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Targeting Angiogenesis By Phytochemicals

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Abstract

Cancer is a major cause of death worldwide and angiogenesis is critical in cancer progression. Development of new blood vessels and nutrition of tumor cells are heavily dependent on angiogenesis. Thus, angiogenesis inhibition might be a promising approach for anticancer therapy. Anti-angiogenic small molecule and phytochemicals as a cancer treatment approach are focused in these main points; modes of action, adverse effects, mechanisms of resistance and new developments. Treatment with anti-angiogenic compounds might be advantageous over conventional chemotherapy due to the fact that those compounds mainly act on endothelial cells, which are genetically more stable and homogenous compared to tumor cells and they show lower susceptibility to acquired drug resistance (ADR). Targeting the VEGF (vascular endothelial growth factor) signalling pathway with synthetic small molecules inhibiting Receptor Tyrosine Kinases (RTKs) in addition to antagonizing VEGF might be a promising approach. Moreover, beneficial effect of phytochemicals were proven on cancer-related pathways especially concerning anti-angiogenesis. Plant phenolics being an important category of prominent phytochemicals affect different pathways of angiogenesis. Green tea polyphenols (epigallocatechin gallate) and soy bean isoflavones (genistein) are two examples involving an anti-angiogenic effect.

Abbreviations: AADR: Acquired Drug Resistance; AITC: Allyl Isothiocyanate; ANG2: Angiopoietin 2; AP-1: Activator Protein 1; APN: Aminopeptidase N; ARE: Antioxidant Response Element; BAEC: Bovine Aortic Endothelial Cells; BPGF-1: Bone-Derived Growth Factor-1; bFGF: Basic Fibroblast Growth Factor; BRCA1: Breast Cancer 1, early onset; CAM: Chicken Chorioallantoic Membrane; CD31: Cluster of Differentiation 31; COX: Cyclooxygenase; CREB: cAMP Response Element Binding; DHA: Docosahexenoic Acid; EGCG: Epiallocatechin Gallate; EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; EPA: Eicosapentaenoic Acid; ERK: Extracellular Signal-Regulated Kinase; FAK: Focal Adhesion Kinase; FGFR: Fibroblast Growth Factor Receptor; HER: Human Epidermal Growth Factor Receptor; HGF: Hepatocyte Growth Factor; HIF: Hypoxia-Inducible Factor; HUVEC: Human Umbilical Vein Endothelial Cells; IκB: Inhibitor of Kappa B; IL: Interleukin; iNOS: Inducible Nitric Oxide Synthase; JAK2: Janus Kinase 2; JNK: Janus Kinase; KDR: Kinase Insert Domain Receptor; LOX: Lysyl Oxidase; MAP-Kinase: Mitogen-Activated Protein Kinase; MCP-1: Monocyte Chemoattractant Protein1; MIF: Migration Inhibitory Factor; MMP: Matrix Metalloproteinase; MT1-MMP: Membrane-Type 1 Matrix Metalloproteinase; MVD: Microvessel Density; NFκB: Nuclear Factor Kappa B; NO: Nitric Oxide; NOS: Nitric Oxide Synthase; Nrf2: Nuclear Factor (erythroid-derived 2)-like 2; PAI-1: Plasminogen Activator Inhibitor-1; pAKT: Phosphorylated Akt; PAR: Protease Activated Receptor; PDGF: Platelet-Derived Growth Factor; PEITC: Phenethyl Isothiocyanate; PGC-1a: Peroxisome Proliferator- Activated Receptor Coactivator-1a; PGE2: Prostaglandin E2; PGG: Penta-1,2,3,4,6-O-Galloyl-beta-d-Glucose; PI3: Phosphatidylinositide 3; PIGF: Platelet-Inhibitor Growth Factor; PKC: Protein Kinase C; PTK: Protein Tyrosine Kinase; RA: Rosmarinic Acid; ROS: Reactive Oxygen Species; RTK: Receptor Tyrosine Kinase; RWPC: Red Wine Polyphenolic Compound; SC: Shark Cartilage; SFN: Sulforaphane; Sirt1: Silent Information Regulator 1; Src: V-Src Sarcoma; STAT-3: Signal Transducer And Activator of Transcription 3; TGF: Transforming Growth Factor; TIMP1: Tissue Inhibitor of MMP-1; TNF: Tumor Necrosis Factor; uPAR: Urokinase-Type Plasminogen Activator Receptor; VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Factor Receptor; VSMC: Vascular Smooth Muscle Cell

Introduction

Angiogenesis is the growth of new blood vessels to ensure wound healing, reproduction and development of cells. It is strictly regulated and various inhibitors and stimulators play role to maintain it in balance [1]. Tumor growth and metastasis depend on angiogenesis and stimulators are upregulated disrupting the angiogenesis balance [1,2]. Tumor blood vessels have a different structure with irregular branches and they are more heterogenous compared to normal blood vessels [3]. Various pathways such as VEGF, EGF, FGF and HGF ensure the heterogeneity of tumor blood vessel structure and upregulated angiogenesis.

Secondary plant metabolites are valuable sources of small molecules and various drugs were identified from plants. Combined therapy approach targeting multiple components of angiogenesis with phytochemicals might be promising to achieve an effective anti-cancer therapy [4].

Therapy with phytochemicals

Natural products from botanical sources (phytochemicals) continue to attract interest for various applications including cancer treatment with their effect on cancer-related biological pathways such as angiogenesis [5,6]. Throughout nature in flora, marine wildlife and microbial products might involve effective active principles which contain a multitude of diverse molecular entities. For natural products

from marine or microorganisms, three reviews are helpful in that regard [7-9].

Herbal ingredients have been used for more than 10000 years by mankind to influence body functions and curing diseases [10]. Indian Ayurveda and Traditional Chinese Medicine are successful examples for traditional therapeutic paradigms.

Phytochemicals are mostly classified as secondary plant metabolites. Various anti-angiogenic effects of phytochemicals including flavonoids, sulphated carbohydrates, triterpenoids, catechols, tannins and aromatic substances have been reported [9,10]. Wholesome herbal extracts have been investigated in terms of anti-angiogenic activities [11] identifying molecules targeting different pathways of angiogenesis. Nitric oxide synthase (NOS) and VEGF are of special importance for their interaction with well-known secondary plant metabolites from different botanical sources [12].

Anti-angiogenic Phytochemicals

In vitro studies serve as the main source of evidence for anti-angiogenic activities of phytochemicals. Single steps of angiogenesis such as apoptosis, proliferation, migration and protease production in addition to complex cascades leading to neovascularization have been investigated [11]. Culturing of microvascular endothelium cells can be difficult for such experiments [13]. VEGF and MMPs are prominent angiogenic effectors and the effect of phytochemicals on the corresponding regulatory pathways can be screened via endothelial or chicken embryo cell cultures [14].

Various phytochemicals target the transcription factor Nrf2 (nuclear factor (erythroid-derived 2)- related factor), which triggers an antioxidant defense response by ARE (antioxidant response element)-mediated induction of Phase II detoxifying and antioxidant enzymes [15,16]. Nrf2 can be activated by caloric restriction mimetic agents and caloric restriction together with activation of enzymes playing role in plasma membrane redox system. Thus, Nrf2 can be implicated in the cancer protection induced by caloric restriction [17]. Induction of Nrf2 activation with caloric restriction can lead to prevention of vascular aging by antioxidant defense activities of endothelial cells [18]. Antiangiogenic phytochemicals have been proven to be active in some cases via mostly *in vitro* animal studies, human studies are rare.

Polyphenols

Plant phenolics are found in various botanical sources and they are probably the best analyzed phytochemical category. More than 5000 flavanoids, which is the most important phenolics class in human diets, are described in literature classified in 10 chemical groups [19]. Various effects such as anti-inflammation, inhibition of cell proliferation, antioxidation, detoxification of mutagenic metabolites, apoptosis and inhibition of angiogenesis are exerted on cancer-related biochemical pathways by the phenolic phytochemicals [19]. Some examples of phenolics are mentioned below giving more importance to reported mechanisms for angiogenesis control, resistance and side effects.

Green Tea: Tea leaves are known for their relaxative and stimulative effects for long time. They have been recently investigated for health-related effects. Catechins such as epigallocatechin gallate (EGCG), which is the most prominent phytochemical category in green tea, are observed to involve anticancer activity including antioxidant, anti-inflammatory, photoprotective and antiphotocarcinogenic effects in *in vivo, in vitro* and in chemical assays.

MMPs (type IV collagenases, zinc dependent proteinases involved in matrix turnover) and VEGF expressions are decreased whereas an increase in expression of TIMP1 (tissue inhibitor of MMP) have been observed upon green tea catechin treatments [14,20]. EGCG degrades the basement membrane via MMP inhibition and facilitates cell invasion in tumor cells. It also deregulate the expression of membrane-type 1 matrix metalloproteinase (MT1-MMP) which generates an active form of MMP-2 from proMMP-2 [10].

MAP kinase family members Erk-1 and Erk-2 influence VEGF expression. Thus, inhibition of them leads to lower expression of VEGF. EGCG might exert its effect by chelation of divalent cations essential for the activity of some receptor kinases that are involved in Erk-1 and -2 activation. Moreover, EGCG downregulates VEGF expression via inhibition of activator protein 1 (AP-1) which binds to the promoter region of VEGF. Inhibition of VEGFR-1 and -2 tyrosine phosphorylation has also been reported [21]. EGCG is able to influence COX-2 expression since COX-2 promoter involve binding sites for NFκB and AP-1. Reduced COX-2 level leads to a reduced activation of MMP and angiogenic PGE2 expression [21].

EGCG has an inhibitory activity against platelet-induced growth factor-BB (PIGFBB) induced intracellular signalling transduction pathway in vascular smooth muscle cells (VSMCs), several MAP-kinase isoforms in VSMCs after PDGF-BB activation and the tyrosine phosphorylation of various kinases. EGCG exerts its interference with angiogenesis by targeting multiple other pathways. It reduces the level of inducible NOS (iNOS) by increased IκB kinase activity [12,21]. Expression of vascular endothelial cell antigens, *e.g.*CD31 are downregulated [22] protein kinase C (PKC) [11,22] together with angiogenic factors MMP-2 and -9, VEGF, CD31 [23] activities are reduced and EGFR signalling is suppressed [24].

Soy beans isoflavones: Genistein: Soy beans, whose 55% production occurs in America and the rest in Asia, are one of the most important global crops**.** Differences among Caucasian and Asian populations were observed in terms of cancer prevalence as a result of epidemiological studies.

Genistein, an isoflavone phytoestrogen isolated from soy beans, has been well studied in terms of its pharmacological features. Like other phenolics, it inhibits bFGF-induced neovascularization as well as migration and proliferation of endothelial cells [9] in addition to downregulation of VEGF expression [12]. MMP/TIMP proteolytic balance is shifted towards proteolysis inhibition upon genistein exposure. Moreover, it suppresses the VEGF/bFGF-stimulated increase of TIMP-1 expression and decrease in TIMP-2 expression [10]. It was shown to inhibit angiogenesis in renal cell carcinoma [25].

Further anti-angiogenic effects include; inhibition of NFκB, inhibition of TGF-β signaling being an important feature in up-regulating angiogenesis, inhibition of protein tyrosine kinase (PTK) and PTK-mediated signaling pathways, modulation of the Akt signaling pathway, down-regulation of several genes relevant for angiogenesis pathways (Type IV collagenases, protease M, VEGF, uPAR, neuropilin, bone-derived growth factor-1 (BPGF-1), lysophosphatidic acid receptor, aminopeptidase, thrombospondin-1, proteinase-activated receptor), suppression of AP-1/CREB-binding to the COX-2 promoter leading to lower COX-2 levels (COX-2 increases cell proliferation and VEGF production), dose-dependent inhibition of expression/excretion of VEGF, PDGF, tissue factor, urokinase plasminogen activator, MMP-2 and -9 as well as up-regulation of angiogenesis inhibitors: plasminogen activator inhibitor-1, endostatin, angiostatin, thrombospondin-2 [25-27].

Curcumin fromc curcuma longa: Turmeric, which is a popular Indian spice, takes the yellow color from curcumin. Curcumin involves several functional groups such that two polyphenolic rings are connected by two α,β-unsaturated carbonyl groups.

APN (CD13/aminopeptidase N) is irreversibly inhibited by curcumin. It has been reported that curcumin down-regulates MMP-2 and MMP-9 in addition to TIMP-1 (tissue inhibitor of MMP) up-regulation, and it also down-regulates VEGF and bFGF. VEGFR and EGFR are also inhibited [11] and aminopeptidase inhibition leads to anti-angiogenic effects [13]. iNOS expression is found to decrease which results in less NO production in endothelial cells [11,12]. It has also been reported that COX-1 and COX-2, which play role in angiogenesis in endothelium, as well as inhibition of TNF-α induced activation of NFκB, has been reported to be downregulated [28]. Curcumin in nude mice xenografted with hepatocarcinoma cells inhibited tumor neocapillary density significantly by oral administration [29]. Curcumin inhibits HIF-1 activity leading to down-regulation of HIF-1 target genes. Moreover, curcumin suppressed HIF-1 and VEGF in tumors as shown in mice bearing Hep3B hepatoma [30].

Red wine polyphenols:Resveratrol: RWPCs involve various anti-angiogenic properties such as inhibition of growth factor induced VEGF expression in vascular smooth muscle cells due to their antioxidant properties, by preventing the formation of intracellular reactive oxygen species and phosphorylation of p38 MAP kinase. RWPC treatment also leads to down-regulation of cyclin A gene expression, inhibition of MMP-2, and inhibition of p38 MAPK and PI3-kinase/Akt pathways [31].

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a phytochemical belonging to phytoalexin class produced by plants in case of pathogen attack. Modulation of NFκB, expression [32] and activity of COX enzymes [33] were observed effects of resveratrol. With antioxidant and anti-angiogenic properties, it affects all stages of carcinogenesis and causes reduction in microvessel density [34,35]. Treatment of HUVECs with 1 to 2.5 μmol/l resveratrol significantly reduced VEGF-mediated migration and tube formation but not cell proliferation [36,37]. Same concentration of resveratrol was shown to disrupt VEGF-mediated tyrosine phosphorylation of vascular endothelial (VE)-cadherin and its complex partner, beta-catenin. It also inhibited VEGF-induced endogenous Src kinase activation [37]. iNOS down-regulation and consequently up-regulated VEGF expression were also reported [12]. It can suppress the growth of new blood vessels and capillary endothelial cell growth by targeting both VEGF-and FGF-receptor mediated angiogenic responses through inhibition of MAPK phosphorylation in endothelial cells. Resveratrol can increase mitochondrial function and improve energy balance in mice via stimulating metabolic regulator PGC-1a (peroxisome proliferator- activated receptor coactivator-1a) deacetylation by the sirtuin Sirt1 (Silent Information Regulator 1) [38]. Sirt1 activation by resveratrol inhibits breast carcinogenesis in BRCA1 mutant mice [39]. It has been reported that chemical similarity to phytoestrogens might lead to growth stimulatory effects in human breast cancer cells [40]. Some studies point out that it retards the development of blood vessels leading to suppression of tumor growth.

Other polyphenols: Various other anti-angiogenic phenolic compounds can be found in different sources e.g. pomegranate, parsley, celery and *Silybum marianum*. Pomegranate involves diverse key components in different categories: *i.e.* catechins and epicatechins, anthocyanidins and flavonoids. Decline in COX activity, NO production and VEGF expression together with upregulation of the anti-angiogenic migration inhibitory factor (MIF) are leading factors for anti-angiogenic activity. Combretastatin, a stilbenoid derivative isolated from *Combretum caffrum*, targets tubulin, inhibits angiogenesis and reduces metastasis. Parsley, celery and onion are other sources involving anti-angiogenic flavonols They exert the corresponding effects by interaction with multiple key structures in the pathway of angiogenesis, e.g. COX-2, EGF-receptor or NFκB transcription protein. Silybinin, a flavolignan isolated from *Silybum marianum*,decreases VEGF secretion, iNOS, COX and HIF-1α expression [12,41-43].

OptiBerryIH141 is a cyanidin belonging to antho-cyanines class isolated from berries. It inhibits H_2O_2-and TNF-α-induced VEGF expression, basal MCP-1 transcription and angiogenesis [44]. 3-Hydroxy-flavone is a flavonol which prevents VEGF/bFGF-induced MMP-1 and uPA expression. It activates pro-MMP-2 and modulates their inhibitors TIMP-1 and -2 and PAI-1 [10]. Apigenin, isolated from *Petroselinum crispum*, inhibits expression of hypoxia-inducible factor 1 (HIF-1), VEGF and TIMP-1 [10] in various types of cancer cells under normoxic and hypoxic conditions leading to antiangiogenesis effects and autophagy in tumors [43,45]. Combretastatin belongs to the stilbenoid phenol class. Its binding to tubulin reduces metastasis by inhibiting angiogenesis [10].

Quercetin, which is a flavone found in red grapes, citrus, apples, onions, raspberries, cherries, broccoli, and leafy greens, inhibits angiogenesis through multiple mechanisms such as interaction with the COX-2 and lipoxygenase (LOX)–5 enzymes, the EGF receptor, the HER-2 intracellular signaling pathway, and the NF-κB nuclear transcription protein. [46,47]. It was shown to inhibit hypoxia-induced VEGF expression in NCI-H157 cells together with suppression in STAT-3 tyrosine phosphorylation [11,48]. Inhibition of STAT-3 function is correlated with decrease in VEGF expression implying that STAT-3 inhibition might be involved in angiogenesis inhibition [49]. It was shown to possibly enhance the anticancer effect of tamoxifen through antiangiogenesis in a prostate cancer xenograft model [50].

Rosmarinic Acid (RA), a water-soluble polyphenolic compound found in many *Lamiaceae* herbs, involves an antiangiogenic effect with its ability to reduce the intracellular ROS level, H_2O_2-dependent VEGF expression, and IL-8 release of endothelial cells [51]. Figure 1 represents the inhibitory effects of antiangiogenic phytochemicals and nutraceuticals on cancer progression.

Other classes of phytochemicals and nutraceuticals

α-Tocopherol has been studied to reduce VEGF levels [10]. Iscador,
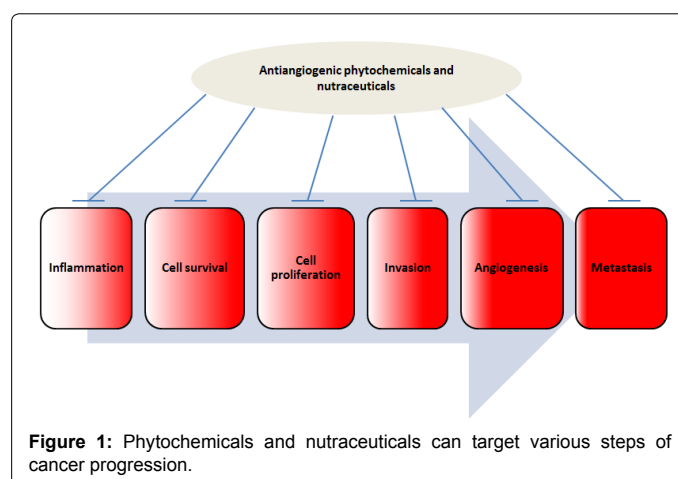

Figure 1: Phytochemicals and nutraceuticals can target various steps of cancer progression.

a widely used extract of *Viscum album*L. (Viscaceae), has been shown to have antiangiogenic effect through downregulation of VEGF, and it induces apoptosis of cancer cells [52,53]. It was reported to reduce lung metastases and increase survival rate in a mouse model [54].

γ-Tocotrienol from palm (*Nigella sativa*) inhibited cobalt(II) chloride-induced accumulation of HIF-1α and paracrine secretion of VEGF, which leads to decreased activation of ERK-1/ERK-2 in a study conducted with SGC-7901 (human gastric adenocarcinoma) cell line [55].

Alliin, found in garlic, involves inhibitory effect against FGF-2-induced human endothelial cell tube formation and VEGF-induced angiogenesis in a chick chorioallantoic membrane (CAM) model [56].

Allyl isothiocyanate (AITC) has antiangiogenic properties with its inhibitory effect against NO synthesis and TNF-α production as shown in a C57BL/6 mouse model bearing B16-F10 melanoma cells [57].It reduced vessel sprouting in Swiss albino mice into which Ehrlich ascites tumor cells were transplanted with antiangiogenic activity associated with reduction of VEGF expression [58]. Intraperitoneal administration of AITC decreased *in vivo* capillary formation in mouse B16F-10 melanoma model [57]. AITC suppressed HUVEC proliferation, migration, invasion and tube formation [59].

Artemisinin, a sesquiterpene extracted from *Artemisia annua*L. (Asteraceae), has been used clinically as an antimalarial drug [60]. It decreased the VEGF expression in tumor cells and the KDR/flk-1 expression in endothelial cells [11,61]. It involved an inhibitory effect on NF-κB activation [62] and its anti-angiogenic effect is superior to its cytotoxicity effect.

Artesunate, a semisynthetic derivative of artemisinin, inhibited angiogenesis in a dose-dependent manner significantly. It inhibited cell proliferation of human umbilical vein endothelial cell (HUVEC) more than that of cancer cells, fibroblast cells, and human endometrial cells indicating that antiangiogenic activity of artesunate is greater than its cytotoxicity. An *in vivo* study, where human ovarian cancer cells (HO-891) were transplanted in nude mice to evaluate the antiangiogenic effect of artemisinin, has shown that tumor growth was decreased and microvessel density was reduced without any toxicity to the host animals. Its antiangiogenic potential was also found in K562 cells *in vitro* and *in vivo* [63].

Caffeic acid, isolated from *Coffea arabica*, suppressed STAT-3-mediated HIF-1 and VEGF expression, consequently vascularization and angiogenesis are inhibited in mice bearing Caki-I human renal carcinoma cells [64].

Capsaicin, an alkaloid isolated from chili pepper, which belongs to the *Capsicum* genus, showed inhibitory activity against VEGF-induced proliferation, DNA synthesis, capillary-like tube formation of primary cultured human endothelial cells, VEGF-induced vessel sprouting in a rat aortic ring assay. It also inhibits VEGF-induced vessel formation together with VEGF-induced p38 MAPK, p125 (FAK), and AKT activation as shown in a mouse Matrigel plug assay [65]. It also inhibits chemotactic motility, and induced G1 phase arrest in endothelial cells [10]. It was reported that capsaicin inhibited carcinogenesis of the skin, colon, lung, tongue and prostate depending on signal transducers and activators of transcription (STAT)3 inhibition in multiple myeloma cells [66]. In these studies, capsaicin blocked both the inducible and the constitutive activation of STAT3 and this effect is associated with downregulation of the expression of the genes involved in cell survival, proliferation and angiogenesis [67].

Dovitinib, which is a quinolone with a strong affinity for FGFR in addition to multiple RTKs, has been shown to involve efficacy against metastatic renal cell carcinoma in clinical trials [68].

Eicosapentaenoic acid (EPA), an omega-3 fatty acid, was observed to lower VEGF-stimulated tube formation and migration in HUVECs [69]. In addition, certain matrix metalloproteinases (MMPs) associated with endothelial cell migration were diminished upon conjugated EPA treatment [70]. Docosahexenoic acid (DHA) is another omega-3 fatty acid having similar antiangiogenic effects with EPA. Treatment with EPA and DHA reduced COX-2 and VEGF expression levels, resulting in diminution of microvessel formation in tumor mice [29] probably via deregulation of extracellular signal-regulated kinases (ERK-1/2) and HIF-1 in colon cancer cells. Besides, they showed to inhibit tumor invasion of brain-metastatic melanoma cells by downregulating COX-2 mRNA expression [71]. Particularly, DHA decreased the expression of β-catenin target genes such as MMPs and VEGF, leading to antiangiogenic and antimetastatic effects [72].

Emodin, which is an anthraquinone derivative isolated from the rhizomes of *Rheum palmatum*, suppressed various angiogenic processes both *in vitro* and *in vivo* [73]. It inhibited bFGF-induced proliferation, migration and tube formation of HUVECs stimulated with VEGF in a dose-dependent manner [36]. Furthermore, emodin induced cell cycle arrest of HUVECs in the G0/G1 phase. It also decreased VEGF-induced tube formation of human dermal microvascular endothelial cells. Basal secretion of MMP-2 is inhibited by emodin. *In vivo*, it suppressed angiogenesis in the chicken CAM and VEGF-induced angiogenesis of the Matrigel plug in mice [36].

Flavopiridol, isolated from *Dysoxylum binectariferum*, decreaseed hypoxia-mediated HIF-1α expression, tumor cell migration and VEGF secretion in human U87MG and T98G glioma cell lines, reduced vascularity of intracranial syngeneic GL261 gliomas upon flavopiridol treatment in animal models supported the *in vitro* data [74].

Gambogic acid, isolated from gamboge tree, *Garciniahanburyi*, was reported to inhibit VEGFR-2 and downstream kinases such as c-Src, FAK, and AKT. In HUVEC and human prostate cancer cells (PC3), it inhibited angiogenesis [75].

Gingerol, contained in ginger, inhibited capillary-like tube formation, endothelial cell sprouting in rat aorta and formation of new blood vessels in mouse cornea [76].

Hypericin, an isolate from *Hypericumperforatum*, has been shown to block the invasion and migration of endothelial cells and inhibit matrix metalloproteinases as well as *in vitro* capillary-like tube formation. Its antiangiogenic effect was also observed in animal experiments [77,78]. Hyperforin, another bio-active compound of *Hypericumperforatum*, inhibited angiogenesis *in vitro* as well as *in vivo* [79].

Isoliquiritigenin, which is a flavonoid found in licorice, reduced cell migration and invasion of the human prostate cancer cells DU145 and LNCaP [29]. It was studied that a disruption in c-Jun N-terminal kinase (JNK)/activator protein-1 (AP-1) pathway could be responsible for decreased production of proangogenic factors [80].

Lariciresinol, a lignan isolated from flaxseed (Linum usitatissimum), has been found to attenuate tumor growth and angiogenesis, and reduce microvessel density (MVD) in hormone responsive preclinical breast cancer models (DMBA-induced mammary carcinoma in rats and MCF-7 breast cancer xenografts in athymic mice) [81].

Liver and lung metastases of lymphoma and melanoma cells in

experimental and spontaneous metastasis models were inhibited upon subcutaneous administration of bLfcin (0.5 mg/mouse) [82]. Ability of bLf to inhibit tumor angiogenesis was found at the same study by the reduced number of tumor-induced blood vessels and tumor growth suppression in the early stage of carcinogenesis [82].

Luteolin, a commonly observed flavone, could cause a decrease in VEGF-induced survival and proliferation of HUVECs through PI3K/AKT-dependent pathways [83].

ML-1, which is a lectin, potentiates anticancer efficacy of TNF-α [41,84,85]. Gallotannin, which is referred as penta-1,2,3,4,6-O-galloyl-beta-d-glucose (PGG) isolated from Gallnut of *Rhus chinensis* MILL, has been reported to inhibit proliferation, migration and tube formation of endothelial cells [86,87] and also induce apoptosis in prostate cancer cells [88,89].

Oleanolic acid is a triterpene isolated from Clove (*Syzygium aromaticum).* Its main antiangiogenic effects are; inhibition of BAEC (bovine aortic endothelial cells) proliferation [10] and induction of iNOS and COX-2.

Perillyl alcohol, which can be found in lavender and citrus, caused a decrease in VEGF release from cancer cells and an induction in Ang2 expression by endothelial cells. This implies that perillyl alcohol might suppress neovascularization and induce vessel regression [90].

Phenethyl isothiocyanate (PEITC) has been observed to suppress HUVEC survival, migration and tube formation [91]. It effectively interfered with hypoxia-induced HIF transcriptional activity and the induction of the endogenous HIF target genes VEGF-A, BNIP3, CAIX and GLUT1 in human MCF7 breast cancer cells [92].

Sanguinarine, a quaternary ammonium salt from the group of benzylisoquinoline alkaloids isolated from bloodroot (*Sanguinaria Canadensis*), exerted its antiangiogenic effect by directly suppressing the proliferative effect of VEGF on endothelial cells through downregulation of VEGF-induced AKT activation [93].

Shark cartilage (SC) is another source of anti-angiogenic natural compounds with its observed ability to inhibit bFGF induced angiogenesis in the Matrigel mouse model [94].

Sulforaphane (SFN), an isothiocyanate isolated from broccoli (*Brassica oleraceaitalica*), was shown to inhibit NF-κB-regulated VEGF expression in human prostate cancer cells [95]. Its antiangiogenic activity also worked through activation of forkhead homeobox type O transcription factors, inhibition of MEK/ERK and PI3K/AKT pathways as observed in HUVECs [96]. It also reduced both the proliferation and the matrigel-dependent tube forming ability of HUVEC cells [97]. SFN caused reduction of microcapillary density in a placental vessel fragment outgrowth assay in a dose dependent manner in *ex vivo* tissue culture models [98]. SFN was observed to reduce blood vessel density in MIA-PaCa2 xenografts *in vivo* [99]. SFN was able to inhibit tubulin polymerization *in vitro* and in intact cells had been recognized [100,101]. Tubulin plays important role in angiogenesis in addition to proliferation of endothelial cells, and it is essential for morphogenesis and migration [100,101].

Taxol, a diterpene obtained from the bark of *Taxus brevifolia*, involves antiangiogenic activity via inhibition of VEGF production and HIF-α expression shown in human leukemia cell lines [102]. It binds to tubulin dimers causing interruption of mitosis and chromosome breakage [10,103]. Ginkgolide B is another diterpene causing downregulation of VEGF [11]. EGb 761 is a diterpene isolated from

ginkgo leaf extract. T-Lymphocytes are the main spleen cell population involved in inducing angiogenesis and this effect is reduced by EGb 761. It also downregulates VEGF, platelet derived from growth factor, transforming growth factor-β2 and iNOS (without influencing iNOS-mediated NO production) [104].

Ursolic acid, a triterpene isolated from rosemary (*Rosmarinus officinalis*), reduceed VEGF, NO and proinflammatory cytokine levels. It also inhibited capillary formation in C57BL/6 mice bearing B16-F10 melanoma cells [105]. In addition, it caused inhibition of BAEC (bovine aortic endothelial cells) proliferation [10] and induction of iNOS and COX-2. Growth of prostate cancer xenografts was dramatically suppressed by ursolic acid *in vivo* [66]. It was reported to inhibit tumor promotion, metastasis, angiogenesis and proliferation of a variety of tumor cells, including human multiple myeloma cells [106] melanoma cells [107] and breast cancer cells [108]. It inhibited cell proliferation and induced apoptosis in human androgen-independent DU145 and androgen-dependent LNCaP prostate cancer cell lines [109]. These results were correlated with the inhibition of the canonical NF-κB signaling pathway as well as STAT3 phosphorylation through the upstream inhibition of JAK2 and Src activation [110].

Perspectives for phytochemicals in anti-angiogenic cancer therapy

Despite promising experimental results for most of the compounds in the literature, clinical trials for them yielded irregular results. Clinical trials should be performed in a well organized and randomized manner with placebo controls. Same criterias of evidence based medicine should be referred for phytochemicals to develop anti-cancer drugs.

Pharmacological effects are limited due to metabolism of secondary plant metabolites in the vertebrate organism [111]. This may be overcome by using modified derivatives of phytochemicals with improved pharmacological features [28]. Animal experiments are required to understand the potential of phytochemicals for anti-angiogenic treatment of cancer. This step is a prerequisite for clinical trials.

Cancer therapy with phytochemicals might be promising for collecting further experimental knowledge to enable pharmacological refinement of future therapeutic options.

Conclusıon

Cancer progression involves many steps including angiogenesis, which is essential for development of new blood vessels and thus nutrition of tumor cells.Various signalling pathways play role in angiogenesis. Targeting the VEGF (vascular endothelial growth factor) signalling pathway with synthetic small molecules might be a promising option. Many synthetic small molecules and phytochemicals have been identified to be anti-angiogenic and observed to bind to VEGFR-Tyrosine Kinase domain with high affinity as validated by molecular docking. Further studies are required to understand the angiogenesis mechanism to identify new therapy options with small molecules and phytochemicals.

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