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Natural remedies and functional foods as angiogenesis modulators

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Angiogenesis definition and background

Vertebrate cells need an appropriate microenvironment surrounded by blood capillaries to ensure maintaining their normal functions and the convenient microenvironment that formed a balanced composition of oxygen and nutrient substances, and metabolic wastes resulting from the vital activities of the cells is ensured by the cardiovascular or circulatory system (Pittman, 2013). The system is established via two mechanisms: vasculogenesis and angiogenesis. Both these mechanisms are essential for the formation of a vascular network in the early stages of embryonic development as well as in the rest of the lifespan (Drake, 2003). Although angiogenesis is defined as a complex process of expansion and remodeling of a preexisting vascular structure, vasculogenesis refers to the de novo blood vessel constitution accomplished by the de novo generation of endothelial cells, which includes a series of differentiation processes from mesodermal progenitors into angioblasts and then from angioblasts into endothelial cells (Patan, 2004; Risau and Flamme, 1995). In normal physiology, angiogenesis has a major role in tissue growth, healing, reproduction, and development of the fetus during pregnancy (Felmeden et al., 2003). All cells in the body desperately need oxygen to maintain their vital activities within homeostasis and the diffusion distance of oxygen within the tissues is restricted to 100–200 μm (Grimes et al., 2014; Varol, 2017). When a cell stays away from the capillary blood vessels farther than the appropriate diffusion distance of oxygen, it is inevitable that physiological stresses such as hypoxia along with starvation and acidification occur within the cell (Wenger et al., 2015; Carmeliet and Jain, 2000). Therefore, a cell that is deprived of oxygen can release proangiogenic growth factors, along with other positive regulation proteins such as vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-beta), fibroblast growth factor (FGF), epidermal growth factor (EGF), matrix metalloproteinase (MMP) enzymes, angiopoietins, and integrin proteins to initiate the formation of the surrounding blood capillaries (Weis and Cheresh, 2011; Salajegheh, 2016; Carmeliet, 2005). There are also angiogenesis suppression (antiangiogenic) factors such as angiopoietin-2, platelet factor-4, thrombospondin-1 and -2, endostatin, angiostatin,

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osteopontin, collagen, kininogens, and the tissue factor pathway inhibitor (TFPI) as well as angiogenesis-inducing (angiogenic) factors in the body (Ribatti, 2009; Mousa and Davis, 2017). The regulation of the balance between angiogenesis activators and inhibitors in the body provides an angiogenic switch that affects the formation of capillaries, and the direction in which the balance between these factors in the microenvironment is dominant regulates the opening and closing of the angiogenic switch (Varol, 2017; Carmeliet, 2005; Hanahan and Weinberg, 2011; Bouck et al., 1996; Hicklin and Ellis, 2005). Briefly, if the amount of the antiangiogenic factors is greater than the amount of the angiogenic factors, the angiogenic switch is closed and the existing blood vessels begin to decompose or no change occurs in their structures. In other words, if the amount of the angiogenic factors in the microenvironment is greater than the amount of the antiangiogenic factors, the angiogenic switch is opened and the constitution of new capillaries from existing blood vessels is triggered (Varol, 2017; Carmeliet, 2005; Ribatti, 2009). During the menstrual cycle in a healthy woman, for example, the development of the endometrium leads to opening the angiogenic switch and the formation of highly developed vascularity, although shedding of the endometrium leads to the degradation of the surrounding blood vessels, which then again undergo angiogenesis for the renovation of the endometrium (Smith, 2001; Folkman, 2006). It is widely known that mutual communication between the adjacent cells and their microenvironment plays an important role in the regulation of the angiogenic switch as well as the regulation of tissue shrinkage and destruction or tissue growth and development (Carmeliet and Jain, 2000; Ribatti, 2009; Quail and Joyce, 2013). Many changes in the microenvironment can have an important role in the determination of the fate of the angiogenic switch due to the mutual communication between the cells or the some genetic mutation (Varol, 2017; Carmeliet and Jain, 2000; Kerbel, 2000). These factors include mechanical stress depending on the proliferation and growing rates of cells in a tissue, the presence of metabolic stress factors such as low glucose level (hypoglycemia), a low pH level (acidification) due to metabolic waste accumulation because of aggressive metabolic activity, iron deficiency (hypoferremia), deprivation of oxygen (hypoxia), the infiltration of cells related to the immune and inflammatory systems into the tissues, and the rearrangement of the metabolic pathways. After the angiogenic switch is opened, a series of cellular processes is operated under the control of cells, soluble factors, and extracellular matrix components (Salajegheh, 2016). Two types of angiogenesis, called sprouting angiogenesis and intussusceptive angiogenesis, can be observed both in utero and in adults (Burri and Tarek, 1990; Caduff et al., 1986). There is limited information in the literature about the intussusceptive angiogenesis compared to sprouting angiogenesis, which was reported for the first time by Ausprunk and Folkman (1977). Ausprunk and Folkman (1977) reported that sprouting angiogenesis can initially progress without cell division, although proliferation is essential for sustained sprouting and further outgrowth. Sprouting angiogenesis is especially induced by the cells that have a hypoxic condition in their microenvironment due to poor tissue perfusion. These cells initiate a series of processes that can be listed as the enzymatic degradation of the capillary basement membrane at the localization of the angiogenic stimulus, the debilitation of the contacts between endothelial cells, the proliferation of endothelial cells and their migration in a directed way to connective tissue, the formation of capillary-like structures (tubulogenesis), the anastomosis of the new tubular sprouts (vessel fusion), the synthetization of the new basement membrane, and the stabilization of pericytes (Ausprunk and Folkman, 1977; Ribatti and Crivellato, 2012; Adair and Montani, 2010). On the other hand, the word "intussusception" means growth within itself and intussusceptive angiogenesis, defined as capillary vessel growth within itself, is briefly carried out by an extension of the vessel wall into the lumen, causing a single vessel to split in two (Djonov et al., 2000; Burri et al., 2004). As an alternative to sprouting angiogenesis, intussusceptive angiogenesis has an important role in the formation of a vascular system in embryos where growth is rapid and resources are limited, although it can be observed throughout life (Burri et al., 2004; Djonov et al., 2003). In intussusceptive angiogenesis, there is no need for immediate endothelial cell proliferation, extensive migration, basement membrane degradation, or invasion of the surrounding tissue because it is a rapid and efficient process in a metabolically and energetically more economic manner, and only requires reorganization of existing endothelial cells that thereby form less leaky capillaries (Kurz et al., 2003). Intussusceptive angiogenesis, also called splitting angiogenesis, occurs by the processes that can be listed as capillary plexus expansion that provides a broad endothelial surface for metabolic exchange; the formation of changes in the position, form, and size of the perfused capillary segments as a result of the arborization and the creation of a hierarchical tree; and the modification and optimization of the supplying vessel branching geometry and flow property by remodeling the branches, which includes not only the formation of new branches but also the removal of existing ones as a response to the alterations in metabolic requirements (Djonov et al., 2003; Kurz et al., 2003).

Molecular mechanism of angiogenesis

As previously mentioned, angiogenesis has emerged as a sophisticated molecular phenomenon that includes a complex balance between the amount of angiogenic and antiangiogenic factors, which determines the fate of the angiogenic switch and thereby the formation, modification, stabilization, or degradation of the existing capillary vessels (Varol, 2017; Carmeliet, 2005; Hanahan and Weinberg, 2011; Bouck et al., 1996; Hicklin and Ellis, 2005). Therefore, many molecular signaling pathways include proangiogenic and antiangiogenic factors that are given in Table 1.1 and Table 1.2 (Carmeliet and Jain, 2000; Carmeliet, 2005; Kumar et al., 2016). As can be seen in Tables 1.1 and 1.2, the majority of the angiogenesis activators and inhibitors are growth factors such as hepatocyte growth factors (HGF), transforming growth factors (TGF), platelet-derived growth factors (PDGFs), and vascular endothelial growth factors (VEGFs); the other factors generally take a complementary role in the angiogenic and antiangiogenic pathways (Kumar et al., 2016). Endogenous antiangiogenic factors usually work as inhibitors of the components of the capillary vessels or endogenous angiogenic factors (Carmeliet and Jain, 2000). Vascular endothelial growth factor (VEGF) family members, for instance, play an important role

Table 1.1 Angiogenic factors.

Angiogenic factors	References
Vascular endothelial growth factor (VEGF) family members	Holmes and Zachary (2005)
Neuropilin-1 (NRP-1)	Parikh et al. (2004)
Angiopoietin 1 (Ang1) and Ang1 receptor (Tie2)	Suri et al. (1996)
Platelet-derived growth factor-BB (PDGF-BB) and receptors	Saik et al. (2011), Marx et al. (1994)
Fibroblast growth factor (FGF)	Presta et al. (2005)
Hepatocyte growth factor (HGF)	Xin et al. (2001)
Monocyte chemoattractant protein-1 (MCP-1)	Hong et al. (2005)
Nitric oxide synthase (NOS)	Murohara et al. (1998)
Cyclooxygenase-2 (COX-2)	Gately (2000)
Inhibitor of differentiation 1 (Id1) and Id3	Lyden et al. (1999)
Vascular endothelial cadherin	Gory-Fauré et al. (1999)
Platelet endothelial cell adhesion molecule (PECAM-1 or CD31)	Horak et al. (1992)
Plasminogen activators and matrix metalloproteinases (MMPs)	Mignatti and Rifkin (1996)
Plasminogen activator inhibitor-1 (PAI-1)	McMahon et al. (2001)
Transforming growth factor beta-1 (TGF-β1), TGF-β receptors	Pepper (1997)
Prominin-1 (AC133 or CD133)	Fargeas (2006)
Integrins $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha 5\beta 1$	Kim et al. (2000)
Chemokines	Strieter et al. (2004)
Ephrins	Cheng et al. (2002)
Leptin	Bouloumié et al. (1998)
Endoglin	Ten Dijke et al. (2008)

Table 1.2 Antiangiogenic factors.

Antiangiogenic factors	References
VEGFR-1; soluble VEGFR-1	Shibuya (2006)
Soluble NRP-1	Geretti and Klagsbrun (2007)
Angiopoietin 2 (Ang2)	Lobov et al. (2002)
Thrombospondin-1 (TSP-1), TSP-2	Tolsma et al. (1993)
Angiostatin and related plasminogen kringles	Tarui et al. (2002)
Prothrombin kringle-2; antithrombin III fragment	Kim et al. (2002)
Fragment of SPARC	Jendraschak and Sage (1996)
Osteopontin fragment	Hirama et al. (2003)
Prolactin	Ueda et al. (2006)
Canstatin	Kamphaus et al. (2000)
Vascular endothelial growth inhibitor (VEGI)	Zhai et al. (1999)
Platelet factor-4	Bikfalvi (2004)
Maspin	Zhang et al. (2000)
MMP inhibitors	Raza and Cornelius (2000)
Meth-1; Meth-2	Vázquez et al. (1999)
Proliferin and proliferin-related protein	Jackson et al. (1994)
Restin	Ramchandran et al. (1999)
IFN-α, -β, -γ; IP-10, IL-4, IL-12, IL-18	Voest et al. (1995), Cao et al. (1999), Volpert et al. (1998), Strieter et al. (1995), Jablonska et al. (2010), Beatty and Paterson (2001)
Retinoids	Majewski et al. (1993)
Vasostatin	Pike et al. (1998)
Calreticulin	Pike et al. (1999)
Endostatin (collagen XVIII fragment)	O'Reilly et al. (1997)

through a family of cognate receptor kinases in endothelial cells to stimulate angiogenesis and vasculogenesis, although vascular endothelial growth factor receptor-1 (VEGFR-1), soluble VEGFR-1, platelet factor-4, prolactin, and the fragment of the matricellular protein SPARC (secreted protein acidic and rich in cysteine) act as the inhibitors of VEGF (Carmeliet and Jain, 2000; Kumar et al., 2016; Holmes and Zachary, 2005).

Although neuropilin-1 (NRP-1) integrates the survival and angiogenic signals, the soluble isoform of NRP-1 inhibits VEGF, VEGF-B, and PIGF (placental growth factor), which are members of the VEGF family (Schuch et al., 2002; Olofsson et al., 1998; Zhang et al., 2009). Angiopoietin-1 contributes to the formation of capillary vessels by playing a substantial role in the vessel remodeling, maturation, and stabilization or inhibiting permeability, whereas angiopoietin-2 acts as the antagonist of angiopoietin-1 (Stratmann et al., 1998). On the other hand, there are some antiangiogenic factors such as prothrombin kringle-2, antithrombin III fragment, trombospondins (TSP-1 and TSP-2), endostatin, vasostatin, calreticulin, interferons (IFN-α, IFN-β and IFN-γ), interferon gamma-induced protein 10, and interleukins (IL-4, IL-12 and IL-18) that are directly active on endothelial cell growth, survival, adhesion, and migration (Carmeliet and Jain, 2000; Lee et al., 1998; Lawler, 2002; Coughlin et al., 1998). Understanding the molecular mechanisms of angiogenesis is of great importance to search for new treatment opportunities to cure angiogenesis-dependent diseases such as ocular fundus diseases, neurodegenerative diseases, rheumatoid arthritis, diabetic retinopathy, endometriosis, atherosclerosis, psoriasis, osteoporosis, diabetes, and cancer (Salajegheh, 2016; Lopes et al., 2013).

Screening methods of angiogenesis modulators

Screening functional foods and natural remedies for vasculogenesis and angiogenesis stimulation, inhibition, and the related-signal transduction targeting activities requires in vitro and in vivo assay systems for molecular target identification and validation, and optimization of dose scheduling and a convenient drug combination strategy (Losso, 2007). Researchers expect that an ideal angiogenesis or vasculogenesis assay should be easy, quantitative, reproducible, cost-effective, and rapid, although each assay has limitations (Mousa et al., 2017). The most common in vitro and in vivo angiogenesis assays can be seen in Table 1.3.

Natural angiogenesis modulators

In this part of the chapter, the traditional natural formulations as well as plant and mushroom sources are summarized and put together in Table 1.4, and the natural products that take a role in the modulation of angiogenesis are listed in Table 1.5. It is widely acknowledged that medicinal plants, mushrooms, and herbs are the lead and key sources for human welfare because the relationship between mankind and natural cures is as old as the existence of humankind, and unnatural treatment strategies can cause some

Table 1.3 The most common in vivo and in vitro angiogenesis assays.

Assay system	Experimental model	Specifications	References for assay protocol
Proliferation	MTT Assay	Measures living cells using spectrophotometer, is fast and has high throughput, but an endpoint assay	van Meerloo et al. (2011)
Proliferation	XTT Assay	Measures living cells using spectrophotometer, is water soluble and highly sensitive, but an endpoint assay	Roehm et al. (1991)
Proliferation	WST-1 Assay	Measures living cells using spectrophotometer, is fast and highly sensitive, but an endpoint assay	Peskin and Winterbourn (2000)
Proliferation	LDH Assay	Measures dead and dying cells, is fast and has high throughput, but an expensive and endpoint assay	Smith et al. (2011), Varol (2018)
Proliferation	AlamarBlue Assay	Measures living cells using spectrophotometer, is fast and highly sensitive, but an endpoint assay	Varol (2018), Bonnier et al. (2015)
Proliferation	BrdU Assay	Measures DNA replication, is precise, fast, and nonradioactive, but has a lengthy protocol and DNA damage risk	Darzynkiewicz and Juan (1997)
Proliferation	EdU Assay	Measures DNA replication, is less toxic than BrdU assay, and does not need DNA denaturation, but has expensive reagents	Salic and Mitchison (2008)
Proliferation	Trypan Blue	Measures dead and dying cells using microscopy, is low cost and rapid, but variable and inaccurate	Strober (2015)
Proliferation	PicoGreen	Measures dsDNA amount, is rapid and highly sensitive, but expensive	Varol (2018)
Proliferation	Ki67	Measures cellular proliferation, is convenient for in vivo application, but requires fixation	Soares et al. (2010), Key et al. (1994)
Proliferation	CFSE	Measures living cells, is a live cell analysis, but has a toxic effect	Quah and Parish (2010)
Proliferation	Live/Dead Assays	Measures viable and dead cells, is a live and single cell analysis and rapid, but has some inaccurate results	Lorenzo et al. (1994)
Proliferation	Real-Time Cytotoxicity Assays	Measure viable and/or dead cells, gives real-time results, but is expensive and needs developed equipment	Ke et al. (2011)
Migration	Boyden Chamber Assay	Measures migrated cells, is sensitive, fast, and cost-effective, but time-consuming and technically difficult to set up	Chen (2005)

Table 1.3 The most common in vivo and in vitro angiogenesis assays—cont'd

Assay system	Experimental model	Specifications	References for assay protocol
Migration	Wound Healing Assay	Measures migration rate, is convenient, inexpensive, high throughput, and simple, but quantification is somewhat arbitrary	Liang et al. (2007)
Migration	Phagokinetic Track Motility Assay	Measures total cell motility, needs common laboratory equipment and chemicals, but has a lengthy protocol	Nogalski et al. (2012)
Migration	Teflon Fence Assay	Measures migrated cells, is highly sensitive, but technically difficult to set up	Cai et al. (2000)
Migration	Real-Time Cellular Migration Assay	Measures real-time cellular migration, is highly sensitive and simple, but expensive and needs developed equipment	Bird and Kirstein (2009)
In Vitro	Tube or Cord Formation Assay	Measures the formation of tube-like structures, is high throughput, quantifiable, and easy to set up, but dependent on the type of support matrices	Arnaoutova and Kleinman (2010), Varol et al. (2018)
In Vitro	Sprouting Assay	Measures the tubules that form in all three dimensions, closely mimics the in vivo situation, but notoriously difficult to analyze	Janvier et al. (1997)
In Vitro	Coculture Assay	Measures tubulogenesis that is actualized more closely in the in vivo situation, but time-consuming and technically difficult to set up	Bishop et al. (1999), Donovan et al. (2001)
Organ Culture	Whole or partial vessel outgrowth assays (from rat, mouse, chick, porcine or human)	Measures microvessel outgrowth, is widely used, reproducible, and highly sensitive, but technically difficult	Bellacen and Lewis (2009), Nicosia and Ottinetti (1990), Masson et al. (2002), Chau and Figg (2007)
In Vivo	Chorioallantoic Membrane (CAM) Assay	Needs a developing chick embryo, is simple, cost-effective, and convenient for large-scale screening, but sensitive to oxygen tension and hard to observe new capillaries due to preexisting vascular network	Wilting et al. (1991)
In Vivo	Corneal Pocket Assay	Is performed in rabbit, rat, or mice cornea, reliable but expensive, time-consuming, technically difficult, and ethically questionable	Ziche and Morbidelli (2012), Morbidelli and Ziche (2004)
In Vivo	Matrigel Plug Assay	Is performed in mice and provides a natural environment, but expensive and time-consuming	Coltrini et al. (2013)

Continued

Table 1.3 The most common in vivo and in vitro angiogenesis assays—cont'd

Assay system	Experimental model	Specifications	References for assay protocol
In Vivo	Sponge Implant Model	Is performed in mice or rats, technically simple and inexpensive, but time-consuming and has a lengthy protocol	Andrade and Ferreira (2009)
In Vivo	Tumor Models	Allows a realistic model for human cancers in nude mice, but time-consuming and technically difficult to set up	Hoffman (2005)
In Vivo	Dorsal Air Sac Assay (DASA)	Is performed in a dorsal air sac under the skin of mice, technically simple, but invasive and hard to observe new capillaries due to preexisting vascular network	Seon (2015)
In Vivo	Zebrafish Models	Is fast, quantitative, and convenient, but expensive and has some technical problems	Ali et al. (2015)

Table 1.4 Antiangiogenic functional foods and natural remedies.

Natural sources	Findings	Mechanisms	References
Plants			
Acorus calamus	Inhibition of endothelial tube formation	Downregulation of nucleostemin and Oct4	Haghighi et al. (2017)
Allium ascalonicum	Antiangiogenic	Not elucidated	Seyfi et al. (2010)
Aloe vera	Promotion of angiogenesis	Induction of angiogenesis in the CAM assay	Moon et al. (1999)
Angelica sinensis	Promotion of angiogenesis	Promotion of VEGF and stimulation of JNK 1/2 and p38 phosphorylation	Lam et al. (2008)
Artemisia annua	Inhibition of angiogenic factors	Inhibition of major angiogenesis activators such as NO and PGE2 and cytokines VEGF, IL-1β, IL-6, TNF-α	Zhu et al. (2013)
Astragalus membranaceus	Promotion of angiogenesis	Promotion of VEGF, CD34, and eNOS expression	Han et al. (2016)
Camellia sinensis	Prevention of the new blood vessel formation	Inhibition of VEGF family members	Cao and Cao (1999), Rashidi et al. (2017)
Chamaemelum nobile	Antiangiogenic	Inhibition of VEGFR-2 phosphorylation	Guimarães et al. (2016)
Chresta martii	Antiangiogenic	Inhibition of NF-κB	Queiroz et al. (2018)
Cinnamomum zeylanicum	Inhibition of endothelial cell proliferation, cellular migration, and endothelial tube formation	Inhibition of VEGFR2 kinase activity, mitogen-activated protein kinase (MAPK), and signal transducer and activator of transcription 3 (STAT3) signaling	Lu et al. (2009)

Table 1.4 Antiangiogenic functional foods and natural remedies—cont'd

Natural sources	Findings	Mechanisms	References
Combretum hartmannianum	Antiangiogenic	Inhibition of sprouting of microvessels in rat aortic explants	Hassan et al. (2014)
Croton crassifolius	Inhibition of angiogenesis in zebrafish embryo model	Suppression of VEGF-A, Ang, and their receptors	Huang et al. (2015), Wang et al. (2016)
Eurycoma longifolia	Inhibition of endothelial cell proliferation, cellular migration, and endothelial tube formation	Inhibition of angiogenesis in CAM assay, rat aortic ring assay, and tumor xenograft model	Al-Salahi et al. (2013)
Galium aparine	Antiangiogenic	Inhibition of VEGF secretion	Atmaca (2017)
Galium tunetanum	Iridoids (Asperuloside, Geniposidic acid and iridoid V1) of *G. tunetanum* inhibit angiogenesis	Inhibition of angiogenesis in CAM model	Camero et al. (2018)
Gastrodia elata	Inhibition of angiogenesis in CAM assay	Inhibition of NO production and COX-2	Ahn et al. (2007)
Nicotiana glauca	Antiangiogenic	Inhibition of sprouting of microvessels in rat aortic explants	Hassan et al. (2014)
Origanum onites	Antiangiogenic	Inhibition of endothelial cell proliferation, cellular migration, and endothelial tube formation	Bostancıoğlu et al. (2012)
Panax ginseng	Promotion of angiogenesis, stimulation of endothelial cell proliferation, cellular migration, and endothelial tube formation	Upregulation of eNOS and activation of PI3K-Akt pathway	Sengupta et al. (2004), Huang et al. (2005)
Patrinia villosa	Antiproliferative, antimigratory, and antiangiogenic	Induction of focal adhesion kinase (FAK) and protein kinase B (PKB or Akt) phosphorylation	Jeon et al. (2010)
Pinus halepensis	Antiangiogenic	Inhibition of endothelial tube formation and angiogenesis in CAM assay	Kadri et al. (2014)
Pithecellobium jiringa	Inhibition of cellular migration and tube formation of endothelial cells	Downregulation of VEGF expression	Muslim et al. (2012)
Rabdosia rubescens	Antiangiogenic	Inhibition of Akt and MAPK kinases	Meade-Tollin et al. (2004)
Rubus alceifolius	Inhibition of angiogenesis, endothelial migration, and tube formation	Downregulation of VEGF-A expression	Zhao et al. (2014)
Salvia miltiorrhiza	Promotion of cell growth and differentiation	Upregulation of MMP-2, VEGF, VEGFR2 and Tie-1	Lay et al. (2003)
Tamarix nilotica	Antiangiogenic	Inhibition of sprouting of microvessels in rat aortic explants	Hassan et al. (2014)
Tephrosia apollinea	Antiangiogenic	Inhibition of sprouting of microvessels in rat aortic explants	Hassan et al. (2014)
Vitis spp.	Antiangiogenic	Upregulation of VEGF and Flk-1, and inhibition of MMP-2 secretion	Agarwal et al. (2004)

Continued

Table 1.4 Antiangiogenic functional foods and natural remedies—cont'd

Natural sources	Findings	Mechanisms	References
Mushrooms			
Cordyceps militaris	Inhibition of angiogenesis	Abrogation of VEGF production, mitigation of Akt1 and GSK-3β activation, and induction of p38α phosphorylation	Ruma et al. (2014)
Coriolus versicolor	Inhibition of angiogenesis	Inhibition of VEGF	Ho et al. (2004)
Ganoderma lucidum	Inhibition of endothelial cell proliferation and angiogenesis	Inhibition of VEGF and TGF-β 1 secretion	Cao and Lin (2006), Stanley et al. (2005)
Phellinus linteus	Inhibition of angiogenesis	Inhibition of proliferation, migration, tube formation and VEGF-2 phosphorylation, modulation MMP-2, MMP-9, NF-κB, β-catenin, and MAPK expression	Lee et al. (2010a), Park (2015)
Pleurotus tuber-regium	Inhibition of VEGF-induced endothelial proliferation, migration, and tube formation	Downregulation of VEGFR, FGF, ANG-Tie, and MMP gene expression	Lin et al. (2015, 2014)

Traditional name	Ingredients	Findings	Mechanisms	References
Natural formulations				
Buyang-Huanwu	*Angelica sinensis, Astragalus membranaceus, Carthamus tinctorius, Ligusticum chuanxiong, Lumbricus terrestris, Paeonia lactiflora, and Prunus persica*	Promotion of angiogenesis	VEGFR-2 activation through the PI3K/Akt signaling pathway	Cui et al. (2015), Seto et al. (2016)
Bao-Shen-Tiao-Jing-Fang	Placenta Hominis (human placenta), *Angelica sinensis, Cuscuta chinensis, Feces trogopterori, and Morindae officinalis*	Promotion of angiogenesis	Upregulation of VEGF, VEGFR, bFGF, FGF, PDGFR-α, and EGFR	Woo et al. (2007)
Dang-Gui-Bu-Xue-Tang	*Angelica sinensis and Astragalus membranaceus*	Promotion of angiogenesis	Upregulation of VEGFR1/2 expressions and downregulation of sVEGFR1/2 expression	Lei et al. (2003), Lin et al. (2017), Hu et al. (2018)
Danggui-Shaoyao-San	*Aconitum carmichaeli, Alisma orientalis, Astragalus membranaceus, Carthamus tinctorius, Cinnamomum cassia, Lepidium apetalum, Panax ginseng, Periploca sepium, Polygonatum odoratum, Salvia miltiorrhiza, and Seasoned Orange Peel*	Promotion of angiogenesis	Upregulation of eNOS	Seto et al. (2016), Lan et al. (2012), Ren et al. (2015)
Nue-Jing-Yun-Yu-Tang	*Angelicae sinensis, Cuscuta chinensis, Ligustrum lucidum, Lycium barbarum, Salviae miltiorrhizae*, etc.	Promotion of angiogenesis	–	Woo et al. (2007)
Qing-Luo-Yin	*Dioscorea hypoglauca, Phellodendron amurense, Sinomenium acutum, and Sophora flavescens*	Inhibition of angiogenesis	Restoration of the balance of MMP-3 and TIMP-1	Li et al. (2003)

Table 1.4 Antiangiogenic functional foods and natural remedies—cont'd

Traditional name	Ingredients	Findings	Mechanisms	References
Qiliqiangxin	*Aconitum carmichaeli, Alisma orientalis, Astragalus membranaceus, Carthamus tinctorius, Cinnamomum cassia, Lepidium apetalum, Panax ginseng, Periploca sepium, Polygonatum odoratum, Salvia miltiorrhiza, and Seasoned Orange Peel*	Promotion of angiogenesis	Activation of NRG-1/Akt signaling pathway	Wang et al. (2015a)
Triphala Churna	*Emblica officinalis, Terminalia belerica, and Terminalia chebula*	Antiangiogenic and antiproliferative	Phosphorylation of VEGFR2	Lu et al. (2012)
Tongxinluo	*Dalbergia odorifera, Dryobalanops aromatic, Eupolyphaga seu steleophaga, Hirudo, Mesobuthus martensii, Paeonia lactiflora, Panax ginseng, Periostracum cicadae, Santalum album, Scolopendra subspinipes, and Ziziphus spinosa*	Promotion of angiogenesis	Upregulation of VEGF, PI3K, and Akt signaling pathway	Seto et al. (2016), Chang et al. (2012), Yu et al. (2016)
Xiongshao	*Ligusticum chuanxiong and Paeonia lactiflora*	Promotion of angiogenesis	Upregulation of VEGF and bFGF	Seto et al. (2016), Lin et al. (2011)
Xuefu Zhuyu	*Angelica sinensis, Bupleurum chinensis, Carthamus tinctorius, Citrus aurantium, Cyathula officinalis, Glycyrrhiza glabra, Ligusticum chuanxiong, Paeonia lactiflora Pall., Platycodon grandiflorus, Prunus persica, Rehmannia glutinosa Liboschitz*	Promotion of angiogenesis	Upregulation of VEGF and NO expression	Seto et al. (2016), Lin et al. (2018)

significant side effects such as systemic toxicity, drug resistance, nonselective tissue damage, and potential long-term side effects (Varol, 2015). Thus, recent ethnopharmacological surveys show that many patients and physicians opt and credit natural resources such as plants, mushrooms, lichens, marine organisms, and animals for complementary and alternative medicine. It can be clearly observed that many over-the-counter drugs are derived from natural sources or inspired and synthesized from natural products (Varol, 2018). The discovery of natural angiogenesis modulators is of great importance because angiogenesis is considered a key and common target for many diseases that need urgent discovery of new treatment methods, drugs, and strategies. For example, angiogenesis has emerged as a key process in tumorigenesis, although there are more than 200 types of cancer and cancerous tissue has a morphologically and functionally heterogeneous structure, and is composed of various types of cancer cells with different mutations, epigenetic profiles, and characteristics (Varol, 2017; Hansen et al., 2011). Although there are many

Table 1.5 Antiangiogenic natural products.

Natural products	Findings	Mechanisms	References
(2*S*)-7,2′,4′-Trihydroxy-5-methoxy-8-(dimethylallyl) flavanone	Inhibition of endothelial cell proliferation, cellular migration, adhesion, and endothelial tube formation	Downregulation of ROS levels and VEGF expression, and G0/G1 phase cell cycle arrest	Zhang et al. (2013a)
4-Amino-2-sulfanylphenol derivatives	Inhibition of protein kinase and angiogenesis	Inhibition of protein kinase B/Akt and ABL tyrosine kinase	Xu et al. (2013)
4-Hydroxybenzyl alcohol	Inhibition of angiogenesis	Downregulation of VEGF, MMP-9, and NO production	Lim et al. (2007), Laschke et al. (2013)
Acacetin	Inhibition of angiogenesis	Downregulation of STAT signaling and VEGF expression, inhibition of HIF-1α expression and AKT activation	Bhat et al. (2013), Liu et al. (2011)
Aloin	Inhibition of angiogenesis	Downregulation of VEGF expression, and STAT3 and VEGFR2 phosphorylation,	Pan et al. (2013)
Arenobufagin	Inhibition of angiogenesis	Downregulation of VEGFR2 signaling pathway	Li et al. (2012)
Aspfalcholide	Inhibition of angiogenesis	Inhibition of VEGF-induced endothelial cell proliferation, cellular migration, and endothelial tube formation	Ghalib et al. (2012)
Apigenin	Antiangiogenic	Downregulation of HIF-1α and VEGF expression via PI3K/AKT/p70S6K1 and HDM2/p53 pathways	Fang et al. (2007, 2005)
Artemisinin	Antiangiogenic	Downregulation of CD31, VEGF, and VEGFR expression, and NF-κB transcriptional activity	Wei and Liu (2017)
Artesunate	Antiangiogenic	Downregulation of VEGF, KDR/flk-1, and PIGF expression	Vandewynckel et al. (2014), Chen et al. (2004)
Barbatolic acid	Antiangiogenic	Inhibition of endothelial tube formation and cellular migration	Varol (2018)
Bavachinin	Inhibition of endothelial tube formation	Inhibition of HIF-1α and VEGF	Nepal et al. (2012)
Bigelovin	Inhibition of angiogenesis	Inhibition of Ang2 and Tie2	Yue et al. (2013)
Brucine	Inhibition of VEGF-induced cell proliferation, chemotactic motility, and the formation of capillary-like structures	Inhibition of the downstream protein kinases of VEGFR2, including Src, FAK, ERK, AKT, and mTOR and downregulation of VEGF, NO, IL-6, IL-8, TNF-a, and IFN-γ	Saraswati and Agrawal (2013)
Boswellic acid	Inhibition of angiogenesis	Downregulation of VEGF, CD31, and TGF-β1	Saraswati et al. (2011)

Table 1.5 Antiangiogenic natural products—cont'd

Natural products	Findings	Mechanisms	References
β-Escin sodium	Antiangiogenic	Inhibition of endothelial proliferation and migration, regulation of TSP-1, ERK, and MAPK levels	Wang et al. (2008)
β-Eudesmol	Inhibition of angiogenesis and tumor neovascularization	Inhibition of bFGF and VEGD induced pERK1/2	Tsuneki et al. (2005), Ma et al. (2008)
β-Sitosterol	Promotion of endothelial migration and angiogenesis	Induction of VEGF, VEGF receptor Flk-1, and laminin expression	Moon et al. (1999), Choi et al. (2002)
Caffeic acid	Inhibition of angiogenesis	Inhibition of VEGF-induced endothelial proliferation, migration, and tube formation, reduction in JNK-1-mediated HIF-1α stabilization	Kim et al. (2009a), Gu et al. (2016)
Camptothecins	Inhibition of endothelial cell proliferation and tube formation	Inhibition of HIF-1α, MMP-9, and VEGF through suppression of PI3K/Akt-mediated NF-κB activity and enhancing the Nrf2-dependent HO-1 pathway	Jayasooriya et al. (2015), Tsuchida et al. (2003), Kamiyama et al. (2005)
Celastrol	Antiangiogenic	Inhibition of HIF-1α activation, STAT3 phosphorylation, and TLR4-triggered NF-κB activation	Ni et al. (2014)
Chebulagic acid	Antiproliferative, antimigratory, and HUVECs' permeability inhibition	Inhibition of VEGF-A	Lu and Basu (2013)
Cucurbitacin E	Antiangiogenic	Inhibition of VEGFR2-mediated Jak2–STAT3 signaling pathway	Dong et al. (2010)
Curcumin	Inhibition of tube formation, migration, and colony formation	Regulation of the NF-κB/VEGF signaling, STAT3, proliferator-activated receptor gamma, IL-4 and IL-13 production, and TAM polarization	Gao et al. (2015), Huang et al. (2017)
Combretastatins	Inhibition of proliferation and vascularization	Inhibition of tubulin assembly, downregulation of VEGF and VEGFR-2 expression	Su et al. (2016), Sherbet (2017)
Deguelin	Inhibition of tumor vascularization	Inhibition of the HIF-1α-VEGF signaling pathway	Wang et al. (2013a)
Ellagic acid	Inhibition of angiogenesis	Inhibition of VEGF and PDGF receptors, VEGF, MAPK, and PI3K/Akt signaling pathways	Labrecque et al. (2005), Wang et al. (2012)
Emodin	Inhibition of angiogenesis	Inhibition of TRAF6, HIF-1α, VEGF and TRAF6, CD147, MMP9 signaling pathways	Shi and Zhou (2018)

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Table 1.5 Antiangiogenic natural products—cont'd

Natural products	Findings	Mechanisms	References
Epigallocatechin-3-gallate	Prevention of new blood vessel formation	Inhibition of VEGF signaling	Cao and Cao (1999), Moyle et al. (2015)
Farnesiferol C	Inhibition of angiogenesis	Downregulation of VEGF binding to VEGFR1/Flt-1	Lee et al. (2010b)
Fisetin	Inhibition of endothelial cell proliferation, cell-cycle progression, and migration	Downregulation of VEGF and eNOS expression and inhibition of MMPs	Tsai et al. (2018)
Furanodiene	Inhibition of endothelial cell proliferation, migration, and tube formation	Inhibition of VEGF and regulation of the PI3K pathway	Zhong et al. (2012)
Gallic acid	Inhibition of VEGF-mediated in vitro angiogenesis	Inhibition of VEGF secretion, downregulation of AKT phosphorylation and HIF-1α expression, and promotion of PTEN expression	He et al. (2016)
Genistein	Inhibition of endothelial cell proliferation and angiogenesis	Inhibition of VEGF and FGF-2 expression, receptor tyrosine kinase, and suppression of NF-kB, IRF, and Akt signaling pathways	Fotsis et al. (1993), Sasamura et al. (2002), Ruiz and Haller (2006)
Glyceollins	Inhibition of angiogenesis	Inhibition of VEGFR2, FGFR1, HIF-1α, PI3K, Akt, and mTOR	Lee et al. (2013a, 2015)
Herboxidiene	Antiangiogenic	Downregulation of VEGFR2 and HIF-1α	Jung et al. (2015)
Heyneanol A	Inhibition of proliferation and tube formation	Inhibition of bFGF-induced endothelial cell proliferation and capillary tube formation of human umbilical vein endothelial cells	Lee et al. (2006)
Honokiol	Antiangiogenic	Inhibition of HIF pathway	Vavilala et al. (2014)
Hydroxytyrosol	Inhibition of endothelial cell proliferation, cellular migration, and endothelial tube formation	Downregulation of MMP-2 expression	Fortes et al. (2012)
Indole-3-carbinol	Antiangiogenic	Downregulation of PI3K, Akt, mTOR, NF-κB signaling pathways	Ahmad et al. (2013)
Isoliquiritigenin	Inhibition of neovascularization and tube formation	Inhibition of VEGF and VEGFR-2 signaling pathway and downregulation of IRF3/MyD88, ERK/MAPK, JNK/MAPK, Jak1/STAT1, and PI3K/Akt signaling Pathways	Wang et al. (2013b), Jhanji et al. (2011), Wu et al. (2015)

Table 1.5 Antiangiogenic natural products—cont'd

Natural products	Findings	Mechanisms	References
Kushecarpin D	Inhibition of endothelial cell proliferation, cellular migration, adhesion, and tube formation	Inhibition of endothelial cell proliferation via G2/M phase cell cycle arrest	Pu et al. (2013)
Lycopene	Antiangiogenic	Inhibition of MMP-2/uPA system through VEGFR2-mediated PI3K-Akt and ERK/p38 signaling pathways	Chen et al. (2012)
Leucosesterterpenone	Antiangiogenic	Downregulation of phosphorylated ERK1/2	Hussain et al. (2008)
Luteolin	Inhibition of VEGF-induced angiogenesis	Inhibition of VEGF-induced PI3K activity, and VEGFR-2 activitiy	Bagli et al. (2004), Pratheeshkumar et al. (2012a)
Methylalpinumisoflavones	Antiangiogenic	Inhibition of HIF pathway	Liu et al. (2009)
Norisoboldine	Inhibition of VEGF-induced endothelial migration	Inhibition of cAMP, PKA, NF-κB, and Notch1 signaling pathway	Lu et al. (2013)
Oleanolic acid	Inhibition of angiogenesis	Inhibition of VEGFR2, ERK1/2, STAT3, Hedgehog pathways	Niu et al. (2018)
Olivetoric acid	Inhibition of endothelial cell proliferation and tube formation	Inhibition of filamentous actin polymerization	Koparal et al. (2010)
Platycodin D	Antiangiogenic	Inhibition of VEGFR2-mediated signaling pathway	Luan et al. (2014)
Plumbagin	Inhibition of angiogenesis	Inhibition of VEGFR2-mediated Ras/MEK and Ras/Rac/cofilin signaling pathways	Lai et al. (2012)
Pterogynidine	Inhibition of angiogenesis	Reduction of NF-κB activity	Lopes et al. (2009)
Punarnavine	Inhibition of angiogenesis	Downregulation and inhibition of VEGF, ERK, MMP-2, and MMP-9	Saraswati et al. (2013a), Manu and Kuttan (2009)
Quercetin	Inhibition of angiogenesis	Regulation of VEGFR- 2 regulated AKT/mTOR/P70S6K signaling pathways	Pratheeshkumar et al. (2012b)
Raddeanin A	Inhibition of angiogenesis	Inhibition of VEGF-induced phosphorylation of VEGFR2, and PLCγ1, JAK2, FAK, Src, and Akt protein kinases	Guan et al. (2015)
Resveratrol	Inhibition of VEGF-induced angiogenesis	Regulation of Erk1/2, Akt, MAPK phosphorylation, expression of S6 protein, and HIF-1α, IFN-γ secretion, and TAM programming	Wu et al. (2018), Jeong et al. (2014)
Rhamnazin	Antiangiogenic	Inhibition of VEGFR2, Akt, MAPK, and STAT3 phosphorylation	Yu et al. (2015)

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Table 1.5 Antiangiogenic natural products—cont'd

Natural products	Findings	Mechanisms	References
Rhein	Antiangiogenic	Inhibition of PI3K, Akt, ERK, HIF-1α, VEGF, and EGF	Zhou et al. (2015)
Rosmarinic acid	Inhibition of endothelial cell tube formation	Inhibition of endothelial cell proliferation via G2/M phase cell cycle arrest with increase of $p21^{WAF1}$ expression	Kim et al. (2009b)
Rottlerin	Antiangiogenic	Downregulation of ECE-1 and inhibition of cyclin D1 and NF-κB	Maioli and Valacchi (2010), Valacchi et al. (2011)
Salvianolic acid B	Promotion of cell growth and differentiation	Upregulation of MMP-2, VEGF, VEGFR2, and Tie-1	Lay et al. (2003)
Salvicine	Antiangiogenic	Inhibition of bFGF expression	Zhang et al. (2013b)
Santalol	Inhibition of angiogenesis	Inhibition of VEGFR2-mediated AKT, mTOR, and P70S6K signaling pathway	Saraswati et al. (2013b)
Secalonic acid D	Antiangiogenic	Downregulation of HIF-1α, VEGF, Akt, mTOR, p70S6K signaling cascade	Guru et al. (2014)
Silibinin	Antiangiogenic	Downregulation of HIF-1α, VEGF, COX-2, MMP-9 expression, and PI3K, mTOR pathways, and inhibition of EGFR, ERK, Akt, and STAT3 phosphorylation	Tilley et al. (2016), Kim et al. (2014)
Sprengerinin C	Antiangiogenic	Inhibition of VEGFR2, PI3K, Akt, mTOR, MAPK, and MMPs	Zeng et al. (2013)
Streptochlorin	Antiangiogenic	Inhibition of TNF-α-induced NF-κB	Choi et al. (2007)
Taxol	US Food and Drug Administration (FDA) approved antiangiogenic drug	Inhibition of VEGF, HIF-1α production, and disruption of microtubule cytoskeleton	Foa et al. (1994), Escuin et al. (2005)
Taxotere (Docetaxel)	US Food and Drug Administration (FDA) approved antiangiogenic drug	Inhibition of VEGF production and disruption of microtubule cytoskeleton	Avramis et al. (2001), Hotchkiss et al. (2002)
Thymoquinone	Antiangiogenic	Inhibition of VEGF and NF-κB	Paramasivam et al. (2012)
Trabectedin	Antiangiogenic	Upregulation of the inhibitors of matrix metalloproteinases TIMP-1 and TIMP-2	Dossi et al. (2015)
Triptolide	Inhibition of proliferation and angiogenesis	Inhibition of VEGF expression, COX-1, COX-2 and 5-lipoxygenase, and downregulation of NF-κB pathway	Ma et al. (2013), Zhu et al. (2009), He et al. (2010)

Table 1.5 Antiangiogenic natural products—cont'd

Natural products	Findings	Mechanisms	References
Tylophorine	Inhibition of VEGF-induced cell proliferation, cellular migration, and endothelial tube formation	Inhibition of VEGFR2 tyrosine kinase activity and PI3K/Akt/MTOR signaling pathways	Saraswati et al. (2013c)
Ursolic acid	Antiangiogenic	Inhibition of VEGF-A, βFGF, STAT3, Akt, p70S6K, and Hedgehog pathways	Kashyap et al. (2016)
Usnic acid	Inhibition of endothelial cell proliferation, cellular migration, and endothelial tube formation	Suppression of VEGFR2-mediated AKT and ERK1/2 signaling pathways	Song et al. (2012)
Valproic acid	Antiangiogenic	Inhibition of VEGF, VEGFR2, and bFGF	Zhang et al. (2014)
Vincristine	Inhibition of angiogenesis	Inhibition of VEGF production and disruption of microtubule cytoskeleton	Avramis et al. (2001), Mans et al. (2000)
Voacangine	Inhibition of endothelial cell proliferation, VEGF-induced endothelial tube formation, and chemoinvasion	Inhibition of VEGF, VEGFR, and HIF-1α	Kim et al. (2012)
Vulpinic acid	Inhibition of angiogenesis	Inhibition of endothelial tube formation	Koparal (2015)
Withaferin A	Inhibition of angiogenesis	Inhibition of MMP-9, VEGF, Akt, and NF-κB	Lee et al. (2013b), Wang et al. (2015b)
Xanthohumol	Inhibition of angiogenesis	Inhibition of AKT and NF-κB pathways	Dell'Eva et al. (2007)
Zerumbone	Inhibition of angiogenesis	Inhibition of NF-κB, VEGF, and IL-8	Shamoto et al. (2014), Tsuboi et al. (2014)

reliable references about the use of a whole organism or its extract as a modulator of angiogenesis, employing this kind of angiogenesis modulator could lead to some side effects. This is because the organism or its extract contains many different compounds that belong to different chemical classes and that might have some detrimental influences along with synergic beneficial activities. Using a whole organism or its extract should be therefore considered as an angiogenesis modulation tool with unpredictable outcomes, and the active substances within these modulators should be isolated in pure forms and investigated to have an angiogenesis modulation tool with predictable outcomes. On the other hand, appropriately taking advantage of the functional foods and nutraceuticals acting as angiogenesis modulators should be considered safe because they already exist in the human diet.

Concluding remarks and future perspective

It is clear that functional foods and natural remedies are of great importance in complementary, alternative, and/or integrative medicine. Centuries-old traditional knowledge and the modern literature frankly reveal that nature is a substantial and enormous yet entirely unexplored source, although great scientific effort and research funds have been invested in this field by researchers, practitioners, and governments. Great scientific efforts and government financial support, therefore, have continued to be consumed to discover and design novel functional foods and natural remedies. Although both researchers and governments seem to be aware of the importance of natural resources, the natural product studies seem to be in infancy because there is restricted literature about natural product activities on diseases through identifying the related cellular control mechanisms, signal transduction processes, and biological factors. It could be plainly viewed that more in vitro, in vivo, and in silico studies should be performed to identify the multitargets of natural products rather than focusing on a single aspect of the disease. Thus, new combinational treatment strategies can be designed by using natural products as adjuvants or synergistic components. Discovery of functional foods and natural remedies that have a role as angiogenesis modulators has a special significance for employing them as preventive, prophylactic, or therapeutic agents because there are many angiogenesis-borne diseases without convenient medical cures available such as cancer, neurodegenerative diseases, etc. Therefore, more research projects should be developed and more research funds should be provided to light up the activity mechanisms of natural products on the modulation of angiogenesis for employing them to serve for the welfare of patients who have an angiogenesis-dependent disease.

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