REVIEW

Modulation of angiogenesis by dietary phytoconstituents in the prevention and intervention of breast cancer

Sharon C. Reuben[1], Ashwin Gopalan[1], Danielle M. Petit[1] and Anupam Bishayee[2]

[1] Department of Pharmaceutical Sciences, College of Pharmacy, Northeast Ohio Medical University, Rootstown, OH, USA
[2] Department of Pharmaceutical and Administrative Sciences, School of Pharmacy, American University of Health Sciences, Signal Hill, CA, USA

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Breast cancer is the leading cause of cancer-related deaths for women in the United States and the rest of the world. About 8% of women develop breast cancer during the course of their lives. Dietary habits are closely associated with both the risk and progression of breast cancer. Dietary agents have accumulated increasing importance with regards to the prevention and treatment of breast cancer. One such manner by which these compounds can target breast cancer development and progression is through interference with the angiogenic pathways. Angiogenesis is an intricate process that involves the development of new capillaries from previously existing blood vessels. Disruption of this pathway, therefore, provides a novel and effective avenue for therapeutic intervention of breast cancer. Various phytochemicals found in the diet kill breast cancer cells in vitro and prevent as well as suppress breast cancer progression in various preclinical animal models. This review examines the value of dietary phytoconstituents in the prevention and treatment of breast cancer through modulation of the intricate and complex process of angiogenesis. In addition, the potential benefits, challenges, and future directions of research on anti-angiogenic dietary phytochemicals in the prevention and intervention of breast cancer are also addressed.

Keywords:
Angiogenesis / Breast cancer / Chemoprevention / Dietary phytochemicals / Therapy

1 Introduction

Breast cancer remains the primary cause of death in women ages 20–59 [1], with the approximated yearly incidence at one million [2]. The American Cancer Society estimated nearly 270 000 new cases and about 40 000 deaths due to breast cancer in women in the United States in 2010 alone [3]. There has not been any significant improvement in the morbidity or mortality of breast cancer by current treatment modalities, including surgery, radiotherapy, and adjuvant chemotherapy or hormone therapy [4]. Moreover, breast cancer remains highly resistant to chemotherapy as no effective treatment exists for advanced disease conditions [5]. In order to prevent and manage the progression of breast cancer, understanding the etiology of breast cancer development is a matter of paramount importance.

Angiogenesis is an intricate process that involves the formation and spread of new capillaries from previously

Correspondence: Dr. Anupam Bishayee, Department of Pharmaceutical and Administrative Sciences, School of Pharmacy, 1600 East Hill Street, Signal Hill, CA 90755, USA
E-mail: abishayee@auhs.edu
Fax: +1-562-988-1791

Abbreviations: AP-1, activator protein-1; **COX-2,** cyclooxygenase-2; **DMBA,** 7,12-dimethylbenz[*a*]anthracene; **ECM,** extracellular matrix; **EGCG,** epigallocatechin-3-gallate; **ER,** estrogen receptor; **FGFs,** fibroblast growth factors; **GSE,** grape seed extract; **GTE,** green tea extract; **HIF-1,** hypoxia-inducible factor-1; **MAPK,** mitogen-activated protein kinase; **MMPs,** matrix metalloproteinases; **MVD,** microvessel density; **NF-κB,** nuclear factor-κB; **PDGF,** platelet-derived growth factor; **TGF-α and -β,** transforming growth factor-α and -β; **TIMPs,** tissue inhibitors of metalloproteinases; **TSP1,** thrombospondin-1; **uPA,** urokinase serine proteases; **VEGF,** vascular endothelial growth factor

existing blood vessels. Folkman [6] proposed that tumor angiogenesis plays a crucial role in cancer progression. Currently, it is believed that a tumor mass cannot exist in a volume greater than $\sim 1\,mm^3$ without proper vascular supply, which indicates that angiogenesis is critical to neoplastic growth. This ensures an adequate blood supply to the tumor and creates a suitable environment for the proliferation of tumor cells. The process of tumor angiogenesis is implemented when tumor cells themselves secrete and activate angiogenic factors, thereby activating proteolytic enzymes. At this time, endothelial cells concurrently proliferate, migrate, and differentiate [7]. The activated angiogenic factors made by the tumor cells are, therefore, responsible, in part, for the stimulation and regulation of tumor angiogenesis. In addition, local normal cells can indirectly induce other factors that initiate protein synthesis for angiogenic development. When tumor cells develop, they inevitably disrupt the normal processes in the cell and deregulate them to maximize all that is necessary for their own vitality; one of these processes is angiogenesis. A considerable number of various stimulators and inhibitors of angiogenesis have been studied and identified during the last several decades that can help in altering the development of breast cancer by targeting the vital process of angiogenesis.

2 Angiogenesis and breast cancer

Although the process of angiogenesis is needed for the growth and development of both primary and metastatic breast tumors, the greatest level of angiogenic activity occurs in the development of primary malignant breast tumors [8]. Thus, it can be suggested that angiogenesis may act as a separate individual prognostic factor for breast cancer in humans [9, 10]. Preclinical data support the understanding that angiogenesis represents a key factor in breast cancer development and metastasis occurring even before mammary cells transform from a hyperplastic state to a malignant state [11].

Microvessel density (MVD), established by immunohistochemistry, is a mainstream determinant of the occurrence of angiogenesis in both tumor models and pathological samples. This process, in which monoclonal antibodies are targeted against endothelial mitogens, was what initially demonstrated that angiogenesis acts as an independent prognostic marker for primary breast cancer [9]. This principle has also been verified using a related procedure with a different monoclonal antibody for a particular platelet/endothelial cell adhesion molecule, known as CD-31 [12]. A high level of MVD in precancerous tissues would logically be thought to have a strong association to the high risk of developing future breast cancer and acquiring metastatic disease with a shorter relapse-free and overall survival of patients with node-negative breast carcinoma [9, 13]. In fact, one study was able to show that the highest amount of MVD was demonstrated in histopathologically aggressive ductal carcinoma in situ lesions [14].

3 Factors involved in angiogenesis

Malignant tumors require an array of specialized molecules to initiate angiogenic pathways. Endothelial cell proliferation and migration are activated by factors of angiogenesis, such as receptor tyrosine kinase ligands, which include vascular endothelial growth factor (VEGF), acidic and basic fibroblast growth factors (aFGF and bFGF), transforming growth factor-α and -β (TGF-α and -β), tumor necrosis factor-α (TNF-α), platelet-derived growth factor (PDGF), epidermal growth factor, interleukin-8 (IL-8), and angiogenin [15]. In addition to the angiopoitins, which are ligands of the Tie receptor family, these are several of the known factors involved in angiogenesis [16].

VEGF: The most important regulator of human tumor angiogenesis is VEGF, also known as VEGF-A or vascular permeability factor [17]. VEGF binds to three known tyrosine kinase receptors, namely, VEGFR-1 (flt-1), VEGFR-2 (KDR/flk-1), and VEGFR-3 (flt-4), which are present on endothelial cells, and this binding event triggers endothelial cell proliferation [18]. Much research has showed that VEGF and its associated receptors are over-expressed in several types of human cancers, such as breast carcinomas [19]. An inverse correlation exists between VEGF expression and overall survival in both node-positive and -negative breast cancer [20, 21]. Tissue concentration of VEGF has been noted as a predictive measure of cancer-associated mortality and both VEGF and MVD have a positive correlation [22]. A significant relationship has been established among serum VEGF, MVD, and the morphological grade of breast cancer, indicating serum VEGF is a more dependable, non-invasive adjunctive diagnostic criterion for the prognosis and grade assessment of malignancy [23]. Moreover, placental growth factor, a member of the VEGF family, has been shown to stabilize the formation of new capillaries after their endothelial cells have been activated with VEGF [24].

FGFs: FGF is a family of growth factors involved in angiogenesis, embryonic development, and wound healing. They are heparin-binding proteins that interact with heparin sulfate proteoglycans on cell surfaces, which enable FGF signal transduction. Specifically, FGF2, also known as basic FGF, plays a crucial role in angiogenesis [25, 26].

Inflammatory factors: TGF-β1 is an angiogenic molecule released by tumor cells that initiates angiogenesis by producing extracellular matrix (ECM) for newly formed blood vessels. Various important inflammatory angiogenic molecules in addition to TGF-β1 produced by tumor cells include IL-8, cyclooxygenase-2 (COX-2), and nitric oxide synthase (NOS). Together, these molecules manipulate tumor vasculature expansion [17].

Nuclear factor-κB (*NF-κB*): NF-κB, a pro-inflammatory transcription factor, is usually present in the cytoplasm and becomes induced after being released from the inhibitory protein (IκB). It then is moved into the nucleus to begin gene transcription. NF-κB initiates expression of more than 200 genes that act to inhibit apoptosis while activating cellular transformation, proliferation, invasion, metastasis, and angiogenesis [27].

Activator protein-1 (*AP-1*): AP-1 is a heterodimeric, early response transcription factor composed of proteins belonging to the c-fos and c-jun families. It regulates the expression of a variety of genes involved in differentiation, proliferation, and apoptosis. It has been related to the transactivation of VEGF, but does not directly act on its promoter [28].

Matrix metalloproteinases (*MMPs*): MMPs are a group of enzymes involved in the degradation of ECM. Comprising this group are collagenases (MMP-1, MMP-8, and MMP-13), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3, MMP-7, and MMP-10), and elastase (MMP-12) [29]. Another group of endogenous inhibitors known as tissue inhibitors of metalloproteinases (TIMPs) exist in equilibrium with MMPs under normal physiological conditions, but not during the process of angiogenesis. MMP expression increases when there is tissue progression from benign to pre-invasive, invasive, and metastatic breast cancer [30]. The AP-1 transcription complex, activated by various mechanisms involving growth factors, cell–cell interactions and cell–matrix interactions, is known to modulate MMP expression [30]. Emerging evidence shows that microscopic metastatic diseases remain dormant and ''*growth-restricted*'' until tumor angiogenesis begins [31].

Thrombospondin-1 (*TSP1*): TSP1 is an endogenous suppressor of capillary morphogenesis. Expression of TSP1 is induced during inflammation and several other pathological conditions. The over-expression of this molecule results in a reduction in the number and diameter of tumor capillaries. The absence of TSP1 is correlated with an increased amount of VEGF and higher activity of MMP-9 [32]. Additionally, the p53 tumor suppressor gene inhibits angiogenesis by stimulating the production of TSP1 [33].

Urokinase serine proteases (*uPA*): The uPA exists as another set of tumor-promoting proteases. Normal and neoplastic cells make and secrete uPA, which interacts with cell surface receptor uPAR to convert the zymogen plasminogen into the active enzyme plasmin. Growth factor and oncogenes monitor the expression of uPA and uPAR, as well as inhibitors of uPA, such as plasminogen activator inhibitors (PAIs) [29]. Over-expression of uPA leads to the metastatic phenotype, and the addition of gelatinases to increased levels of uPA acts as a poor prognostic marker for breast cancer [34].

Hypoxia-inducible factor-1 (*HIF-1*): Increased metastasis and poor survival in cancer patients is connected to low oxygen tension in tumors [35]. States of hypoxia, or low oxygen states, are often primary inducers of angiogenesis. HIF-1 is made of two subunits, namely, hypoxic response factor (HIF-1α) and aryl hydrocarbon receptor nuclear translocator (HIF-1β), which is the continuously expressed subunit. HIF-1 also controls various hypoxia-regulated gene expressions [36]. The tumor suppressor gene Von Hippel-Lindau (VHL) is responsible for inducing HIF-1α to activate expression of the angiogenic factors, including VEGF, VEGFR-1, PDGF, COX-2, and NOS [37]. HIF-1α expression increases as normal breast tissue evolves into ductal hyperplasia and then into invasive ductal carcinoma. This occurs even more in poorly differentiated than well-differentiated states as an association has been noted between VEGF and estrogen receptor (ER) expression and growth [38]. In addition, the expression of carbonic anhydrase, an HIF-1α-dependent enzyme that plays an important role in pH regulation, is linked to poorer prognosis and less relapse-free survival of patients with invasive breast cancer [39].

HER-2/neu, c-erbB-2: The levels of *HER-2/neu* gene has been shown to be augmented in greater than 3 out of 10 breast cancer patients and is associated with high-grade tumors with poor prognosis for the disease state [40]. The *HER-2/neu* gene has also been known to be amplified during the process of angiogenesis [41]. Signaling through *HER-2/neu* increases the expression of VEGF [42].

Pleiotrophin (*PTN*) *and midkine* (*MK*): PTN was initially discovered as a neurite growth-promoting factor in rat brains. It has been implicated in many cancer-related activities such as proliferation and angiogenesis, specifically by enhancing plasmin levels and upregulating uPA expression. Further studies have indicated its role in angiogenesis along with MK [26].

4 Anti-angiogenic targets in breast cancer

As previously discussed, breast tumor development and invasion are extensively supported by the angiogenic process. Though angiogenesis is present at length, the tumor endothelium differentiation often does not reach a properly established vessel complex, which then takes on an atypical morphology. As a result, tumor angiogenesis becomes a target to inhibit tumor endothelial cell proliferation and thus acts as a modality to restrain tumor growth [43]. Much of the research currently being conducted concerning this venue of therapy has been focused on interfering with the formation of new vessels to inhibit tumor proliferation. Experimental and clinical evidence suggest that angiogenesis is a critical component of tumor development and this process is essential for all tumor growth, not limited to a subset of breast cancer. Hence, agents that can prevent or abolish tumor angiogenesis are expected to yield a greater benefit to women with breast cancer [44].

It is important to examine natural inhibitors and their effects on the prevention and treatment of breast tumor through angiogenic regulation. These effects may be related to several mechanisms, including the inhibition of synthesis and release of angiogenic factors from tumor cells; increase in the production of factors targeted against angiogenesis; suppression of the activation of tumor endothelial cells; promotion of the apoptotic action on tumor endothelial cells; interruption of capillary vessel development and organization; and lastly, disturbance of ECM and basement membrane biosynthesis and remodeling (reviewed in Ref. [45]). The aforementioned anti-angiogenic strategies are interrelated, and thus targeting one step could result in the modulation of another towards the suppression of angiogenesis. Also, there is a possibility that a single natural inhibiting agent can offset more than one angiogenic element [46]. If tumor angiogenesis is targeted at the early stage of multi-stage carcinogenesis, there is an increasing potential to maintain a dormant state of the tumor without progressing to a malignant state [29]. A novel hypothesis has been proposed describing *''angioprevention''*, the idea of effective tumor chemopreventive agents to target tumor angiogenesis [47]. Angioprevention is based on the fact that neo-angiogenesis prohibition can be applied for both cancer prevention and to suppression of neoplastic mass development

5 Dietary phytoconstituents, breast cancer, and angiogenesis

Epidemiological studies have suggested the possibility that dietary and nutritional status can influence as much as one-third of human malignancies [48]. Strengthening this evidence, many dietary compounds, obtained from fruits, vegetables, nuts, and spices, have demonstrated their ability to suppress various tumors, such as those in the breast [48, 49]. In regards to breast cancer, consumption of specific types of fruits and vegetables has shown a decreased incidence and risk of cancer development [50]. One can logically deduce that these dietary bioactive constituents modulate multiple pathways used by cancer cells in the processes of cell proliferation, apoptosis, angiogenesis, invasion, and metastasis [51–53]. In the past decade, multiple dietary phytochemicals have demonstrated breast cancer chemopreventive properties [54, 55] with many of these molecules sharing anti-angiogenic properties as their underlying mechanisms [56]. Furthermore, additional studies suggest that phytoconstituents of dietary origin could have an important impact on cellular physiology and homeostasis, and thereby could influence the equilibrium between pro- and anti-angiogenic factors [57]. The following section presents evidence that dietary phytochemicals, representing distinct chemical groups, may contribute to the chemoprevention and therapy of breast cancer by modulating the angiogenic process.

6 Breast cancer chemoprevention and therapy by dietary phytochemicals with anti-angiogenic mechanisms: in vitro evidence

Apple phytochemicals: The apple is a ubiquitous fruit found around the world. It is used in various food items, such as sauces, jams, and pies. It has been shown that extracts of the Red Delicious variety of apples prevented 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mammary cancer in rats at doses comparable to human consumption of one, three, and six apples a day [58]. The peel of an apple contains substantial anti-oxidant and anti-proliferative properties against breast tumor cell lines. An example is the peel of the Gala apple variety, which has been found to suppress the growth as well as clonogenic survival of breast carcinoma cell lines, namely, MCF-7 and MCF-7:Her18, and also has been found to decrease the levels of proliferative cell nuclear antigen (PCNA), which acts as a cell proliferation marker (Table 1). In addition, the same extract was found to induce G_0–G_1 mitotic phase arrest in breast cancer cells while increasing the levels of tumor suppressor protein maspin, which decreases cell invasion, metastasis, and angiogenesis [59].

Catechins: Tea (*Camellia sinensis*) is the second most widely consumed beverage in the world after water. Every year, approximately 2.5 million metric tons of dried tea leaves are produced. Black tea comprises almost 80% of this production, and is consumed predominantly in the Indian subcontinent as well as in Western countries. About 20% of the production is green tea, consumed primarily in East Asian countries such as China and Japan. The consumption of black tea has many health benefits, including cancer prevention, due to the presence of polyphenols and other phytochemicals. Consumption of green tea may reduce the risk of developing breast cancer according to several epidemiological studies [60–62]. Bioactive constituents of green tea include predominantly epigallocatechin-3-gallate (EGCG) as well as catechin, catechin gallate (CG), gallocatechin (GC), epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and gallocatechin-3-gallate (GCG). Initial cellular studies have revealed that green tea extract (GTE) as well as EGCG could inhibit the proliferation of MDA-MB-231 breast cancer cells [63]. EGCG alone has been found to inhibit the constitutive activation of NF-κB, VEGF promoter activity, and cellular production of VEGF in MDA-MB-231 breast cancer cells [64]. EGCG also suppressed the growth of HER-2/neu-overexpressing mouse mammary tumor virus (MMTV)-HER-2/neu NF639 cells by interfering with HER-2/neu signaling through decreases in phosphatidylinositol 3-kinase, Akt kinase and NF-κB activities [65]. GTE or EGCG showed a decrease in protein and transcript levels of VEGF in MDA-MB-231 cells. GTE alone lowered c-fos and c-jun RNA transcripts, indicating that AP-1-responsive regions present in human VEGF promoter may be involved in the inhibitory effect of GTE in breast cancer. Moreover, GTE suppressed the expression of protein

Table 1. In vitro evidence for the use of anti-angiogenic dietary components to prevent and treat breast cancer

Phytochemicals	Dietary source	Active constituents	Anti-angiogenic effects in breast cancer	References
Apple phytochemicals	Apples	Phenols, flavonoids, anthocyanins	Suppressed the growth of MCF-7 and MCF-7:Her18 cells and reduced the expression of PCNA protein levels; increased the expression of the maspin protein	Reagan-Shaw et al. [59]
Catechins	Green tea (*Camellia sinensis*)	EGCG, CG, GC, EC, EGC, ECG, GCG	Inhibited the growth of MDA-MB-231 cells	Sartippour et al. [63]
			Inhibited the activation of NF-κB, VEGF promoter activity, and VEGF production in MDA-MB-231 cells	Masuda et al. [64]
			Inhibited NF-κB and HER-2/neu signaling in MMTV-HER-2/neu NF639 cells	Pianetti et al. [65]
			Decreased the peptide and transcript levels of VEGF in MDA-MB-231 cells	Sartippour et al. [66]
			Decreased bFGR protein and aFGR and bFGR transcript levels in MDA-MB-231 cells	Sartippour et al. [67]
			Suppressed the growth and invasiveness of MDA-MB-231 cells; inhibited AP1, NF-κB and secretion of uPA	Slivova et al. [68]
			Decreased VGEF production in MCF-7 and MDA-MB-231cells	Leong et al. [69]
			Inhibited the invasion of MDA-MB-231 cells with reduced expression of VEGF and MMN-9; blocked the activation of STAT3	Leong et al. [70]
Curcumin	Turmeric (*Curcuma longa*)	Diferuloylmethane	Inhibited the proliferation of MCF-7 cells with reduced expression of pS2 and TGF-β; inhibited invasion, down-regulated MMP-2, upregulated TIMP-1, and suppressed VEGF and bFGF in MDA-MB-231 cells	Shao et al. [72]
			Suppressed the basal VEGF synthesis in and release from MDA-MB-231 cells	Schindler and Mentlein [73]
			Inhibited MPA-induced secretion of VEGF in T47-D cells	Carroll et al. [74]
Ellagitannins	Pomegranate (*Punica granatum*), berries, and nuts	Punicalagin	Down-regulated VEGF in MCF-7 and MDA-MB-231 cells and upregulated MIF in MDA-MB-231 cells	Toi et al. [81]
		Ellagic acid	Inhibited the growth of MDA-MB-435S cells with anti-angiogenic effect by blocking NDPK-B	Rumjahn et al. [82]
Flavones	Fruits, vegetables, nuts, tea, and wine	Apigenin	Inhibited the proliferation of and induced apoptosis in MDA-MB-231 cells	Parajuli et al. [84]
			Inhibited VEGF release from MDA cells	Schindler and Mentlein [73]
			Reduced MPA-dependent production of VEGF mRNA and protein and also PR from T47-D cells; abrogated the secretion of VEGF from BT-474 cells	Mafuvadze et al. [85]
Genistein	Soybean (*Glycine max*)	4′,5,7-Trihydroxy-isoflavone	Inhibited the growth of MDA-MB-435 and 435.eB cells and suppressed MMP-2 and -9 secretion	Li et al. [88]
			Inhibited the invasion of MCF-7 and MDA-MB-231 cells, down-regulated MMP-9 and upregulated TIMP-1	Shao et al. [89]
			Arrested MCF-7 and MDA-MB-231 cells in the G_2/M phase and down-regulated several MMP genes	Kousidou et al. [90]
			Reduced adhesion and mortality of MDA-MB-231 cells; inhibited NF-κB, AP-1 and secretion of uPA	Valachovicova et al. [91]

Table 1. Continued

Phytochemicals	Dietary source	Active constituents	Anti-angiogenic effects in breast cancer	References
			Inhibited expression of VEGF, MMP-2, MMP-9 and uPA in MCF-7/HER-2 cells	Yu et al. [92]
			Reduced the survival of and inhibited uPA secretion from F3II cells	Farina et al. [93]
			Increased VEGF secretion in MELN cells	Beteau-Lozano et al. [94]
Lignans	Flaxseed (*Linum usitatissimum*)	Enterodiol, Enterolactone	Inhibited secretion of VEGF from MCF-7 cells	Bergman Jungeström et al. [97]; Saarinen et al. [98]
Resveratrol	Grapes (*Vitis vinifera*), red wine, berries, peanuts, plums and legumes	3,4,5-Trihydroxy-*trans*-stilbene	Reduced the secretion of VEGF from MDA-MB-231 cells	Garvin et al. [102]
Silymarin	Milk thistle (*Silybum marianum* L. Gaertner), artichokes, (*Cynara scolymus*), turmeric and coriander	Silybin	Decreased VEGF secretion from MCF-7 and MDA-MB-468 cells	Jiang et al. [103]
			Suppressed PMA-induced invasion of MCF-7 through inhibition of MMP-9; blocked the activation of AP-1 via MAPK	Lee et al. [104]
			Decreased TPA-induced MMP-9 expression via inhibition of COX-2 in MCF-7 and MDA-MB231 cells	Kim et al. [105]
Sulphoraphane	Broccoli, cauliflower, cabbage, and Brussels sprouts (*Brassica oleracea*)	1-Isothio-cyanato-4-methylsulfinyl-butane	Suppressed TPA-induced invasiveness and MMP-9 activity in MDA-MB-231 cells	Rose et al. [110]
			Depressed the aggressive behavior of MDA-MB-231 cells; down-regulated MMP7 and MMP-14; decreased the production of pro-inflammatory cytokines, VEGF and PDGF	Hunakova et al. [30]
			Inhibited the proliferation of MCF-7 cells with p38 MAPK activation; suppressed TPA-induced COX-2 expression and p38 MAPK phosphorylation in M13SV1 cells	Jo et al. [111]

kinase C, another VEGF transcription modulator [66]. In an extension of the previous study, GTE or EGCG has been shown to inhibit bFGF protein and reduced the transcript levels of both aFGF and bFGF in MDA-MB-231 cells [67]. Slivova et al. [68] showed that green tea polyphenols (GTP) containing the aforementioned catechins as well as gallic acid inhibited the growth and suppressed the invasive characteristics of MDA-MB-231 cells through inhibition of cell adhesion and migration as well as proteolytic degradation of the ECM. The anti-invasive activity of GTP has been linked to the inhibition of constitutively active transcription factors AP-1 and NF-κB, which further suppressed the secretion of uPA from breast carcinoma cells. A standardized preparation of GTE has been shown to decrease VEGF production in MCF-7 and MDA-MB-231 cells [69]. Further studies revealed that GTE also inhibited the invasion of MDA-MB-231 cells, reduced the expression of VEGF and MMN-9, and blocked the activation of STAT3 [70].

Curcumin: Curcumin (diferuloylmethane) is a yellow colored polyphenol obtained from the rhizome of *Curcuma longa*, popularly known as turmeric. Curcumin is commonly used as a coloring and flavoring agent in Indian cuisine. The anti-carcinogenic activity of curcumin has been reported in a variety of breast cancer cell lines, several preclinical animal models of mammary cancer and at least one early clinical trial [71]. In concurrence with inhibition of the expression of ER downstream genes, including pS2 and TGF-β, curcumin's anti-proliferative effect on ER-positive MCF-7 human breast cancer cells has been documented. Curcumin has also been found to exert significant anti-invasive effects in ER-negative MDA-MB-231 human breast cancer cells through the upregulation of TIMP-1 and the

down-regulation of MMP-2 as well as suppression of the transcript levels of two angiogenesis factors, namely, VEGF and bFGF [72]. In a similar study, curcumin exhibited an inhibitory effect on basal VEGF synthesis and its secretion from MDA-MB-231 cells [73]. Curcumin reduced medroxyprogesterone acetate (MPA)-induced secretion of VEGF from T47-D human breast cancer cells in a dose-responsive manner. Interestingly, secretion of VEGF from cells exposed to progesterone or progestins other than MPA remain unaffected by curcumin treatment [74].

Ellagitannins: Ellagitannins are a group of bioactive polyphenols frequently present in a multitude of fruits and nuts, including pomegranates, raspberries, strawberries, almonds, and walnuts. Pomegranate (*Punica granatum*), recently termed as a ''*superfruit*'', is gaining incredible importance because of its beneficial properties related to prevention and therapy of a number of ailments, including cancer [75, 76]. Compared with any other commonly consumed fruit juice, pomegranate juice has been found to contain the highest concentration of ellagitannins as well as the unique ellagitanin, namely, punicalagin [77]. Polyphenols derived from the pomegranate juice exhibited significant growth inhibitory and cytotoxic activities on MCF-7 and MDA-MB-231 cells [78, 79] and an inhibitory response on the formation of neoplastic lesions in ex vivo murine mammary gland organ culture models [78, 80]. Angiogenic suppression could, in part, be responsible for the mediation of the breast cancer inhibitory effects, as pomegranate juice polyphenols down-regulate VEGF in MCF-7 and MDA-MB-231 cells and upregulate migration inhibitory factor (MIF) in MDA-MB-231 cells [81]. MDA-MB-435S human breast cancer cells mediate angiogenesis via P2Y receptor signaling by secreting nucleoside diphosphate kinase-B (NDPK-B). Ellagic acid, possibly due to the anti-angiogenic effect mediated by inhibition of secreted NDPK-B, retarded the growth of MDA-MB-435S cells [82].

Flavones: Apigenin belongs to the flavone family of phytochemicals commonly found in various fruits, vegetables, nuts, and plant-based beverages, including tea and wine [83]. *Scutellaria*, an herb also used as herbal tea, is known to contain apigenin. This flavonoid was shown to reduce cell proliferation of malignant cell lines of MDA and MB-231, while leaving non-cancerous cells unaffected [84]. Treatment of MDA breast cancer cells with apigenin reduced VEGF secretion from these cells [73]. Breast cancer incidence has been seen to be higher in women who are treated with estrogen and progestin hormone replacement therapy. The underlying basis for this mechanism relies on the fact that progestin induces the production of VEGF mRNA transcription and VEGFR-2 in T47D human breast cancer cells. Mafuvadze et al. [85] showed that apigenin blocked MPA-mediated induction of VEGF mRNA and protein as well as reduced progesterone receptor (PR) levels in T47-D cells. Apigenin also diminished MPA-induced secretion of VEGF from BT-474 mammary carcinoma cells.

Genistein: Soy isoflavones, predominantly derived from soybean (*Glycine max*), have received considerable attention during the past decade as dietary components with inhibitory properties against breast cancer. Recently in a study conducted in women in Shanghai, China, plasma isoflavone concentrations have been found to be inversely associated with the risk of non-proliferative and proliferative benign fibrocystic conditions as well as breast cancer [86]. Genistein (4′,5,7-trihydroxyisoflavone), the predominant soy isoflavone, has been shown to be cytotoxic against several breast cancer cells [87]. Genistein was found to inhibit the growth of MDA-MB-435 and 435.eB breast carcinoma cells (established by transfecting c-erbB-2 cDNA into MDA-MB-435 cells) with concomitant suppression of MMP-2 and MMP-9 secretion [88]. Genistein has been found to inhibit the invasion of MCF-7 and MDA-MB-231 cells, and this effect was accompanied by the down-regulation of several MMP genes and upregulation of TIMP-1 [89, 90]. Further studies with genistein in the MDA-MB-231 cell line demonstrated reduced adhesion and mortality of MDA-MB-231 cells. Also, genistein was shown to inhibit NF-κB, AP-1 and secretion of uPA [91]. Another study demonstrated that genistein inhibited expression of VEGF, MMP-2, -9 and uPA in HER-2/neu-overexpressing MCF-7/HER-2 breast cancer cells [92]. The anti-cancer and anti-angiogenic properties of genistein have also been investigated in F3II mouse mammary carcinoma cells. Genistein induced spindle-cell morphology, reduced mortality of and uPA secretion from F3II cells, but did not modify the MMP-2 and -9 produced by tumor cells [93]. In contrast, the study conducted by Buteau-Lozano et al. [94] reported that genistein up-regulated VEGF expression in MELN breast cancer cells (derived from MCF-7 cells) by an ER-dependent mechanism.

Lignans: Dietary lignans, present in a variety of foods, fruits, vegetable, and cereals, represent a major source of phytoestrogens. One of the most abundant plant lignans in foods consumed in North America and Europe is laricir-esinol, obtained from flaxseed (*Linum usitatissimum*). Following ingestion, lariciresinol is metabolized initially to secoisolariciresinol, and subsequently to enterolignans, such as enterodiol and enterolactone. An inverse relationship between high dietary lignan intake and breast cancer risk has been established through epidemiological studies [95, 96]. Estrogen-induced secretion of VEGF from MCF-7 cells was inhibited by enterodiol and enterolactone [97, 98].

Resveratrol: Resveratrol (3,4,5-trihydroxy-*trans*-stilbene) is a dietary phytochemical derived from a myriad of popular foods including grapes, berries, peanuts, plums, legumes, and red wine. Resveratrol is one of the most widely studied dietary chemopreventive and anti-cancer compounds [99, 100]. Based on an epidemiological study, resveratrol consumption from grapes (but not from wine) accounted for 50% or greater reductions in breast cancer risk in woman [101]. Garvin et al. [102] showed a reduction in VEGF secretion in MDA-MB-231 cells following resveratrol treatment.

Silymarin: Silymarin is a complex mixture of polyphenolic flavonoids isolated from the seeds of milk thistle (*Silybum marianum* L. Gaertner). Silibinin (also known as silybin) is the major active component of silymarin. The most common dietary source of silymarin (besides milk thistle) is artichoke (*Cynara scolymus*), whereas several spices (e.g. turmeric and coriander), grapes, beet greens, peanuts, and berries contain varying amounts of this natural product. Exposure of MCF-7 and MDA-MB-468 breast cancer cells to silymarin resulted in a dose-responsive decrease in the secreted VEGF levels in the conditioned media without any visible alteration in cell morphology [103]. Silibinin has been shown to reduce phorbol myristate acetate (PMA)-induced invasion of MCF-7 through inhibition of MMP-9 gene transcriptional activity by blocking the activation of AP-1 via the mitogen-activated protein kinase (MAPK) signaling pathway [104]. Silibinin also down-regulates 12-*O*-tetradecanoyl phorbol-13-acetate (TPA-induced) MMP-9 expression through inhibition of COX-2 expression in MCF-7 and MDA-MB231 cells [105].

Sulforaphane: Sulforaphane belongs to the isothiocyanate group of phytochemicals that naturally exists in commonly consumed cruciferous vegetables, such as broccoli, cauliflower, cabbage, and Brussels sprouts (*Brassica oleracea*). Several epidemiological studies suggest a reduction in breast cancer risk from a diet rich in cruciferous vegetables [106, 107]. Sulforaphane has been found to exert cytotoxic effects on breast tumor cells [108, 109]. A broccoli extract rich in sulforaphane has been shown to inhibit MMP-9 activity in MDA-MB-231 cells as well as TPA-induced cell invasion [110]. Hunakova et al. [30] confirmed the anti-invasive activity of sulforaphane against MDA-MB-231 cells. This effect was associated with the down-regulation of MMP-7 and MMP-14, while no apparent effect on MMP-1, MMP-3, and MMP-9 was observed. Sulforaphane also reduced the production of IL-1β, IL-4, IL-6, TNF-α, IFN-γ, PDGF, and VEGF. Another study showed that sulforaphane suppressed the proliferation of MCF-7 cells with concurrent deactivation of extracellular signal-regulated kinase (ERK) 1/2 MAPK and activation of P38 MAPK. Additionally, the researchers also reported that sulforaphane inhibited COX-2 expression by activation of P38 MAPK in TPA-treated M13SV1 immortalized human breast luminal epithelial cells [111].

7 Breast cancer chemoprevention and therapy by dietary phytochemicals with anti-angiogenic mechanisms: in vivo evidence

Catechins: The cancer chemopreventive potential of tea has been associated with its polyphenolic and other phytoconstituents. A standardized black tea preparation, known as polyphenon-B, contains a mixture of EGCG, EC, GCG, theaflavins, theaflavinmonogallate-A, theaflavinmonogallate-B, theaflavindigalate, tannin, and caffeine. Feeding of rats with a diet mixed with the aforementioned black tea constituents during the pre-initiation phase of DMBA successfully prevented the occurrence of mammary tumors and reduced tumor multiplicity as well as the tumor burden with a simultaneous inhibition of tumor angiogenesis as marked by a down-regulation of VEGF expression [112] (Table 2). Several studies have investigated the in vivo anti-cancer effects of green tea as GTE using preclinical breast cancer models. In one study, GTE has been found to suppress the size of xenografted MDA-MB-231 tumors in mice as well as tumor vessel density in a dose-dependent manner [63]. Using C3(1)/SV40 spontaneous mammary tumor model in transgenic mice, Leong et al. [69] investigated the chemopreventive effect of GTE and anti-angiogenic mechanisms. Administration of this preparation as the sole source of drinking water delayed tumor development and suppressed tumor growth in experimental animals. Immunohistochemical analyses demonstrated that GTE prevented angiogenesis through a decrease in both ductal epithelial and stromal VEGF expression and a reduction in intratumoral MVD.

Curcumin: Carroll et al. [113] investigated whether curcumin inhibits DMBA-induced and MPA-accelerated mammary tumors in rats. Treatment with curcumin prolonged the latency period, decreased tumor incidence, and reduced tumor multiplicity. Accompanying studies showed that curcumin decreased the expression of VEGF in hyperplastic mammary lesions, though it did not interfere with the expressions of ER and PR.

Flavones: The involvement of anti-angiogenic mechanism in the anti-tumor effects of flavonoid apigenin against breast cancer cells as observed in vitro has also been validated in DMBA-initiated and MPA-accelerated rat mammary tumorigenesis model. In addition to inhibiting both the incidence and multiplicity of breast tumors, apigenin also blocked increase in VEGF expression and suppressed the expression of VEGFR-2, but not that of VEGFR-1, in the regions of hyperplasia [114].

Genistein: The in vitro effects of genistein on breast cancer and angiogenesis have also been replicated in in vivo studies in the nude mouse xenografted with MCF-7 and MDA-MB-231 tumors. In both models, genistein arrested tumor growth, as well as inhibited the mRNA expression of MMP-9. Additionally, there was a decrease in TGF-β1 and VEGF protein levels in the serum and tumor cells of mice transplanted with MDA-MB-231 cells [89]. The anti-tumor and anti-angiogenic activities of genistein have also been investigated in F3II sarcomatoid mouse mammary carcinoma models. Intraperitoneal administration of genistein reduced tumor-induced angiogenesis in syngenic mice implanted with F3II cells [93]. In the MCF-7 xenograft model in mice, dietary genistein-rich soy isoflavone and soy phytochemical concentrate (SPC) reduced tumor volume. When SPC was combined with black or green tea, a further tumor reduction was achieved,

Table 2. In vivo evidence for the use of anti-angiogenic dietary components to prevent and treat breast cancer

Phytochemical	Dietary source	Active constituents	Anti-angiogenic effects in breast cancer	References
Catechins	Black tea (*Camellia sinensis*)	EGCG, EC, GCG, ECG	Prevented DMBA-induced mammary carcinogenesis in rats with inhibition of VEGF expression	Kumaraguruparan et al. [112]
	Green tea (*Camellia sinensis*)	EGCG, CG, GC, EC, EGC, ECG, GCG	Suppressed xenograft size with decreased tumor vessel density	Sartippour et al. [63]
			Inhibited mammary tumorigenesis in C3(1)SV40 mice with reduced VEGF expression and MVD	Leong et al. [69]
Curcumin	Turmeric (*Curcuma longa*)	Diferuloylmethane	Decreased DMBA-initiated and MPA-promoted mammary carcinogenesis in rats with reduction in VEGF expression in hyperplastic lesions	Carroll et al. [113]
Flavones	Fruits, vegetables, nuts, tea, and wine	Apigenin	Attenuated DMBA/MPA mammary tumorigenesis in rats; reduced VEGF and VEGFR-2 expression	Mafuvadze et al. [114]
Genistein	Soybean (*Glycine max*)	4′,5,7-Trihydroxy-isoflavone	Reduced tumor volume and density and down-regulated MMP-9 in xenografted MCF-7 and MDA-MB-231 tumors; lowered TGF-β1 and VEGF in the serum and tumor in MDA-MB-231 model	Shao et al. [89]
			Inhibited formation of new blood vessels in xenografted F3II tumors in mice	Farina et al. [93]
			Together with black or green tea, reduced tumor volume and lowered MVD, ER-α and IGF-I in mice with MCF-7 tumor	Zhou et al. [115]
Lignans	Flaxseed (*Linum usitatissimum*)	Not defined	Inhibited the growth of MDA-MB-435 breast cancer xenografts in mice with reduced levels of VEGF	Dabrosin et al. [116]
		Enterodiol, Enterolactone	Decreased the growth of transplanted MCF-7 cells in mice with reduced MVD and VEGF secretion	Bergman Jungeström et al. [97]
		Enterolactone	Decreased the tumor growth, reduced microvessel area and release of IL-1β in MCF-7 xenograft model	Lindahl et al. [117]
		Enterolactone	Inhibited tumor growth, MVD and VEGF expression in estradiol-induced mammary tumor in mice	Saarinen et al. [118]
		Lariciresinol	Attenuated tumor growth in DMBA mammary cancer in rats and MCF-7 breast cancer xenografts in mice with reduced MVD	Saarinen et al. [98]
Lycopene	Tomato (*Solanum lycopersicum*), watermelon, grapefruit, papaya and guava	(6*E*,8*E*,10*E*,12*E*,14*E*,16*E*,18*E*,20*E*, 22*E*,24*E*,26*E*)-2,6,10,14,19,23,27,31-Octamethyldotriaconta-2,8,10,12,14,16,18,20,22,24,26,30-tridecaene	Afforded protection against DMBA-induced mammary carcinogenesis in rats with reduction in neovascularization	Moselhy and Al mslmani [123]
Proanthocyanidins	Grape seed extract, apples, berries, and cinnamon		Inhibited the growth of xenografted MDA-MB-231 cells in mice with decreased tumor vessel counts and MAPK phosphorylation	Wen et al. [126]
Resveratrol	Grapes (*Vitis vinifera*), red wine, berries, peanuts, plums, and legumes	3,4′,5-Trihydroxy-*trans*-stilbene	Decreased COX-2 and MMP-9 expression and NF-κB activation during DMBA mammary cancer in rats	Banerjee et al. [127]
			Decreased MVD in MDA-MB-231 tumor xenograft in nude mice	Garvin et al. [102]
			Down-regulated HER-2/neu gene expression in mice with spontaneous mammary tumors	Provinciali et al. [128]

possibly through inhibition of MVD, ER-α, and insulin-like growth factor-1 (IGF-1) [115].

Lignans: A diet containing 10% flaxseed, the richest source of mammalian lignans, retarded both the growth and metastasis of transplanted MDA-MB-435 tumors in nude mice. Flaxseed-mediated inhibition of extracellular VEGF levels may represent one mechanistic explanation to the reduced tumor growth and metastasis [116]. The growth of transplanted MCF-7 tumor cells in estrogen-supplemented ovariectomized mice was decreased with simultaneous reduction in tumor vasculature through the dietary administration of flaxseed and its lignans, namely, enterodiol and enterolactone. Using microdialysis technique, the investigators also showed a reduced level of extracellular tumor VEGF in all intervention animal groups compared with that of the basal diet group [97]. A diet with high amounts of flaxseed or enterolactone reduced the growth of estradiol-induced MCF-7 xenograft tumors in mice with a drastic decrease in microvessel area as well as release of stroma-derived IL-1β [117]. Enterolactone alone or in combination with genistein has been shown to have potent tumor inhibitory effects on estradiol-induced breast cancer growth in ovariectomized mice with a parallel inhibition of MVD. Each dietary treatment decreased both stroma- and cancer cell-derived VEGF [118]. The anti-breast cancer effects and potential mechanism of action of another lignan lariciresinol have recently been investigated in two hormone-responsive preclinical breast cancer models, namely, DMBA-induced mammary carcinoma in rats and MCF-7 breast cancer xenografts in athymic mice. In both models, lariciresinol administration through diet was shown to attenuate tumor growth and tumor angiogenesis, as supported by reduced MVD [98].

Lycopene: Lycopene is the most abundant carotenoid responsible for the distinctive deep-red color of tomatoes (*Solanum lycopersicum*) and tomato products, including tomato paste, sauce, and ketchup. Additionally, watermelon, papaya, pink grapefruit, apricots, and pink guavas represent edible sources of lycopene. Higher intake of lycopene has been linked to a lower risk of developing breast cancer [119, 120]. Several in vivo studies have provided support for the anti-breast cancer efficacy of lycopene [121, 122]. A diet supplemented with lycopene afforded a substantial protection against DMBA-induced mammary carcinogenesis in rats. Accompanying histopathological analysis revealed the ability of lycopene to abrogate neovascularization in DMBA-initiated invasive mammary lesions [123].

Proanthocyanidins: Proanthocyanidins are abundant in many dietary sources, including grapes, apples, bilberries, cranberries, cinnamon, and cocoa. Proanthocyanidins present in grape seed extract (GSE) have been shown to exert chemopreventive effects against carcinogen-induced mammary gland cancer in vivo [124, 125]. A recent study has further demonstrated that a standardized preparation of GSE, containing at least 85% procyanidins (a contemporary term for proanthocyanidins), significantly inhibited the growth of MDA-MB-231 cells xenografted in mice. Treatment of tumor-bearing rodents with GSE led to a concurrent reduction of tumor blood vessel density and phosphorylation of MAPK [126].

Resveratrol: Dietary resveratrol resulted in a marked reduction in the incidence and multiplicity of tumors with a concomitant prolongation of latency period in DMBA-induced mammary carcinogenesis in rats. These results were associated with decreased COX-2 and MMP-9 expression as well as suppression of NF-κB activation in tumor tissue [127]. In a transplantable animal model, resveratrol also inhibited the growth of MDA-MB-231 tumor explants in nude mice, improved apoptosis, and inhibited angiogenesis as evidenced by a reduction in tumor MVD [102]. Resveratrol supplementation in drinking water hindered the development of spontaneous mammary tumors in HER-2/neu transgenic mice and reduced both the mean number and size of mammary tumors through down-regulation of HER-2/neu gene expression in neoplastic breast tissue [128].

8 Concluding remarks and future directions

The aforementioned studies describe the inhibitory effects of various dietary compounds on the proliferation and growth of breast cancer cells in vitro and/or in vivo by the inhibition of angiogenesis. The compounds mentioned in this review possess a common mechanism of action of anti-angiogenic activity that work through modulation of the regulatory pathways of neovascularization. For example, some compounds act on malignant cells to decrease their ability to secrete pro-angiogenic factors, while other compounds function to directly target endothelial cell responsiveness to pro-angiogenic factors (summarized in Fig. 1). It is highly likely that targeting both tumor and endothelial cells would slow the growth or spread of malignant cells while simultaneously acting directly on endothelial cells to interfere with the process of angiogenesis, thus maximizing the process more efficiently [129].

The aforementioned dietary phytoconstituents have been used as food products for centuries and thus are ideal for prophylactic long-term use against breast cancer because of their reliability, availability, safety profile, and affordable price. Dietary agents used to suppress angiogenesis can be an important step in the prevention and treatment of breast cancers with distinctive pathological characteristics. The ability of these agents to target a broad range of cancers of the breast is due to their target of angiogenesis, which is common in the pathogenesis across various cancer types [130].

Inherent to all tumor cells is the ability to transform the gene expression of stimulatory angiogenic factors for its own propagation. Studies have shown that while it is probable that a particular type of angiogenic inhibitor may inhibit one type of angiogenic factor, it may not be effective

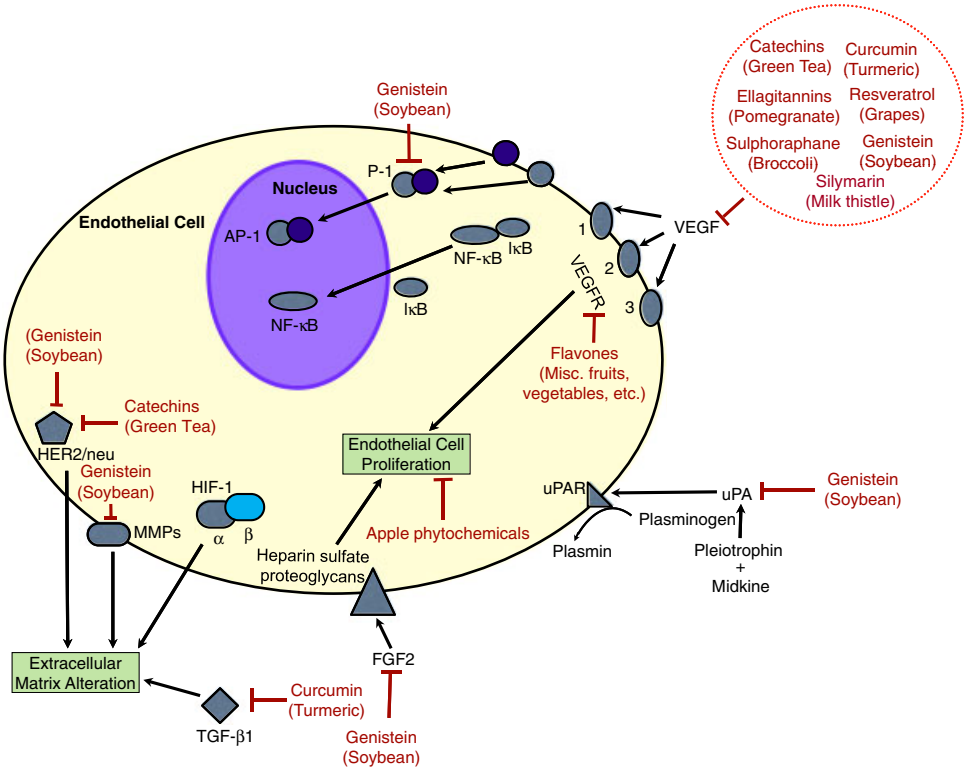

Figure 1. Anti-angiogenic mechanisms of dietary phytochemicals involved in the chemoprevention and treatment of breast cancer. A schematic of an endothelial cell is depicted. Multiple factors involved in endothelial cell proliferation and angiogenesis are highlighted. The naturally occurring phytochemicals (along with their dietary sources in parenthesis) that inhibit various angiogenic pathways are also presented.

in its ability to prohibit the neovascularization process. Hence, the use of a combination of angiogenic inhibitors will naturally have greater therapeutic efficacy, especially when used in combination with chemotherapy and/or radiotherapy in the treatment of breast cancer [131, 132].

The primary intention of anti-angiogenic agents is to inhibit the development and growth of new vasculature during tumor progression without disruption to the essential local biological functions which are dependent on the process of angiogenesis, such as tissue re-growth and wound healing inside the body. Because there is a real risk of the disruption of such angiogenic-dependent normal physiological processes, adverse effects of anti-angiogenic therapy may result in ulceration and bleeding in the gastrointestinal mucosa or other organs. Studies demonstrating the ability to differentiate between targeting the vessel networks in tumor and non-pathogenic blood vessels are required in the future to enhance the efficacy of anti-angiogenic agents.

The anti-angiogenic therapy has generally been considered safe since normal endothelial cells are genetically stable and thus are not prone to the various mutations that tumor cells characteristically undergo [133]. Nevertheless, emerging studies have shown that this may not be the case due to various factors attributable to heterogeneity of endothelial cells, angiogenic factors and tumor cells, tumor microenvironment, compensatory responses to therapy, angiogenesis-independent tumor growth or pharmacokinetic resistance [11]. In order to mitigate such challenges, better understanding of angiogenesis resistance, use of multiple anti-angiogenic agents, and angiogenic inhibitors in combination with other biologically targeted compounds may represent valuable therapeutic strategy.

In summary, the extensive range of studies presented in this article provide convincing evidence that dietary phytoconstituents possess the unique ability to affect tumor angiogenesis, which may be deemed advantageous in the prevention and treatment of human breast cancer.

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