits, tea, and herbs as having a role in proliferative tumor-related processes. In fact, both *in vitro* and *in vivo* experiments have highlighted how such a nutrient may show potent anti-proliferative and pro-apoptotic effects against a vast range of different gastric cancer cells. In particular, studies have reported that quercetin may exert an antimetastatic effect probably by mediating the breakdown of the urokinase plasminogen activator (uPA)/urokinase plasminogen receptor (uPAR) pathway, a molecular system otherwise reported to play a key role in gastric cancer metastatic process because regulating angiogenesis, cell motility, and cytomorphologic changes possibly via regulation of the MMPs, VEGF and VEGF molecular pathways [92]. Within such a perspective, it is possible that the *primum movens* of quercetin beneficial effect on gastric cancer metastases is represented by its reported ability to downregulate the uPA/uPAR function via modulation of NF-kappa B, PKC-delta, ERK1/2, and AMPK activity [92].

Rather importantly, several other proliferative angiogenesis-dependent disorders, such as endometriosis, proliferative retinopathies, psoriasis and rheumatoid arthritis [93] are reported to be therapeutically impacted by nutraceutical compounds, thus confirming a putative role of angiogenesis-mediated effects of such a class of nutrients on cell proliferation. Not surprisingly, early experiments on non-nutraceutical anti- and pro-angiogenic agents have proved the effectiveness of such agents on most of these diseases, including, along with haemangioma and ophthalmic diseases, psoriatic arthritis [94], a condition in which joint morphological changes are associated with dysregulated angiogenesis and subsequent formation of proliferative processes supporting immature vessel formation [95].

A prototypical example of the therapeutic effects of nutraceutical compounds in the treatment of non-neoplastic/angiogenesis-related disorders is represented by the case of the use of curcumin in the treatment of endometriosis. While, inflammation is reported to play a critical role in such a condition because leading to ectopic cell proliferation, apoptosis and angiogenesis [96], studies in experimental rats have demonstrated that direct exposure of endometriosis tissues to curcumin results in a significant reduction of inflammatory processes, VEGF protein expression and microvessel formation [97], thus suggesting that the beneficial anti-endometriosis effects of curcumin may be mediated by a reduction in ectopic endometrium cell proliferation normally supported by neo-angiogenesis.

1.6. *Nutraceuticals and lymphangiogenesis*

Vascular endothelial growth factors (VEGF)-C and VEGF-D, and their cognate receptor tyrosine kinase, VEGFR-3, are critical regulators of lymphangiogenesis. In tumor-bearing mice, oleuropein, the most abundant phenolic compound in olives, reduced high-fat-diet induced expression of angiogenesis (CD31, VE-cadherin, VEGF-A, and VEGFR-2), lymphangiogenesis (LYVE-1, VEGF-C, VEGF-D, and VEGFR-3), and hypoxia (HIF-1α and glucose transporter-1, GLUT-1) markers [80]. Curcumin suppressed VEGF-C induced lymphangiogenesis in a Matrigel plug assay in mice, and VEGF-C induced tube formation in human dermal lymphatic endothelial cells, demonstrating its anti-lymphangiogenic action *in vivo* and *in vitro* [98]. Curcumin exerts an anti-lymphangiogenesis activity in gastric cancer cells by inhibiting HMGB1/VEGF-D signaling pathway [99].

2. Concluding remarks

The notion of angioprevention includes functional components in food, that when administered regularly, may inhibit tumor growth and possibly other non-neoplastic condition progression by modulating angiogenesis.

It is important to distinguish the effect of nutraceuticals on tumor growth and on tumor angiogenesis, and inflammation. In any case, a wide overlapping between these biological activities exists. In fact, natural compounds with anti-oxidant activity have the capacity to modulate angiogenesis as well as chronic inflammation is strictly related

with the angiogenic phenotype and tumor growth. Moreover, nutraceuticals act as potential modifiers of the impaired innate immunity and deficiencies in certain nutrients may affect immunocompetence. Several studies have established the modulatory effects of individual food components on the immune response using *in vitro* or *in vivo* experiments in humans and animal models in both healthy and pathological conditions, including tumors. In this context, nutraceuticals may also intervene in the cross-linking between the interaction between angiogenesis and innate immunity in the modulation of tumor growth and angiogenesis.

Several components from food resources have shown potent anti-angiogenic efficacy with different mechanisms of action, including inhibition of endothelial cell proliferation, inhibition of the pro-angiogenic growth factors, scavenging of reactive oxygen species, inhibition of MMPs along with suppression of tumor growth and invasion, blocking of VEGF-mediated tyrosine phosphorylation of vascular endothelial cadherins, inhibition of COX-2 expression and IL-1β production.

The identification of dietary sources of anti-angiogenic molecules has been aided through observational epidemiologic studies, which have allowed to identify specific foods associated with reduced risk for cancer and other angiogenesis-related disorders. Natural anti-angiogenic molecules are present in numerous dietary sources and may impact on a wide spectrum of mechanisms that can suppress the growth and migration of tumors and other angiogenesis-related conditions. The control of blood vessel growth through dietary anti-angiogenesis may redefine cancer as a diseases that can be suppressed throughout an individual's lifetime.

Rather importantly for the practical implications of the current study, natural compounds are relatively low toxic and have multi-target actions, therefore, while determining a potentially low impact on the body, they may regulate a number of biological/molecular mechanisms of key importance to the body health. In this research area, new discoveries and advancements towards their application in therapeutic settings are expected for the near future.

Credit author statement

Antonio Rampino, Domenico Ribatti: Conceptualization; writing-original draft; writing review; Roberto Tamma, Tiziana Annese, Anna Margari: Figures and editing.

Declaration of competing interest

The Author declares no conflict of interest.

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