Carrillo, P. et al. (2023). Extracellular Matrix Remodeling Enzymes as Targets for Natural Antiangiogenic Compounds. In: Papadimitriou, E., Mikelis, C.M. (eds) Matrix Pathobiology and Angiogenesis. Biology of Extracellular Matrix, vol 12. Springer, Cham. https://doi.org/10.1007/978-3-031-19616-4_6

Libro: Matrix Pathobiology and Angiogenesis.

ISBN: 978-3-031-19615-7

Extracellular Matrix-Remodeling Enzymes as Targets for Natural Antiangiogenic Compounds

Paloma Carrillo[1,2] *, Melissa García-Caballero[1,2] *, Manuel Bernal[1,2†], María Inmaculada Manrique-Poyato[1†], Beatriz Martínez-Poveda[1,2,3], Ana R. Quesada[1,2,4], Miguel Ángel Medina[1,2,4]§.

[1]Universidad de Málaga, Andalucía Tech, Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, E-29071 Málaga, Spain

[2]IBIMA (Biomedical Research Institute of Málaga), E-29071 Málaga, Spain

[3] CIBER de Enfermedades Cardiovasculares (CIBERCV, Instituto de Salud Carlos III, Madrid)

[4]CIBER de Enfermedades Raras (CIBERER), E-29071 Málaga, Spain

*, † These authors contributed equally §Corresponding author

Abstract Angiogenesis, or new blood vessels formation, comprises a series of tight regulated and coordinated steps guided by the balance between proangiogenic and antiangiogenic signals. Although physiological angiogenesis occurs in some context such as embryogenesis or wound healing, it is a very restricted process in adults, therefore, it is associated to several pathologies as cancer, arthritis or age-related macular degeneration. For this purpose, plenty of compounds from natural sources have been studied and their antiangiogenic potential has been demonstrated. Most of them are isolated from plants, such as the major catechin found in green tea epigallocatechin-3-gallate *(*EGCG) or the isoflavonoid genistein. Nevertheless, compounds with antiangiogenic potential can be found in several species of animals, fungi, algae or bacteria, for instance, aeroplysinin-1, AD0157, carrageenan derivates and rapamycin, respectively. The extracellular matrix (ECM) remodeling plays a key role in the formation of new blood vessels. The degradation of the ECM components not only provides a structural scaffold for the nascent vessels, but it is also strongly involved in endothelial cell signaling, promoting or inhibiting this complex process. In this regard, targeting the ECM components entails an interesting therapeutic strategy for the treatment of angiogenesis-related diseases. This book chapter is an updated overview of natural compounds with an antiangiogenic effect with the capability to target one or more EMC components.

Keywords Angiogenesis, Extracellular matrix, Natural antiangiogenic compounds

1. The extracellular matrix and its role in angiogenesis

The extracellular matrix (ECM) term refers to the non-cellular component present within all tissues and organs that provides physical, adhesive and mechanical support for the cells. The ECM participates in crucial biochemical and biophysical processes for tissue morphogenesis, differentiation, homeostasis, and storage and release of bioactive molecules (Theocharis et al. 2019). Although each tissue has an ECM with a unique topology and composition, which is defined during tissue development, the ECM is generally composed of laminin, nidogens, type IV collagen, and heparan sulphate proteoglycans (HSPG), that separate cells from the interstitial matrix (Walker et al. 2018). In the space limited by the basement membranes, named as extracellular/pericellular space, a complex molecular network created by interactions of matrix components and interactions with non-matrix molecules establish the dialogue between the cellular components and their microenvironment, further defining cell behavior and function (Muncie and Weaver 2018). In fact, the crosstalk between the ECM components and the proteases, growth factors, cytokines and chemokines that bind to the ECM plays a pivotal role in physiological but also in pathological processes, ultimately orchestrating complex signaling cascades and the cell response to extracellular stimuli. It is worth mentioning that the ECM is a dynamic structure since its composition and structural organization change during embryogenesis, adult physiological conditions and pathological contexts such as cancer, inflammation and wound healing (Yamada et al. 2019; Walma and Yamada, 2020; Winkler et al. 2020). These variations include the presence of specific proteins typical of embryogenesis or associated with tissue remodeling.

One of the physiological processes that take place in the ECM environment is angiogenesis or the blood vessel growth from the existing vasculature. The new blood vessel is composed of two interacting cell types, endothelial cells, which form the inner lining of the vessel wall, and perivascular cells, also known as pericytes, vascular smooth muscle cells or mural cells, that envelop the surface of the vascular tube (Carmeliet and Jain 2011). It has been largely described how in the angiogenic process the ECM is not a mere physical scaffolding for the endothelial cells but regulates each step of the cascade. The multiple stages that make up angiogenesis are finely coordinated and occur in a sequential and interdependent manner. For the formation of new blood vessels through the process of angiogenesis, pro-angiogenic factors signal the quiescent endothelial cells that conform the capillaries, promoting the activated state in these cells and the differentiation into stalk or proliferating cells and tip or migrating cells. This activation includes a cascade of events that promotes the detachment of mural cells from the vessel, the degradation of the underlying basement membrane, the migration and proliferation of endothelial cells and the formation of an immature capillary structure (Vaeyens et al. 2020). Once the new capillary is formed, takes place its remodeling, the recruitment of mural cells and the deposition of a new basement membrane to complete vessel maturation. In all these events endothelial cells interact with the matrix producing proteases necessary for the ECM degradation and molecules for the formation of the new basement membrane (Ma et al. 2020) (Fig 1).

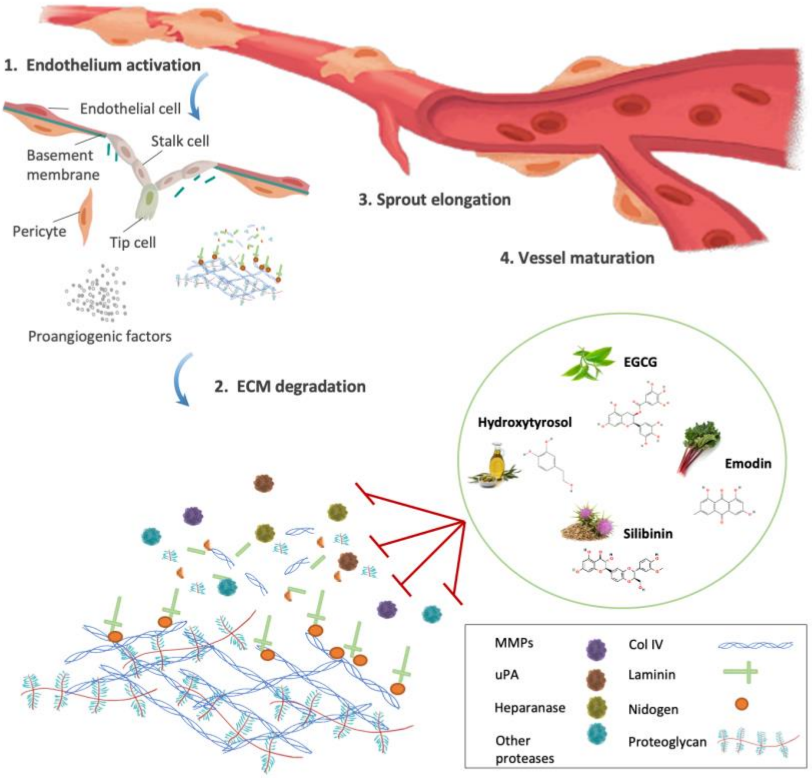

Fig 1. The angiogenic process and families of compounds targeting ECM enzymes. The scheme illustrates the 4 main steps of the angiogenic processes: 1) Endothelium activation, characterized by the binding of proangiogenic factors to their respective receptors on endothelial cells and the subsequent differentiation into tip and stalk cells, parallel to the mural cells detachment mural cell detachment; 2) ECM degradation, in which the activated endothelium releases proteolytic enzymes in order to degrade the basement membrane and the surrounding ECM. Several natural compounds have a pleiotropic effect and target different ECM enzymes resulting in the inhibition of the angiogenic process. Some examples are ECGC, emodin, hydroxytyrosol or silibinin, which can simultaneously inhibit various ECM proteases; 3) sprout elongation, when the activated endothelial cells proliferate and migrate across the ECM; and 4) vessel maturation, final step in which the elongation

stops. Finally, basement membrane is restored, and mural cells are recruited giving rise to a mature vessel.

In a physiological scenario, the above-mentioned steps of angiogenesis are finely coordinated by a delicate balance between pro-angiogenic and anti-angiogenic signals, being the ECM network a key player in the maintenance of this balance. In fact, a plethora of angiogenesis regulatory factors, both stimulators and inhibitors, are either matrix molecules or fragments derived from the ECM. The number of endogenous inhibitors of angiogenesis that are produced by the ECM protease-mediated cleavage is continuously growing. Some of the, such as endostatin, vastatin, and restin, among others, are being explored for the design of antiangiogenic therapies for neoplastic and non-neoplastic angiogenesis-related diseases (Ma et al. 2020).

Finally, the mechanical properties of the ECM, determined by their composition, can profoundly affect cell behavior (Marchand et al. 2019). The ECM stiffness and spatial dimensionality establish tensile forces that act through the tubulin and the actin cytoskeleton providing traction, directionality and orientation for the migrating cells in the nascent vessel (Marchand et al. 2019). Thus, stimulated endothelial cells directly influence the physico-mechanical properties of the surrounding ECM to support vessel formation through changes in protein synthesis, polymerization and fibril formation (Nia et al. 2020; Vaeyens et al. 2020). Figure 1 summarizes the angiogenic process and different compounds targeting more than one ECM enzymes.

2. Pharmacological targeting of ECM by natural compounds in pathological angiogenesis

Judah Folkman's studies promoted a fundamental change in the concept of angiogenesis, which went from being understood as a physiological process mainly associated with embryonic development and wound healing, to being considered a potent pharmacological target with great possibilities for the treatment of diseases that courses with impaired regulation of the process (Quesada et al. 2010; Ribatti, 2021). The basis for antiangiogenic therapy in cancer and other angiogenesis-dependent diseases was then established. However, the apparent simplicity of the model of activation and inactivation of the "angiogenic switch" as a pharmacological strategy against the onset and development of certain diseases, is in contrast with the complexity of the process itself (Quesada et al. 2007). Precisely, this inherent complexity is the basis of most of the observed complications related to the use of anti-angiogenic therapies, since different drawback, such as development of compensatory mechanisms, redundancy in the activation pathways and multiplicity in the effectors, have been described in relation to the use of angiogenic inhibitors in clinics and disease models (Medina et al., 2007; Jászai and Schmidt 2019). For example, as a consequence of these events, the initial optimism about the VEGF-targeting therapy in the treatment of cancer, was rapidly discarded (Vasudev and Reynolds 2014). Currently, the pharmacological modulation of angiogenesis is mostly conceived as a multi-target strategy, and research in this field is focused to the identification of new targets for the pharmacological modulation of this process and the finding and evaluation of potential anti-angiogenic drugs with high effectiveness for the treatment of angiogenesis-dependent diseases, either as monotherapy or in a combinatory approach (Quesada et al. 2006; Lopes-Coelho et al. 2021).

In the search of new potential modulators of angiogenesis, bioactive compounds derived from natural products, including terrestrial and marine plants, fungus, microorganisms, sponges, and even foods (fruits, vegetables, spices, seeds, oils…), are gaining increasing attention as drug candidates or lead structures for drug design, due to their unusual chemical features. In fact, the use of therapeutic compounds derived from plants for the inhibition of pathological angiogenesis may render a series of advantages, such as general availability, low price of products, multiple pharmacological activities, and a good profile of ADME and tolerability (Khalid et al. 2016; Lu et al. 2016; Ribeiro et al. 2018). In line with the concept of multi-target strategy in the therapeutic intervention of angiogenesis, the ECM represent a complex network of molecules that could be potential pharmacological anti-angiogenic targets. Among these molecules, those enzymes that participate in the remodeling of the ECM, revised in the next section, have received a special interest in biomedical and pharmacological research (Su et al. 2016; Liu and Khalil 2017; Fields 2019; Mohan et al. 2019).

Table 1 includes an updated compilation of natural antiangiogenic compounds that have been reported to target different enzymes involved in ECM remodeling. For many compounds included in Table 1, it has been described a pleiotropic function, acting on different ECM remodeling enzymes (see also Figure 1). This is the case of compounds such as curcumin, hydroxytyrosol, genistein, luteoin or epigallocatechin-3-gallate (EGCG). It is also worth mentioning that many of these compounds show other bioactivities, exhibiting antioxidative and anti-inflammatory potential.

In addition, Figure 2 shows the distribution of the compounds listed in Table 1 into the different kingdoms (Figure 2A) and the ECM molecular targets of these compounds (Figure 2B).

Table 1. Natural antiangiogenic compounds targeting ECM enzymes

Natural product	**Source**	**Kingdom**	**Molecular Target**	**Reference**
(+)-Catechin	Several plants	Plants	Elastase Collagenase	Wittenauer et al. 2015
12-O-(2′E,4′E-decadienoyl)-4-hydroxyphorbol-13-acetyl	*Daphne genkwa*	Plants	MMP-3	Wang et al. 2018
20(R)-Ginsenoside Rg3	*Panax ginseng* (root)	Plants	MMP-2 MMP-9	Yue et al. 2006
3-Hydroxyflavone	Several plants	Plants	MMP-1 MT1-MMP MMP-2 TIMP-1 TIMP-2 uPA PAI-1	Kim 2003
3′ -Hydroxygenkwain	*Daphne genkwa*	Plants	MMP-3	Zhou et al. 2021
4-Methylumbelliferone	Apiaceae family	Plants	MMP-2	García-Vilas et al. 2013
7-Epiclusianone	*Garcinia brasiliensis*	Plants	Cathepsin B and G	Murata et al. 2010
Acacetin	*Robinia pseudoacacia* & *Turnera diffusa*	Plants	MMP-2	Bhat et al. 2013
Acidic mucopolysaccharide	*Holothuria leucospilota*	Animals	MMP-2 MMP-9	Zhang et al. 2009
AD0157	*Paraconiothyrium sp.*	Fungi	MMP-2	García-Caballero et al. 2014
Aeroplysinin-1	*Aplysina aerophoba* (and other species of Verongida order)	Animals	MMP-2 uPA PAI-1	Martínez-Poveda et al. 2013 Rodríguez-Nieto et al. 2002
AITC (Allyl isothiocyanate)	*Brassica nigra,* *Lepidum sativum,* *Wasabia japonica,* *Raphanus sativus* & *Sinapis species*	Plants	TIMP-1	Thejass and Kuttan 2007a
Alitretinoin	Several foods of animal origin	Animals	MMP-2	Kvestad et al. 2014
Aloe-emodin	*Aloe vera* and others	Plants	MMP-2 uPA	Cárdenas et al. 2006
Andrographolide	*Andrographis paniculata*	Plants	MMP-2 MMP-9	Pratheeshkumar and Kuttan 2011
Apigenin	*Matricaria recutita,* *Daphne genkwa &* *Chamaemelum nobile*	Plants	MMP1 MT1-MMP MMP-2 MMP-3 TIMP-1 TIMP-2 uPA	Lamy et al. 2012 Kim 2003 Zhou et al. 2021

			PAI-1	
Apigenin-7-O-β-D-glucoside	*Daphne genkwa*	Plants	MMP-3	Zhou et al. 2021
Aplidine (Dehydrodidemnin B)	*Aplidium albicans*	Animals	MMP-2 MMP-9	Taraboletti et al. 2004
Arctigenin	*Arctium lappa* (seed)	Plants	MMP-2 MMP-9 Heparanase	Lou et al. 2017
Baicalein	*Scutellaria baicalensis*	Plants	MMP-2 Elastase	Liu et al. 2003 Sartor et al. 2002
Baicalin	*Scutellaria baicalensis*	Plants	MMP-2	Liu et al. 2003
Bestatin	*Streptomyces olivoreticuli*	Monera	Heparanase MMP-9	Hossain et al. 2016
BITC (Benzyl Isothiocyanate)	Brassicaceae family	Plants	MMP-2	Boreddy et al. 2011
C3G (Cyanidin- 3-O-glucoside)	Several plants and food	Plants	MMP-2	Anwar et al. 2014
Carnosic acid	*Rosmarinus officinalis* (leaves)	Plants	MMP-2	López-Jiménez et al. 2013
Carnosol	*Rosmarinus officinalis* (leaves)	Plants	MMP-2	López-Jiménez et al. 2013
κ and λ−carragenaans	Red algae	Protist	Heparanase	Niu et al. 2015 Ishai-Michaeli et al. 1990
Celastrol	*Trypterigium wilfordii*	Plants	MMP-1 MMP-9	Li et al. 2012
Chymostatin	*Streptomyces sp*	Monera	Cathepsins A, B, D, K	Vidal-Albalat and González 2016 Umezawa et al. 1970
Cryptotanshinone	*Salvia miltiorrhiza*	Plants	MMP-2 MMP-9 TIMP-1 TIMP-2	Zhang et al. 2018
CS5931	*Ciona savignyi*	Animals	MMP-2 MMP-9	Liu et al. 2014
Cucurbitacin E	Cucurbitaceae family	Plants	MMP-2 MMP-9	Sinha et al. 2016
Curcumin	*Curcuma longa* (rhizome)	Plants	MMP-2 MMP-9 MT1-MMP TIMP-2 uPA Elastase	Yodkeeree et al. 2009 Thaloor et al. 1998 Liu et al. 2003 Sartor et al. 2002
DADS (Diallyl disulfide)	*Allium sativum*	Plants	MMP-2 MMP-9 TIMP-1	Meyer et al. 2004 Thejass and Kuttan 2007b
Damnacanthal	*Morinda citrifolia* (root)	Plants	MMP-1 MMP-2 TIMP-1 TIMP-4 uPA	García-Vilas et al. 2017a

			PAI-1	
Danshensu	*Radix Salviae Miltiorrhizae*	Plants	MMP-2 MMP-9	Zhang et al. 2010a
Daphnetin	*Changbai daphne*	Plants	MMP-2	Kumar et al. 2016
Daphnodorin G	*Daphne genkwa*	Plants	MMP-3	Zhou et al. 2021
DATS (Diallyl trisulfide)	*Allium sativum*	Plants	MMP-2 MMP-7 MMP-9 uPA	Lai et al. 2015
Defibrotide	Porcine mucosal DNA	Animals	Heparanase	Barash et al. 2018
Demethoxycurcumin	*Curcuma aromatica* (rhizome)	Plants	MMP-9	Kim et al. 2002
Dihydroartemisinin	*Artemisia annua*	Plants	MMP-9	Wang et al. 2011
ECAP (Epicatechin 3-O-β-D-allopyranoside)	*Davallia bilabiata*	Plants	MMP-2 TIMP-2 MMP-14	Liu et al. 2017
EGCG (Epigallocatechin-3-gallate)	*Camellia sinensis* (leaves)	Plants	MMP-2 MMP-9 MT1-MMP uPA Elastase Collagenase PAI-1	Oku et al. 2003 Yamakawa et al. 2004 Cale et al. 2010 Jankun et al. 1997 Madhan et al. 2007 Wittenauer et al. 2015 Donà et al. 2003 Sartor et al. 2002
Elaiophylin	*Streptomyces melanosporus* 17JA11	Monera	MMP-2 MMP-9	Lim et al. 2018
Ellagic Acid	*Phyllanthus urinaria*	Plants	MMP-2 MMP-9	Wang et al. 2012 Huang et al. 2011b Huang et al. 2011a
Embelin	*Embelia ribes* (fruit)	Plants	MMP-2 MMP-9 PAI-1	Lin et al. 2013 Huang et al. 2014
Emodin	*Rheum palmatum* (root and rhizome)	Plants	MMP-2 MMP-9 uPA Trypsin	Kwak et al. 2006 Jedinák et al. 2006a Shi and Zhou 2018
Esculetin	*Artemisia scoparia*	Plants	MMP-2	Park et al. 2016
Farnesiferol C	*Ferula assafoetida*	Plants	MMP-2	Lee et al. 2010

Ferulic acid	*Cimicifuga heracleifolia*, *Angelica sinensis* & *Lignsticum chuangxiong*)	Plants	MMP-2 MMP-9	Yang et al. 2015
Formononetin	*Astragalus membranaceus* (dried root)	Plants	MMP-2 MMP-9	Wu et al. 2015
Gallic acid	*Toona sinensis* (leaf)	Plants	MMP-2 MMP-9	Hseu et al. 2011
Genistein	Soybeans	Plants	MMP-1 MMP-2 MMP-9 MT1-MMP TIMP-1 TIMP-2 uPA PAI-1	Yu et al. 2012 Kim 2003 Fajardo et al. 1999
Genkwanin	*Daphne genkwa*	Plants	MMP-3	Zhou et al. 2021
Ginsenoside compound K	*Panax ginseng*	Plants	MMP-2 MMP-9	Shin et al. 2014
Halofuginone	*Dichroa febrifuga*	Plants	MMP-2	Elkin et al. 2000
Harmine	*Peganum harmala* (seed)	Plants	MMP-2 MMP-9 TIMP-1	Hamsa and Kuttan 2010
HBA (4-Hydroxybenzyl alcohol)	*Gastrodia elata*	Plants	MMP-9	Laschke et al. 2011
Homocysteine	Methionine	Animals Plants Fungi Monera Protist	MMP-2 uPA PAI-1	Rodríguez-Nieto et al. 2002 Midorikawa et al. 2000
Hydrangenol	*Hydrangea macrophylla*	Plants	MMP-2	Gho et al. 2019
Hydroxygenkwanin-5-O-β-D-glucoside	*Daphne genkwa*	Plants	MMP-3	Zhou et al. 2021
Hydroxytyrosol	*Olea europaea* (virgin olive oil)	Plants	MMP-1 MMP-2 MMP-9 TIMP-1 TIMP-2 TIMP-4	García-Vilas et al. 2017b Scoditti et al. 2012 Fortes et al. 2012

			uPA uPAR	
Hyperforin	*Hypericum perforatum*	Plants	MMP-2 uPA	Martínez-Poveda et al. 2005a
Hypericin	*Hypericum sp*	Plants	MT1-MMP uPA Trypsin	Jedinák et al. 2006a Lavie et al. 2005 Martínez-Poveda et al. 2005b
Hyperoside	Hypericum & Crataegus Genera	Plants	MMP-2 MMP-7 uPA	Jedinák et al. 2006a Wu et al. 2020 Liu et al. 2016
Imperatorin	*Angelica dahurica* & *Angelica archangelica*	Plants	MMP-2	Li et al. 2021
Ipobscurine-A	*Ipomoea obscura*	Plants	MMP-2 MMP-9 TIMP-1	Hamsa and Kuttan 2011
Isoliquiritigenin	*Glycyrrhiza uralensis* (root)	Plants	MMP-2 MT1-MMP TIMP-2	Kang et al. 2010 Wang et al. 2013
Kahweol	*Coffea Arabica* (coffee bean)	Plants	MMP-2 uPA	Cárdenas et al. 2011
Leupeptin	*Streptomyces exfoliatus*	Monera	Cathepsins A, B, D, K	Baici and Gyger-Marazzi 1982 Vidal-Albalat and González 2016
Lupeol	Several plants	Plants	MMP-2 MMP-9 Elastase	Mitaine-Offer et al. 2002 Vijay Avin et al. 2014
Luteolin	Several plants	Plants	MMP-2 MMP-9 ADAMTS-4/5 Elastase	Pratheeshkumar et al. 2012 Lamy et al. 2012 Moncada-Pazos et al. 2011 Siedle et al. 2007
Luteolin-5-O-β-D-glucopyranoside	*Daphne genkwa*	Plants	MMP-3	Zhou et al. 2021
Lycopene	*Solanum lycopersicum*	Plants	MMP-2 TIMP-2 uPA	Chen et al. 2012

Melatonin	Several species	Plants Animals Monera Fungi Protist	MMP-2 MMP-9	Yan et al. 2021
Nobiletin	*Citrus depressa* & *Citrus reticulate* (fruit)	Plants	MMP-2 uPA	Kunimasa et al. 2010
Novobiocin	*Streptomyces niveus*	Monera	MMP-2	Yang et al. 2003
Oleanolic acid	Several plants	Plants	Elastase	Kim et al. 2009
Oleuropein	*Olea europaea* (virgin olive oil)	Plants	MMP-9	Scoditti et al. 2012
Panduratin A	*Boesenbergia rotunda*	Plants	MMP-2	Lai et al. 2012
PG (Piceatannol-3-O-β-D-glucopyranoside)	*Rheum undulatum* (rhizome)	Plants Fungi	MMP-9	Kim and Ma 2019
Phloretin	Several plants	Plants	MMP-2 MMP-3 Cathepsin S Elastase	Leu et al. 2006 Hsiao et al. 2019
Picroside II	*Picrorhiza kurroa*	Plants	MMP-9	Lou et al. 2019
Piperlongumine	*Piper longum* (fruit)	Plants	MMP-2 MMP-9	Kumar and Agnihotri 2021
PITC (phenyl isothiocyanate)	*Brassica nigra*, *Lepidum sativum*, *Wasabia japonica*, *Raphanus sativus* & *Sinapis species*	Plants	TIMP-1	Thejass and Kuttan 2007a
Protocatechuic acid	Pleurotus tuber-regium & *Agrocybe aegerita* (sclerotium)	Fungi	MMP-2	Hu et al. 2018
Punarnavine	*Boerhaavia diffusa*	Plants	MMP-2 MMP-9 TIMP-2	Saraswati et al. 2013a
Quercetin	Several plants	Plants	MMP-2 MMP-9 Trypsin Thrombin uPA Elastase	Tan et al. 2003 Scoditti et al. 2012 Pilátová et al. 2010

				Jedinák et al. 2006a Kanashiro et al. 2007 Sartor et al. 2002
Rapamycin	*Streptomyces hygroscopicus*	Monera	ADAM10	Zhang et al. 2010b
Resveratrol	Several Plants	Plants	MMP-2 MMP-9	Zhang et al. 2010b Scoditti et al. 2012 Cao et al. 2005
Rhaponticin	*Rheum undulatum*	Plants	MMP-9	Kim and Ma 2018
Rhein	*Rheum palmatum, Cassia tora, Polygonum multiflorum* and Aloe *barbadensis*	Plants	Trypsin uPA	Jedinák et al. 2006a
Salicin	Genus *Salix* (willow bark)	Plants	Thrombin	Jedinák et al. 2006a
Silibinin	*Silybum marianum* (fruits)	Plants	MMP-2 uPA Trypsin Thrombin	Singh et al. 2005 Jedinák et al. 2006a Jiang et al. 2000
Sulforaphane	Brassicaceae family	Plants	MMP-2 TIMP-2	Bertl et al. 2006
Sulodexide	Porcine intestinal mucosa	Animals	Heparanase MMP-9	Masola et al. 2012
Syringic acid	Pleurotus tuber-regium & *Agrocybe aegerita* (sclerotium)	Fungi	MMP-2	Hu et al. 2018
Tannic acid	Several plants	Plants	PAI-1	Cale et al. 2010
Tanshinone IIA	*Salvia miltiorrhiza* (dried root and rhizome)	Plants	MMP-2 TIMP-2	Tsai et al. 2011
Theaflavin-3,3'-digallate	*Camellia sinensis* (black tea)	Plants	PAI-1	Jankun 2011
Theaflavin-3'-gallate	*Camellia sinensis* (black tea)	Plants	PAI-1	Jankun 2011

TICMs (Trypsin inhibitor from extract of *C. melo* seeds)	*Cucumis melo* (seeds)	Plants	MMP-2 MMP-9	Rasouli et al. 2017
Toluquinol	*Penicillium sp.*	Fungi	MMP-2	García-Caballero et al. 2013
Triptolide	*Trypterygium wilfordii*	Plants	ADAM10	Soundararajan et al. 2009
Tylophorine	*Tylophora indica*	Plants	MMP-2 MMP-9	Saraswati et al. 2013b
Ursolic acidc	Several plants	Plants	MMP-2 MMP-9 TIMP-1 uPA Cathepsin B Elastase	Kanjoormana and Kuttan 2010 Cárdenas et al. 2004 Ying et al. 1991 Jedinák et al. 2006b Mitaine-Offer et al. 2002
Zerumbone	*Zingiber zerumbet* (rhizome)	Plants	MMP-9	Samad et al. 2018
β-Carotene	Several plants and food	Plants	MMP-2 MMP-9 TIMP-1 TIMP-2	Guruvayoorappan and Kuttan 2007
γ-tocotrienol	Several plants and food	Plants Animals	MMP-9	Li et al. 2011

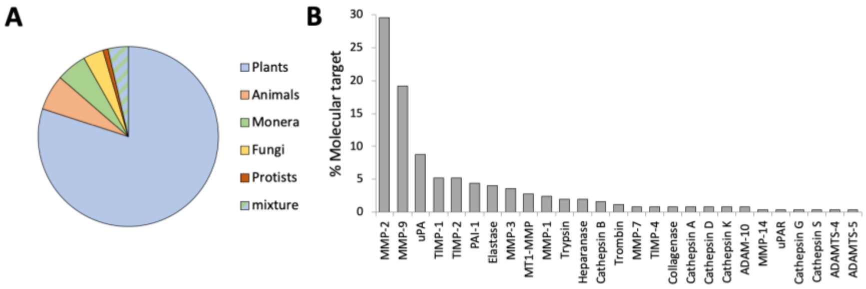

Fig 2. Distribution of natural antiangiogenic compounds according to kingdoms and ECM targets. A) Distribution of natural antiangiogenic compounds into the different kingdoms. Mixture category includes all those compounds that are present in more than one kingdom. B) Graph shows molecular target distribution for the final 110 natural compounds; 27 different enzymes are involved in the ECM remodeling.

3. Matrix remodeling enzymes as therapeutic targets in angiogenesis

The main players involved in the ECM remodeling are presented in this section, with a focus on how they can be potential therapeutic targets in modulating angiogenesis. Matrix metalloproteinases (MMPs) are members of an enzyme family of calcium-dependent endopeptidases that require a zinc ion for their catalytic activity. This family targets molecules including growth factors, matrix components, cytokines, adhesion and signaling molecules (Quintero-Fabián et al. 2019). MMPs, synthesized and secreted as inactive latent enzymes (zymogens) that can be activated after their cleavage by diverse proteases, including other MMPs. MMPs are active at neutral pH catalyzing the normal turnover of various ECM macromolecules. The MMPs can be classified into six different groups: gelatinases, collagenases, matrilysins, stromelysins, membrane-bound MMPs (MT-MMPs), and other MMPs according to their substrate specificity and domain homology (Cui et al. 2017). MT-MMPs are located on the plasma membrane by a transmembrane domain or by a GPI anchor, being active, once furin convertases recognize a specific motif on their core protein. MMPs function is controlled by other proteases, or by binding with matrix components, and inhibited by MMP tissue inhibitors, named as TIMPs (Cui et al. 2017).

Although MMPs are the main ECM remodeling enzymes studied as therapeutic targets in pathological angiogenesis, there are plenty of compounds isolated from natural sources with the capability to inhibit additional ECM remodeling enzymes, such as those which belongs to the PA (plasminogen activator) system, heparanase or cathepsins, and whose antiangiogenic activity had been demonstrated.

ADAMs are families of zinc-dependent transmembrane proteases that contains disintegrin, cysteine-rich, and epidermal growth factor (EGF) domains, and ADAMTSs, are proteases secreted in the ECM that contains the thrombospondin (TSP) type-1 motifs instead of EGF motifs (Zhong and Khalil 2019). In the MMP and ADAMTS families there are more than 20 members and their role in angiogenesis has been largely studied in the context of cancer (Sun et al. 2015; Quintero-Fabián et al. 2019).

Elastases are serine proteases produced by the pancreas which participate in the breakdown of elastin, a protein that offer elasticity to connective tissue. Elastases catalyse the cleavage of carboxyl groups present in small hydrophobic amino acids, such as glycine, valine and alanine. Around eight genes encode elastase or elastase-like enzymes, four of which are classified as chymotrypsin-like (Heinz 2020).

Other crucial proteases involved in the ECM remodeling during angiogenesis are the serine proteases urokinase plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA), which participate in the plasminogen to active plasmin conversion (Gonias and Zampieri 2020). Plasminogen activators/plasmin cascade can target different matrix elements and molecules and activate MMPs (Breuss and Uhrin 2012; Gonias and Zampieri 2020). Granzymes are serine proteases present in the ECM that, being produced by immune and non-immune cells, can modulate the cell-matrix interactions by degradation of matrix and junctional proteins, as well as by interacting with cell surface receptors (Velotti et al. 2020). Recently, the role of some members of this family has been described in the modulation of angiogenesis (Wroblewski et al. 2017; Li et al. 2021).

Cysteine cathepsins, although present in the intracellular endolysosomal compartments, exert also their functions in the ECM by degrading numerous matrix and adhesion molecules and activating pro-uPA and MMPs. Some cathepsins are secreted in the ECM and are able to function in slight acidic conditions, prevalent in diseases including cancer and osteoarthritis (Vizovišek et al. 2019; Vidak et al. 2019). Aside from proteases, glycosaminoglycan (GAG) degrading enzymes are also implicated in the remodeling of ECM modifying the proteoglycan (PG) structure and the HS size (Smock and Meijers 2018). Six hyaluronic acid (HA)-degrading enzymes [hyaluronidases 1–4 (HYALs-1, -2, -3, and-4), HYALP, and PH20) have been described in humans (Dogné and Flamion 2020). Some of them are active in acidic or/and in neutral pH and they degrade high molecular weight HA to smaller bioactive fragments in the ECM (Dogné and Flamion 2020). They trigger biological events such as angiogenesis, inflammation, and cancer progression (Piperigkou et al. 2021). Another GAG-degrading enzyme with pronounced functions in ECM remodeling is heparanase (Masola et al. 2018). Heparanase is an endoglucuronidase that cleaves HS chains, releasing bioactive HS fragments of 4–7 kDa. It is overexpressed in some diseases and involved in the control of processes such as cancer cell growth, metastasis, and angiogenesis (Masola et al. 2018), by activation of VEGF and FGF pathways through HS cleavage and subsequent release of these proangiogenic factors (Jayatilleke and Hulett 2020).

In the last years numerous studies have shown the important role of these proteolytic and glycolytic enzymes in the modulation of angiogenesis, and their potential as pharmacological targets in the therapeutical inhibition of these process in angiogenesis-dependent diseases, such as cancer. Despite the initial efforts to develop successful pharmacological approaches focused on the inhibition of ECM enzymes, the clinical trials performed in this line have revealed important side effects derived from the blockage of these enzymes, such as the musculoskeletal syndrome observed with nearly all the inhibitors of MMPs tested (Fingleton 2008). After the first discouragement, the better understanding about the roles of the different members of these families of ECM-enzymes in angiogenesis and related diseases has led to reopen the door to this pharmacological strategy (Winer et al. 2018). Therefore, the discovery and development of new inhibitors, highly selective and potent, that avoid the broad spectrum targeting of different members of the same family of enzymes, may open new avenues for the search of pharmacological alternatives in the treatment of angiogenesis-dependent pathologies. In this context, natural bioactive compounds represent a very attractive source of new putative drugs targeting ECM-related enzymes, and bibliography about their potential activity in these targets is summarized in this chapter.

4. Natural antiangiogenic compounds targeting MMPs

The role of MMPs in angiogenesis and other disease-related processes promoted the search of chemical inhibitors of these enzymes aiming at developing new pharmacological strategies. As mentioned above, although the first inhibitors tested in the clinics failed in the attempt to use them as therapeutic drugs, due to the broad-spectrum inhibition exhibited and the consequent side effects, the interest in the discovery of more selective and potent drug candidates is increasing year to year. The identification of new compounds (natural and synthetic) that target MMPs is still a hot spot in pharmacological research (Lenci et al. 2021).

After analyzing the current literature regarding the natural compounds exhibiting antiangiogenic activity, the conclusion is that a large number of them has been described to affect MMPs production, secretion or activity. Due to the important role of MMPs in angiogenesis, in many cases the inhibition of these key ECM remodeling family of enzymes is included as a part of the mechanism of action of the compounds capable to interfere with the angiogenic process. It is important to remark that MMP activities can be inhibited by TIMPs, which bind to the highly conserved zinc binding site of active MMPs at molar equivalence (Saraswati et al. 2013). The balance between MMPs and TIMPs plays a key role in angiogenesis regulation and is critical for the eventual ECM remodeling (Nagase et al. 2006; Quintero-Fabián et al. 2019).

Curcumin, isolated from the rhizome of *Curcuma longa* plant, is a powerful angiogenesis inhibitor and it has important inhibitory properties in the tumor initiation and growth. Human umbilical vein endothelial cells (HUVECs) treated with curcumin were inhibited to form tubes, although migration and attachment were not affected in the Matrigel assay. Importantly, upon curcumin treatment, HUVECs exhibit a decrease in the gelatinolytic activities of secreted 53-kDa and 72-kDa MMPs and displays an effect at the transcriptional and post-transcriptional level (Thaloor et al. 1998).

Mediterranean diet is an immense source of natural products, many of them with antiangiogenic and antiinflammatory properties. For example, hydroxytyrosol is one of the active compounds of the virgin olive oil and it shows a wide spectrum of proteins involved in ECM remodeling, such as MMPs. It has been reported that endothelial cells treated with hydroxytyrosol decrease MMP-1 and MMP-2 expression, and increase TIMP-1, TIMP-2 and TIMP-4 levels (García-Vilas et al. 2017b). On the other hand, it has been observed reduced angiogenic response on endothelial cells incubated with some of the Mediterranean diet polyphenolic compounds, due to the inhibition of PMA-induced COX-2 protein expression and prostanoid production, as well as MMP-9 protein release and gelatinolytic activity (Scoditti et al. 2012).

One of the most important isoflavone is the genistein, which increases MMP-2 and MMP-9 secretions and activities by VEGF stimulation. In addition, exposure to genistein decreases activation of JNK and p38, induced by VEGF. This kind of mechanism constitutes a common pathway for many compounds to exert their antiangiogenic activity and their cancer protective function (Yu et al. 2012). Interestingly, genistein blocks VEGF/bFGF stimulation by the TIMP-1 increased and TIMP-2 decreased expression levels (Kim 2003).

Luteolin is a flavonoid found in many plants (medicinal herbs and same fruits), which suppressed VEGF-induced phosphorylation of VEGF receptor 2 and many downstream targets such as ERK, mTOR, MMP-2 and MMP-9, among many others (Pratheeshkumar et al. 2012). Other effects observed in cells treated with luteolin are the modulation of IL-6Rα expression levels, the MMP-2 secretion and the expression of SOCS3 (Suppressor of Cytokine Signaling 3). These effects trigger a reduction in the endothelial cell proliferation and migration (Lamy et al. 2012).

Panduratin A, a chalcone isolated from Boesenbergia rotunda, suppresses MMP-2 secretion and F-actin stress fiber formation in endothelial cell, affecting cell migration (Lai et al. 2012). Punarnavine shows anti-angiogenic effects *in vitro* and *in vivo* (inhibits endothelial cell migration, invasion and capillary structure formation, suppresses peritoneal angiogenesis in an Ehrlich ascites carcinoma tumor model and decreases the neovascularization in the sponge implant assay). Additionally, it increases TIMP-2 expression in HUVECs (Saraswati et al. 2013). Other natural compounds like Allyl isothiocyanate (AITC) and Phenyl isothiocyanate (PITC) display an in vitro antiangiogenic activity in HUVECs by enhancing the production of TIMP-1 (Thejass and Kuttan 2007).

5. Natural antiangiogenic compounds targeting PA system

As indicated before, the PA system participates is the conversion of plasminogen to plasmin, which is an active proteolytic enzyme involved in the fibrinolytic process. This conversion is carried out by uPA or tPA, although there are some other players in this enzymatic system, such as uPA receptor (uPAR), plasminogen activator inhibitors (PAI-1/2) and plasmin inhibitors (α2-antiplasmin – α2-AP – and α2-macroglobulin – α2-MG –). The PA system does not only regulate angiogenesis through the proteolytic degradation of ECM components, but also by interfering in intracellular signaling and modulating gene transcription (Stepanova et al. 2016), therefore it is assumed as a suitable antiangiogenic target. A compilation of natural antiangiogenic compounds that target PA system proteins is included in Table 1.

The potential of natural compounds as inhibitors of uPA, together with the identification of their mechanism of action, is very studied. Regarding to uPA-targeting compounds, it should be pointed out the polyphenol EGCG, a flavonoid which is the most abundant catechin in green tea and it is recognized as the main responsible of green tea health benefits (Nagle et al. 2006). EGCG has been described as an antiangiogenic compound both *in vitro* and *in vivo* (Cao and Cao 1999; Xu et al. 2011), mostly in the context of vascular tumors as a chemopreventive or adjuvant setting (Jung and Ellis 2002; Fassina et al. 2004). Interestingly, this compound has been shown to inhibit uPA activity by direct binding to the enzyme, consequently interfering with its ability to recognize its substrates (Jankun et al. 1997). EGCG also inhibits PAI-1 with an IC_{50} of 0.091 μM (Cale et al. 2010).

Silibinin (silybin) is a flavonoid produced by the herb *Silybum marianum* (milk thistle), representing the major component of the plant extract silymarin. The interest in this compound aroused from its hepatoprotective effects and its potential anti-neoplastic activity (Wing Ying Cheung et al. 2010). Regarding uPA targeting, silibinin shows a potent *in vitro* uPA inhibitory activity with an IC_{50} of 21 μM (Jedinák et al. 2006a). In the same way, hyperoside, another flavonoid found in traditional medicinal plants of the genera Hypericum and Crataegus, exhibiting antiangiogenic potential, has also the capability to directly inhibit uPA (IC_{50} 8.3 μM), (Jedinák et al. 2006a; Liu et al. 2016; Wu et al. 2020). Other flavonoids, such as salicin or quercetin, are thrombin and uPA inhibitors and have been described to exert antiangiogenic effects *in vivo* and *in vitro* (Kong et al. 2014; Zhao et al. 2014; Song et al. 2017).

Not only polyphenols but also other chemicals found in plants, present both PA system and angiogenic inhibitor effects. This is the case of hypericin, a naphthodianthrone found in Hypericum species, which can inhibit uPA activity (Jedinák et al. 2006a) and shows antiangiogenic activity *in vitro* and *in vivo* in dark conditions (Lavie et al. 2005; Martínez-Poveda et al. 2005), or some anthraquinones present in herbs used in traditional medicine, such as rhein or emodin. Rhein (4, 5-dihydroxyanthraquinone-2-carboxylic acid) is extensively found in medicinal herbs and its potential role as hepatoprotective, nephroprotective, antiinflammatory, antioxidant, anticancer, and antimicrobial compound has been suggested (Zhou et al. 2015). The antiangiogenic effect of rhein has been described *in vitro* and *in vivo* (Fernand et al. 2011; He et al. 2011) and this compound also targets uPA, directly inhibiting its activity *in vitro* (Jedinák et al. 2006a). In the same way, emodin has been used in traditional Chinese medicine as antibacterial or antiinflammatory and has demonstrated a great antiangiogenic potential in the context of tumor angiogenesis (Kwak et al. 2006; Lin et al. 2015; Qu et al. 2015; Shi and Zhou 2018; Zou et al. 2020).

The mentioned compounds have been described as direct inhibitors of uPA enzymatic activity, but additionally, several natural antiangiogenic compounds are able to produce an indirect inhibition of these enzymes, for example, by decreasing its expression or by preventing its release from the cell. This is the case of curcumin, a polyphenolic compound extracted from *Curcuma longa* (turmeric), described as an inhibitor of angiogenesis (Bhandarkar and Arbiser 2007), which inhibits uPA secretion in casein zymographies of tumoral HT1080 cells without directly affecting uPA enzymatic activity (Yodkeeree et al. 2009). Hydroxytyrosol, an antiangiogenic phenolic compound present in olive oil, decreases the uPA expression whereas increases the uPAR expression levels in endothelial cells, what has been proposed to contribute to its mechanism of action in the angiogenesis inhibition (García-Vilas et al. 2017b). In the same way, Aeroplysinin-1, a secondary metabolite isolated from a marine sponge, shows antiantiangiogenic effects with a decrease in uPA and an increase in PAI-1 activity in plasminogen zymographies (Rodríguez-Nieto et al. 2002). Other examples are damnacanthal, a noni anthaquinone characterized as antiangiogenic which produces a decrease in the uPA/PAI-1 ratio in endothelial cells (García-Vilas et al. 2017a), or aloe-emodin, a hydroxyanthraquinone from Aloe vera and other plants, that produces a decrease in uPA production in endothelial and tumor cells (Cárdenas et al. 2006).

Belonging to PA system, PAI are involved in the inhibition of plasminogen activation by uPA. Although uPA and PAI-1 have opposite effects regarding plasminogen activation, both are known to stimulate angiogenesis, depending on the context (Isogai et al. 2001; Devy et al. 2002; Stepanova et al. 2016; Song et al. 2019). Among the natural compound described to inhibit PAI, a number of them show antiangiogenic activity. The polyphenol tannic acid is produced by a wide range of edible plants, so its consumption is highly frequent around the world. Among its therapeutic potential, activities against oxidation, allergy, inflammation, cancer, dysentery, different infections (parasites, bacteria, virus), etc. have been described (Sharma et al. 2019). In addition, this compound has been shown to inhibit angiogenesis *in vitro* (Chen et al. 2003), and to strongly inhibit PAI-1 activity with an IC_{50} of 0.7 nM (Cale et al. 2010).

Other polyphenols, the black tea theaflavins theaflavin-3'-digallate and theaflavin-3,3'-digallate, have been described to inhibit angiogenesis (Gao et al. 2016 a,b). Both theaflavins can inhibit the PAI activity, showing the theaflavin-3'-digallate a more potent activity than the theaflavin-3,3'-digallate (Jankun 2011). Furthermore, the hydroxybenzoquinone embelin, isolated from *Embelia ribes* fruit (vidanga), inhibits PAI-1 activity at low concentrations (IC_{50} 1,62 μM) and it has also been studied for its antiangiogenic potential (Lin et al. 2013; Coutelle et al. 2014; Narayanaswamy et al. 2014; Rouch et al. 2015).

6. Natural antiangiogenic compounds targeting heparanase

Heparanase is an ECM remodeling enzyme that represent an interesting target in antiangiogenic therapy. The substrates of heparanase are HSPGs which are involved in self-assembly and integrity of both BM and ECM (Elkin et al. 2001) structures which must be degraded to allow the endothelial cell migration and a growth factor availability during angiogenesis. Some natural antiangiogenic compounds that directly target the heparanase enzymatic activity, such as defibrotide and sulodexide, are included in Table 1. Defibrotide is a mixture of single-stranded oligodeoxyribonucleotides isolated from porcine mucosal DNA, with recognized antiangiogenic activity *in vitro* and *in vivo* (Koehl et al. 2007). The direct inhibition of heparanase by this compound has been reported in an *in vitro* model of multiple myeloma (Mitsiades et al. 2009; Mohan et al. 2019). Sulodexide is a highly purified mixture of GAGs isolated from porcine intestinal mucosa which directly targets heparanase enzymatic activity (Masola et al. 2012) and shows antiangiogenic potential *in vitro* (Niderla-Bielińska et al. 2019).

Beside the natural inhibitors of heparanase mentioned above, that show the capability of inhibiting directly the enzymatic activity of this protein, other natural compounds are able to produce an indirect inhibition of heparanase. For example, bestatin, a compound which inhibits heparanase expression and angiogenesis in a diabetic retinopathy model (Hossain et al. 2016). Furthermore, carrageenans are polysulfated polygalactans obtained from red algae that can inhibit the release of heparin-binding growth factors and they are potent inhibitors of endothelial and cancer cell proliferation. Nevertheless, these molecules can result toxic or proinflammatory due to their high molecular weight, so an interesting strategy was the production of low molecular weight depolymerized variants which have shown a great anti-angiogenic activity (Chen et al. 2007; Yao et al. 2014; Niu et al. 2015; Poupard et al. 2017; Mohan et al. 2019).

7. Natural antiangiogenic compounds targeting cathepsins

Cathepsins are proteases involved in both, physiological and pathological angiogenesis and, although they are normally found into cells – inside endosomes and lysosomes –, some of them are at the extracellular space. Among them, cathepsins B, K, L, S are involved in angiogenesis (Vidak et al. 2019), representing potential targets of natural compounds that could be candidates to antiangiogenic drugs. Natural antiangiogenic compounds targeting cathepsins are included in Table 1.

The peptidyl aldehydes leupeptin and chymostatin, isolated from *Streptomyces exfoliatus* and *Streptomyces sp*. respectively, have been described as cathepsin A, B, D and K inhibitors (Vidal-Albalat and González 2016). These natural molecules show antiangiogenic potential, since leupeptin interferes bFGF-induced angiogenesis in guinea pig cornea (Tamada et al. 2000) and chymostatin inhibits angiogenesis in a hamster sponge angiogenesis model (Muramatsu et al. 2000).

Additionally, 7-epiclusianone, a prenylated benzophenone found in *Garcinia brasiliensis* (bacupari) and used in traditional Brazilian medicine for inflammation (Santa-Cecília, et al. 2011), is a cathepsin B inhibitor (Vidal-Albalat and González 2016) that has shown antiangiogenic potential *in vitro* (Taylor et al. 2019). Finally, ursolic acid is a known natural angiogenesis inhibitor (Cárdenas et al. 2004; Kanjoormana and Kuttan, 2010) found in many plants, fruits, and herbs, and is also able to inhibit cathepsins B, L and D (Jedinák et al. 2006b; Vidal-Albalat and González 2016).

8. Natural antiangiogenic compounds targeting ADAMs and ADAMTS

Like the proteases mentioned above, some natural compounds characterized as antiangiogenic are also known to inhibit some ADAMs and ADAMTS members (Table 1).

Focusing in ADAMs family, ADAM8, ADAM9, ADAM10 ADAM 15 and ADAM17 are members that are specially involved in angiogenesis (Donners et al. 2010; van der Vorst et al. 2012). The natural compounds rapamycin (sirolimus), produced by the soil bacterium *Streptomyces hygroscopicus*, and triptolide, isolated from the medicinal plant *Tripterygium wilfordii* Hook F, exhibit antiangiogenic potential *in vivo* and *in vitro* (He et al. 2010; Wang et al. 2019) and have been described to indirectly inhibit ADAM10 by decreasing its expression in SweAPP N2a cells and leukemia cells respectively (Wetzel et al. 2017). The natural compound luteolin, a common flavonoid produced by several plants (López-Lázaro 2009), inhibits angiogenesis *in vivo* and *in vitro* (Bagli et al. 2004) and controversially, it also has been reported to inhibit ADAMTS 4/5 activity (Moncada-Pazos et al. 2011) which have shown to have an antiangiogenic role (Kumar et al. 2012).

9. Natural antiangiogenic compounds targeting elastases

Human neutrophil elastase (HNE) produces endothelial cell damage, promotes tumor cells intravasation (Grechowa et al. 2017; Deryugina et al. 2020) and is capable to degrade angiogenic factors such VEGF and bFGF (Ai et al. 2007). Despite this apparent antiangiogenic role of HNE, there are some natural antiangiogenic compounds that have also shown an inhibitory effect on HNE, such as the previously mentioned EGCG, which inhibits neutrophil-dependent angiogenesis *in vivo* (Donà et al. 2003) and strongly inhibits HNE enzymatic activity in A459 cells (Xiaokaiti et al. 2015). The above mentioned luteolin, the flavonoid compound found in bee pollen and propolis, phloretin (the major polyphenol compound in apples) and the triterpene compound lupeol have also been described to inhibit HNE and angiogenesis (Bagli et al. 2004; Siedle et al. 2007; Lin et al. 2008; Nema et al. 2012; Vijay Avin et al. 2014; Kangsamaksin et al. 2017; Hsiao et al. 2019).

Furthermore, there are natural antiangiogenic compounds which have been reported to inhibit other elastases, such as the polyphenolic compound (+)-catechin (present in tea) or the triterpenoid oleanoic acid (present in olive oil), which inhibit porcine pancreatic elastase (PPE) activity (Guruvayoorappan and Kuttan, 2008; Kim et al. 2009; Wittenauer et al. 2015; Li et al. 2016; Yee et al. 2017). The pentacyclic triterpenoid ursolic acid, present in many plants such as *Rosmarinus officinalis* (rosemary) inhibits leukocyte elastase (Ying et al. 1991) and angiogenesis, and all of them inhibits also angiogenesis (Cárdenas et al. 2004; Kanjoormana et al. 2010).

10. Conclusions

The aims of this chapter have been to highlight the important role of the ECM in the vascular remodeling and to revise the current literature to classify the natural compounds that exhibit an antiangiogenic activity and affect the production, secretion or activity of ECM enzymes. The ECM is a rich source of growth factors and enzymes that control and influence vascular morphogenesis and homeostasis by regulation of its composition. In the last years, a plethora of ECM molecules have emerged as promising targets for the treatment of several human diseases, such as cancer, fibrosis and inflammation, among others. Interestingly, some of the natural antiangiogenic compounds mentioned in this chapter are currently in clinical trials for the evaluation of their possible therapeutic role in different pathological context related to aberrant angiogenesis, mainly in cancer (https://clinicaltrials.gov/). This is the case of EGCG, which is being studied for the improvement of endothelial function in cardiovascular diseases and several types of cancer, and silibinin or quercetin, which are being tested for the treatment of different cancers. In the context of angiogenesis-dependent ocular pathologies, hydroxytyrosol is being investigated for the treatment of wet macular degeneration, and atarin is in clinical trials for diabetic retinopathy. Of note, much of the compounds compiled in the chapter in base of their antiangiogenic potential and their inhibitory activity on ECM-degrading enzymes have been used (as a part of extracts or herb infusions) for long time in traditional medicine for the treatment of different affections, as is the case of luteolin (Lin et al. 2008), and even some of them are approved for their use in certain clinical settings, as is the case of rapamycin, defibrotide or (+)-catechin.

Although promising, the identification of ECM-based inhibitors of angiogenesis used for clinical applications is still limited and much efforts are needed to unravel their therapeutic potential. Hence, a better understanding on the ECM proteins, their ligands and the molecular interactions between the matrix molecules will help researchers and clinicians to identify new biomarkers and antiangiogenic strategies, further developing novel ECM-based strategies for the treatment of pathological conditions. In this context, nature represents a rich source of new antiangiogenic molecules with the potential to inhibit ECM-degrading enzymes, representing this activity a feasible part of their mechanism of action in the modulation of angiogenesis. The complexity of the angiogenesis process and the better results achieved by multi-target pharmacological strategies point to the great interest of these natural compounds, which in most of the cases show multiple molecular targets and pleiotropic bioactivities. Future research directions towards the optimization of the existing tools used in the characterization of natural antiangiogenic compounds interfering with the ECM-degrading enzymes will offer a valuable benefit in the design of novel ECM-based strategies in the antiangiogenic therapy.

Conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by grants PID2019-105010RB-I00 (Spanish Ministry of Science, Innovation and Universities), UMA18-FEDERJA-220, UMA18-FEDERJA-267 and PY20_00257 (Andalusian Government and FEDER) and funds from PAIDI group BIO 267 (Andalusian Government). The "CIBER de Enfermedades Raras" and "CIBER de Enfermedades Vasculares" are initiatives from the ISCIII (Spain). Melissa García Caballero was supported by Beatriz Galindo Program from the Spanish Ministry of Science and Innovation and Manuel Bernal was supported by Juan de la Cierva – Incorporación Program (IJC2018-037657-I), Spanish Ministry of Science and Innovation. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

References

Ai S, Cheng XW, Inoue A, et al (2007) Angiogenic activity of bFGF and VEGF suppressed by proteolytic cleavage by neutrophil elastase. Biochemical and Biophysical Research Communications 364:395–401. https://doi.org/10.1016/j.bbrc.2007.10.027

Bagli E, Stefaniotou M, Morbidelli L, et al (2004) Luteolin inhibits vascular endothelial growth factor-induced angiogenesis; inhibition of endothelial cell survival and proliferation by targeting phosphatidylinositol 3′-kinase activity. Cancer Research 64:7936–7946. https://doi.org/10.1158/0008-5472.CAN-03-3104

Bhandarkar SS, Arbiser JL (2007) Curcumin as an inhibitor of angiogenesis. In: The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. Springer US, Boston, MA, 185–195. https://doi.org/10.1007/978-0-387-46401-5_7

Breuss JM, Uhrin P (2012) VEGF-initiated angiogenesis and the uPA/uPAR system. Cell Adhesion & Migration 6:535–540. https://doi.org/10.4161/cam.22243

Cale JM, Li S-H, Warnock M, et al (2010) Characterization of a novel class of polyphenolic inhibitors of plasminogen activator inhibitor-1. Journal of Biological Chemistry 285:7892–7902. https://doi.org/10.1074/jbc.M109.067967

Cao Y, Cao R (1999) Angiogenesis inhibited by drinking tea. Nature 398:381–381. https://doi.org/10.1038/18793

Cárdenas C, Quesada AR, Medina MA (2006) Evaluation of the anti-angiogenic effect of aloe-emodin. Cellular and Molecular Life Sciences 63:3083–3089. https://doi.org/10.1007/s00018-006-6399-6

Cárdenas C, Quesada AR, Medina MÁ (2004) Effects of ursolic acid on different steps of the angiogenic process. Biochemical and Biophysical Research Communications 320:402–408. https://doi.org/10.1016/j.bbrc.2004.05.183

Carmeliet P, Jain RK (2011) Molecular mechanisms and clinical applications of angiogenesis. Nature 473:298–307. https://doi.org/10.1038/nature10144

Chen H, Yan X, Lin J, et al (2007) Depolymerized products of lambda-carrageenan as a potent angiogenesis inhibitor. Journal of agricultural and food chemistry 55:6910–7. https://doi.org/10.1021/jf070183+

Chen X, Beutler JA, McCloud TG, et al (2003) Tannic acid is an inhibitor of CXCL12 (SDF-1alpha)/CXCR4 with antiangiogenic activity. Clinical cancer research: an official journal of the American Association for Cancer Research 9:3115–23

Coutelle O, Hornig-Do H, Witt A, et al (2014) Embelin inhibits endothelial mitochondrial respiration and impairs neoangiogenesis during tumor growth and wound healing. EMBO Molecular Medicine 6:624–639. https://doi.org/10.1002/emmm.201303016

Cui N, Hu M, Khalil RA (2017) Biochemical and biological attributes of matrix metalloproteinases. Progress in Molecular Biology and Translational Science, *147*, 1-73. https://doi.org/10.1016/bs.pmbts.2017.02.005

Deryugina, E., Carré, A., Ardi, V., Muramatsu, T., Schmidt, J., Pham, C., & Quigley, J. P. (2020). Neutrophil elastase facilitates tumor cell intravasation and early metastatic events. *IScience*, *23*(12), 101799. https://doi.org/10.1016/j.isci.2020.101799

Devy L, Blacher S, Grignet-Debrus C, et al (2002) The pro- or antiangiogenic effect of plasminogen activator inhibitor 1 is dose dependent. The FASEB Journal 16:147–154. https://doi.org/10.1096/fj.01-0552com

Dogné S, Flamion B (2020) Endothelial glycocalyx impairment in disease. The American Journal of Pathology 190:768–780. https://doi.org/10.1016/j.ajpath.2019.11.016

Donà M, Dell'Aica I, Calabrese F, et al (2003) Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. The Journal of Immunology 170:4335–4341. https://doi.org/10.4049/jimmunol.170.8.4335

Donners MMPC, Wolfs IMJ, Olieslagers S, et al (2010) A disintegrin and metalloprotease 10 is a novel mediator of vascular endothelial growth factor–induced endothelial cell function in angiogenesis and is associated with atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology 30:2188–2195. https://doi.org/10.1161/ATVBAHA.110.213124

Elkin M, Ilan N, Ishai-Michaeli R, et al (2001) Heparanase as mediator of angiogenesis: mode of action. The FASEB Journal 15:1661–1663. https://doi.org/10.1096/fj.00-0895fje

Fassina G, Venè R, Morini M, et al (2004) Mechanisms of Inhibition of Tumor Angiogenesis and Vascular Tumor Growth by Epigallocatechin-3-Gallate. Clinical Cancer Research 10:4865–4873. https://doi.org/10.1158/1078-0432.CCR-03-0672

Fernand VE, Losso JN, Truax RE, et al (2011) Rhein inhibits angiogenesis and the viability of hormone-dependent and -independent cancer cells under normoxic or hypoxic conditions in vitro. Chemico-Biological Interactions 192:220–232. https://doi.org/10.1016/j.cbi.2011.03.013

Fields GB (2019) Mechanisms of action of novel drugs targeting angiogenesis-promoting matrix metalloproteinases. Frontiers in Immunology 10:1278. https://doi.org/10.3389/fimmu.2019.01278

Fingleton B (2008) MMPs as therapeutic targets—Still a viable option? Seminars in Cell & Developmental Biology 19(1):61-8. https://doi.org/10.1016/j.semcdb.2007.06.006

Gao Y, Rankin GO, Tu Y, Chen YC (2016b) Theaflavin-3, 3′-digallate decreases human ovarian carcinoma OVCAR-3 cell-induced angiogenesis via Akt and Notch-1 pathways, not via MAPK pathways. International Journal of Oncology 48:281–292. https://doi.org/10.3892/ijo.2015.3257

Gao Y, Rankin GO, Tu Y, Chen YC (2016a) Inhibitory effects of the four main theaflavin derivatives found in black tea on ovarian cancer cells. Anticancer Research 36(2):643–51

García-Vilas JA, Pino-Ángeles A, Martínez-Poveda B, et al (2017a) The noni anthraquinone damnacanthal is a multi-kinase inhibitor with potent anti-angiogenic effects. Cancer Letters 385:1–11. https://doi.org/10.1016/j.canlet.2016.10.037

García-Vilas JA, Quesada AR, Medina MÁ (2017b) Hydroxytyrosol targets extracellular matrix remodeling by endothelial cells and inhibits both ex vivo and in vivo angiogenesis. Food Chemistry 221:1741–1746. https://doi.org/10.1016/j.foodchem.2016.10.111

Gonias SL, Zampieri C (2020) Plasminogen receptors in human malignancies: effects on prognosis and feasibility as targets for drug development. Current Drug Targets 21:647–656. https://doi.org/10.2174/1389450120666191122101658

Grechowa I, Horke S, Wallrath A, et al (2017) Human neutrophil elastase induces endothelial cell apoptosis by activating the PERK-CHOP branch of the unfolded protein response. The FASEB Journal 31:3868–3881. https://doi.org/10.1096/fj.201700012R

Guruvayoorappan C, Kuttan G (2008) (+)-Catechin inhibits tumour angiogenesis and regulates the production of nitric oxide and TNF-α in LPS-stimulated macrophages. Innate Immunity 14:160–174. https://doi.org/10.1177/1753425908093295

He M-F, Huang Y-H, Wu L-W, et al (2010) Triptolide functions as a potent angiogenesis inhibitor. International Journal of Cancer 126:266–278. https://doi.org/10.1002/ijc.24694

He Z-H, Zhou R, He M-F, et al (2011) Anti-angiogenic effect and mechanism of rhein from Rhizoma Rhei. Phytomedicine 18:470–478. https://doi.org/10.1016/j.phymed.2010.10.006

Heinz A (2020) Elastases and elastokines: elastin degradation and its significance in health and disease. Critical Reviews in Biochemistry and Molecular Biology 55:252–273. https://doi.org/10.1080/10409238.2020.1768208

Hossain A, Heron D, Davenport I, et al (2016) Protective effects of bestatin in the retina of streptozotocin-induced diabetic mice. Experimental Eye Research 149:100–106. https://doi.org/10.1016/j.exer.2016.06.016

Hsiao Y-H, Hsieh M-J, Yang S-F, et al (2019) Phloretin suppresses metastasis by targeting protease and inhibits cancer stemness and angiogenesis in human cervical cancer cells. Phytomedicine 62:152964. https://doi.org/10.1016/j.phymed.2019.152964

Isogai C, Laug WE, Shimada H, et al (2001) Plasminogen activator inhibitor-1 promotes angiogenesis by stimulating endothelial cell migration toward fibronectin. Cancer Research 61:5587–94

Jankun (2011) Diverse inhibition of plasminogen activator inhibitor type 1 by theaflavins of black tea. International Journal of Molecular Medicine 27:525–529. https://doi.org/10.3892/ijmm.2011.615

Jankun J, Selman SH, Swiercz R, Skrzypczak-Jankun E (1997) Why drinking green tea could prevent cancer. Nature 387:561–561. https://doi.org/10.1038/42381

Jászai J, Schmidt M (2019) Trends and Challenges in Tumor Anti-Angiogenic Therapies. Cells 8:1102. https://doi.org/10.3390/cells8091102

Jayatilleke KM, Hulett MD (2020) Heparanase and the hallmarks of cancer. Journal of Translational Medicine 18:453. https://doi.org/10.1186/s12967-020-02624-1

Jedinák A, Maliar T, Grančai D, Nagy M (2006a) Inhibition activities of natural products on serine proteases. Phytotherapy Research 20:214–217. https://doi.org/10.1002/ptr.1836

Jedinák, A., Mučková, M., Košťálová, D., Maliar, T., & Mašterová, I. (2006b). Antiprotease and antimetastatic activity of ursolic acid isolated from salvia officinalis. Zeitschrift Für Naturforschung C, 61(11–12), 777–782. https://doi.org/10.1515/znc-2006-11-1203

Jung YD, Ellis LM (2002) Inhibition of tumour invasion and angiogenesis by epigallocatechin gallate (EGCG), a major component of green tea. International Journal of Experimental Pathology 82:309–316. https://doi.org/10.1046/j.1365-2613.2001.00205.x

Kangsamaksin T, Chaithongyot S, Wootthichairangsan C, et al (2017) Lupeol and stigmasterol suppress tumor angiogenesis and inhibit cholangiocarcinoma growth in mice via downregulation of tumor necrosis factor-α. PLoS ONE 12:e0189628. https://doi.org/10.1371/journal.pone.0189628

Kanjoormana M, Kuttan G (2010) Antiangiogenic activity of ursolic acid. Integrative Cancer Therapies 9:224–235. https://doi.org/10.1177/1534735410367647

Khalid EB, Ayman E-ME-K, Rahman H, et al (2016) Natural products against cancer angiogenesis. Tumor Biology 37:14513–14536. https://doi.org/10.1007/s13277-016-5364-8

Kim, M. H. (2003). Flavonoids inhibit VEGF/bFGF-induced angiogenesis in vitro by inhibiting the matrix-degrading proteases. Journal of Cellular Biochemistry, *89*(3), 529–538. https://doi.org/10.1002/jcb.10543

Kim JH, Byun JC, Hyun CG, Lee NH (2009) Compounds with elastase inhibition and free radical scavenging activities from Callistemon lanceolatus. Journal of Medicinal Plants Research 3:914–920

Koehl GE, Geissler EK, Iacobelli M, et al (2007) Defibrotide: An endothelium protecting and stabilizing drug, has an anti-angiogenic potential in vitro and in vivo. Cancer Biology & Therapy 6:686–690. https://doi.org/10.4161/cbt.6.5.3959

Kong C-S, Kim K-H, Choi J-S, et al (2014) Salicin, an extract from white willow bark, inhibits angiogenesis by blocking the ros-erk pathways. Phytotherapy Research 28:1246–1251. https://doi.org/10.1002/ptr.5126

Kumar S, Rao N, Ge R (2012) Emerging roles of ADAMTSs in angiogenesis and cancer. Cancers 4:1252–1299. https://doi.org/10.3390/cancers4041252

Kwak H-J, Park M-J, Park C-M, et al (2006) Emodin inhibits vascular endothelial growth factor-A-induced angiogenesis by blocking receptor-2 (KDR/Flk-1) phosphorylation. International Journal of Cancer 118:2711–2720. https://doi.org/10.1002/ijc.21641

Lai S-L, Cheah S-C, Wong P-F, et al (2012) In vitro and in vivo anti-angiogenic activities of panduratin A. PLoS ONE 7:e38103. https://doi.org/10.1371/journal.pone.0038103

Lamy S, Akla N, Ouanouki A, et al (2012) Diet-derived polyphenols inhibit angiogenesis by modulating the interleukin-6/STAT3 pathway. Experimental Cell Research 318:1586–1596. https://doi.org/10.1016/j.yexcr.2012.04.004

Lavie G, Mandel M, Hazan S, et al (2005) Anti-angiogenic activities of hypericin in vivo: potential for ophthalmologic applications. Angiogenesis 8:35–42. https://doi.org/10.1007/s10456-005-3828-3

Lenci E, Cosottini L, Trabocchi A (2021) Novel matrix metalloproteinase inhibitors: an updated patent review (2014 - 2020). Expert Opinion on Therapeutic Patents 31:509–523. https://doi.org/10.1080/13543776.2021.1881481

Li L, Lin J, Sun G, et al (2016) Oleanolic acid inhibits colorectal cancer angiogenesis in vivo and in vitro via suppression of STAT3 and Hedgehog pathways. Molecular Medicine Reports 13:5276–5282. https://doi.org/10.3892/mmr.2016.5171

Li S, van Dijk CGM, Meeldijk J, et al (2021) Extracellular granzyme k modulates angiogenesis by regulating soluble VEGFR1 release from endothelial cells. Frontiers in Oncology 11: 681967. https://doi.org/10.3389/fonc.2021.681967

Lin S-Z, Xu J-B, Ji X, et al (2015) Emodin inhibits angiogenesis in pancreatic cancer by regulating the transforming growth factor-β/drosophila mothers against decapentaplegic pathway and angiogenesis-associated microRNAs. Molecular Medicine Reports 12:5865–5871. https://doi.org/10.3892/mmr.2015.4158

Lin Y, Shi R, Wang X, Shen H-M (2008) Luteolin, a flavonoid with potential for cancer prevention and therapy. Current Cancer Drug Targets 8:634–646. https://doi.org/10.2174/156800908786241050

Lin Z, Jensen JK, Hong Z, et al (2013) Structural insight into inactivation of plasminogen activator inhibitor-1 by a small-molecule antagonist. Chemistry & Biology 20:253–261. https://doi.org/10.1016/j.chembiol.2013.01.002

Liu J, Khalil RA (2017) Matrix metalloproteinase inhibitors as investigational and therapeutic tools in unrestrained tissue remodeling and pathological disorders. Progress in Molecular Biology and Translational Science, 148: 355-420.

Liu Y, Liu G, Mei J, Wang J (2016) The preventive effects of hyperoside on lung cancer in vitro by inducing apoptosis and inhibiting proliferation through Caspase-3 and P53 signaling pathway. Biomedicine & Pharmacotherapy 83:381–391. https://doi.org/10.1016/j.biopha.2016.06.035

Lopes-Coelho F, Martins F, Pereira SA, Serpa J (2021) Anti-angiogenic therapy: current challenges and future perspectives. International Journal of Molecular Sciences 22:3765. https://doi.org/10.3390/ijms22073765

López-Lázaro M (2009) Distribution and biological activities of the flavonoid luteolin. Mini-Reviews in Medicinal Chemistry 9:31–59. https://doi.org/10.2174/138955709787001712

Lu K, Bhat M, Basu S (2016) Plants and their active compounds: natural molecules to target angiogenesis. Angiogenesis 19:287–295. https://doi.org/10.1007/s10456-016-9512-y

Ma Z, Mao C, Jia Y, et al (2020) Extracellular matrix dynamics in vascular remodeling. American Journal of Physiology-Cell Physiology 319:C481–C499. https://doi.org/10.1152/ajpcell.00147.2020

Marchand M, Monnot C, Muller L, Germain S (2019) Extracellular matrix scaffolding in angiogenesis and capillary homeostasis. Seminars in Cell & Developmental Biology 89:147–156. https://doi.org/10.1016/j.semcdb.2018.08.007

Martínez-Poveda B, Quesada AR, Medina MÁ (2005) Hypericin in the dark inhibits key steps of angiogenesis in vitro. European Journal of Pharmacology 516:97–103. https://doi.org/10.1016/j.ejphar.2005.03.047

Masola, V., Onisto, M., Zaza, G., Lupo, A., & Gambaro, G. (2012). A new mechanism of action of sulodexide in diabetic nephropathy: inhibits heparanase-1 and prevents FGF-2-induced renal epithelial-mesenchymal transition. Journal of Translational Medicine, 10(1), 213. https://doi.org/10.1186/1479-5876-10-213

Masola V, Bellin G, Gambaro G, Onisto M (2018) Heparanase: a multitasking protein involved in extracellular matrix (ECM) remodeling and intracellular events. Cells 7:236. https://doi.org/10.3390/cells7120236

Medina MÁ, Muñoz-Chápuli R, Quesada AR (2007) Challenges of antiangiogenic cancer therapy: trials and errors, and renewed hope. Journal of Cellular and Molecular Medicine 11:374–382. https://doi.org/10.1111/j.1582-4934.2007.00056.x

Mitsiades CS, Rouleau C, Echart C, et al (2009) Preclinical studies in support of defibrotide for the treatment of multiple myeloma and other neoplasias. Clinical Cancer Research 15:1210–1221. https://doi.org/10.1158/1078-0432.CCR-08-1270

Mohan CD, Hari S, Preetham HD, et al (2019) Targeting heparanase in cancer: inhibition by synthetic, chemically modified, and natural compounds. iScience 15:360–390. https://doi.org/10.1016/j.isci.2019.04.034

Moncada-Pazos A, Obaya AJ, Viloria CG, et al (2011) The nutraceutical flavonoid luteolin inhibits ADAMTS-4 and ADAMTS-5 aggrecanase activities. Journal of Molecular Medicine 89:611–619. https://doi.org/10.1007/s00109-011-0741-7

Muncie JM, Weaver VM (2018) The Physical and Biochemical Properties of the Extracellular Matrix Regulate Cell Fate. pp 1–37

Muramatsu M, Katada J, Hayashi I, Majima M (2000) Chymase as a proangiogenic factor. Journal of Biological Chemistry 275:5545–5552. https://doi.org/10.1074/jbc.275.8.5545

Nagase H, Visse R, Murphy G (2006) Structure and function of matrix metalloproteinases and TIMPs. Cardiovascular Research 69:562–573. https://doi.org/10.1016/j.cardiores.2005.12.002

Nagle DG, Ferreira D, Zhou Y-D (2006) Epigallocatechin-3-gallate (EGCG): Chemical and biomedical perspectives. Phytochemistry 67:1849–1855. https://doi.org/10.1016/j.phytochem.2006.06.020

Narayanaswamy R, Shymatak M, Chatterjee S, et al (2014) Inhibition of angiogenesis and nitric oxide synthase (NOS), by embelin & vilangin using in vitro, in vivo & in silico studies. Advanced Pharmaceutical Bulletin 4:543–8. https://doi.org/10.5681/apb.2014.080

Nema NK, Maity N, Sarkar BK, Mukherjee PK (2013) Matrix metalloproteinase, hyaluronidase and elastase inhibitory potential of standardized extract of Centella asiatica. Pharmaceutical Biology 51:1182–1187. https://doi.org/10.3109/13880209.2013.782505

Nia HT, Munn LL, Jain RK (2020) Physical traits of cancer. Science 370:eaaz0868. https://doi.org/10.1126/science.aaz0868

Niderla-Bielińska J, Bartkowiak K, Ciszek B, et al (2019) Sulodexide inhibits angiogenesis via decreasing Dll4 and Notch1 expression in mouse proepicardial explant cultures. Fundamental & Clinical Pharmacology 33:159–169. https://doi.org/10.1111/fcp.12418

Niu T-T, Zhang D-S, Chen H-M, Yan X-J (2015) Modulation of the binding of basic fibroblast growth factor and heparanase activity by purified λ-carrageenan oligosaccharides. Carbohydrate Polymers 125:76–84. https://doi.org/10.1016/j.carbpol.2015.02.069

Piperigkou Z, Kyriakopoulou K, Koutsakis C, et al (2021) Key matrix remodeling enzymes: functions and targeting in cancer. Cancers 13 (6):1441. https://doi.org/10.3390/cancers13061441

Poupard N, Badarou P, Fasani F, et al (2017) Assessment of heparanase-mediated angiogenesis using microvascular endothelial cells: identification of λ-carrageenan derivative as a potent anti angiogenic agent. Marine Drugs 15:134. https://doi.org/10.3390/md15050134

Pratheeshkumar P, Son Y-O, Budhraja A, et al (2012) Luteolin inhibits human prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. PLoS ONE 7:e52279. https://doi.org/10.1371/journal.pone.0052279

Qu W, Wang Y, Wu Q, et al (2015) Emodin inhibits HMGB1-induced tumor angiogenesis in human osteosarcoma by regulating SIRT1. International Journal of Clinical and Experimental Medicine 8:15054–64

Quesada AR, Muñoz-Chápuli R, Medina MA (2006) Anti-angiogenic drugs: from bench to clinical trials. Medicinal Research Reviews 26:483–530. https://doi.org/10.1002/med.20059

Quesada AR, Medina MÁ, Alba E (2007) Playing only one instrument may be not enough: Limitations and future of the antiangiogenic treatment of cancer. BioEssays 29:1159–1168. https://doi.org/10.1002/bies.20655

Quesada AR, Medina MA, Munoz-Chápuli R, Ponce AL (2010) Do Not Say Ever Never More: The Ins and Outs of Antiangiogenic Therapies. Current Pharmaceutical Design 16:3932–3957. https://doi.org/10.2174/138161210794454950

Quintero-Fabián S, Arreola R, Becerril-Villanueva E, et al (2019) Role of matrix metalloproteinases in angiogenesis and cancer. Frontiers in Oncology 9:1370. https://doi.org/10.3389/fonc.2019.01370

Ribatti D (2021) The Fundamental contribution of judah folkman in the setting of angiogenesis assays. In: Vascular Morphogenesis. Methods in Molecular Biology, 2206. Humana, New York, NY. https://doi.org/10.1007/978-1-0716-0916-3_2

Ribeiro A, Abreu RMV, Dias MM, et al (2018) Antiangiogenic compounds: well-established drugs versus emerging natural molecules. Cancer Letters 415:86–105. https://doi.org/10.1016/j.canlet.2017.12.006

Rodríguez-Nieto, S., González-Iriarte, M., Carmona, R., Muñoz-Chápuli, R., Medina, M. A., & Quesada, A. R. (2002). Antiangiogenic activity of aeroplysinin-1, a brominated compound isolated from a marine sponge. The FASEB Journal, 16(2), 1–27. https://doi.org/10.1096/fj.01-0427fje

Rouch A, Vanucci-Bacqué C, Bedos-Belval F, Baltas M (2015) Small molecules inhibitors of plasminogen activator inhibitor-1 – An overview. European Journal of Medicinal Chemistry 92:619–636. https://doi.org/10.1016/j.ejmech.2015.01.010

Santa-Cecília FV, Freitas LA, Vilela FC, et al (2011) Antinociceptive and anti-inflammatory properties of 7-epiclusianone, a prenylated benzophenone from Garcinia brasiliensis. European Journal of Pharmacology 670:280–285. https://doi.org/10.1016/j.ejphar.2011.08.032

Saraswati S, Alhaider AA, Agrawal SS (2013) Punarnavine, an alkaloid from Boerhaavia diffusa exhibits anti-angiogenic activity via downregulation of VEGF in vitro and in vivo. Chemico-Biological Interactions 206:204–213. https://doi.org/10.1016/j.cbi.2013.09.007

Scoditti E, Calabriso N, Massaro M, et al (2012) Mediterranean diet polyphenols reduce inflammatory angiogenesis through MMP-9 and COX-2 inhibition in human vascular endothelial cells: A potentially protective mechanism in atherosclerotic vascular disease and cancer. Archives of Biochemistry and Biophysics 527:81–89. https://doi.org/10.1016/j.abb.2012.05.003

Sharma K, Kumar V, Kaur J, et al (2019) Health effects, sources, utilization and safety of tannins: a critical review. Toxin Reviews 1–13. https://doi.org/10.1080/15569543.2019.1662813

Shi G, Zhou L (2018) Emodin suppresses angiogenesis and metastasis in anaplastic thyroid cancer by affecting TRAF6-mediated pathways in vivo and in vitro. Molecular Medicine Reports 18:5191–5197. https://doi.org/10.3892/mmr.2018.9510

Siedle B, Hrenn A, Merfort I (2007) Natural compounds as inhibitors of human neutrophil elastase. Planta Medica 73:401–420. https://doi.org/10.1055/s-2007-967183

Smock RG, Meijers R (2018) Roles of glycosaminoglycans as regulators of ligand/receptor complexes. Open Biology 8:180026. https://doi.org/10.1098/rsob.180026

Song T, Meng S, Xu S-T, et al (2019) The overexpression of uPA promotes the proliferation and fibrinolytic activity of human umbilical vein endothelial cells. International Journal of Clinical and Experimental Pathology 12:2959–2966

Song W, Zhao X, Xu J, Zhang H (2017) Quercetin inhibits angiogenesis-mediated human retinoblastoma growth by targeting vascular endothelial growth factor receptor. Oncology Letters 14:3343–3348. https://doi.org/10.3892/ol.2017.6623

Stepanova V, Jayaraman P-S, Zaitsev S v., et al (2016) Urokinase-type plasminogen activator (uPA) promotes angiogenesis by attenuating proline-rich homeodomain protein (PRH) transcription factor activity and de-repressing vascular endothelial growth factor (VEGF) receptor expression. Journal of Biological Chemistry 291:15029–15045. https://doi.org/10.1074/jbc.M115.678490

Su S-C, Lin C-W, Yang W-E, et al (2016) The urokinase-type plasminogen activator (uPA) system as a biomarker and therapeutic target in human malignancies. Expert Opinion on Therapeutic Targets 20:551–566. https://doi.org/10.1517/14728222.2016.1113260

Sun Y, Huang J, Yang Z (2015) The roles of ADAMTS in angiogenesis and cancer. Tumor Biology 36:4039–4051. https://doi.org/10.1007/s13277-015-3461-8

Tamada Y, Fukiage C, Boyle DL, et al (2000) Involvement of cysteine proteases in bfgf-induced angiogenesis in guinea pig and rat cornea. Journal of Ocular Pharmacology and Therapeutics 16:271–283. https://doi.org/10.1089/jop.2000.16.271

Taylor WF, Yanez M, Moghadam SE, et al (2019) 7-epi-Clusianone, a multi-targeting natural product with potential chemotherapeutic, immune-modulating, and anti-angiogenic properties. Molecules 24:4415. https://doi.org/10.3390/molecules24234415

Thaloor D, Singh AK, Sidhu GS, et al (1998) Inhibition of angiogenic differentiation of human umbilical vein endothelial cells by curcumin. Cell growth & Differentiation 9:305–12

Thejass P, Kuttan G (2007) Inhibition of endothelial cell differentiation and proinflammatory cytokine production during angiogenesis by allyl isothiocyanate and phenyl isothiocyanate. Integrative Cancer Therapies 6:389–399. https://doi.org/10.1177/1534735407309084

Theocharis AD, Manou D, Karamanos NK (2019) The extracellular matrix as a multitasking player in disease. The FEBS Journal 286:2830–2869. https://doi.org/10.1111/febs.14818

Vaeyens M-M, Jorge-Peñas A, Barrasa-Fano J, et al (2020) Matrix deformations around angiogenic sprouts correlate to sprout dynamics and suggest pulling activity. Angiogenesis 23:315–324. https://doi.org/10.1007/s10456-020-09708-y

van der Vorst EPC, Keijbeck AA, de Winther MPJ, Donners MMPC (2012) A disintegrin and metalloproteases: Molecular scissors in angiogenesis, inflammation and atherosclerosis. Atherosclerosis 224:302–308. https://doi.org/10.1016/j.atherosclerosis.2012.04.023

Vasudev NS, Reynolds AR (2014) Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions. Angiogenesis 17:471–494. https://doi.org/10.1007/s10456-014-9420-y

Velotti F, Barchetta I, Cimini FA, Cavallo MG (2020) Granzyme B in Inflammatory Diseases: Apoptosis, Inflammation, Extracellular Matrix Remodeling, Epithelial-to-Mesenchymal Transition and Fibrosis. Frontiers in Immunology 11: 587581. https://doi.org/10.3389/fimmu.2020.587581

Vidak E, Javoršek U, Vizovišek M, Turk B (2019) Cysteine cathepsins and their extracellular roles: shaping the microenvironment. Cells 8:264. https://doi.org/10.3390/cells8030264

Vidal-Albalat A, González F v. (2016) Natural products as cathepsin inhibitors. Studies in Natural Products Chemistry 50: 179–213. https://doi.org/10.1016/B978-0-444-63749-9.00006-2

Vijay Avin BR, Prabhu T, Ramesh CK, et al (2014) New role of lupeol in reticence of angiogenesis, the cellular parameter of neoplastic progression in tumorigenesis models through altered gene expression. Biochemical and Biophysical Research Communications 448:139–144. https://doi.org/10.1016/j.bbrc.2014.04.090

Vizovišek M, Fonović M, Turk B (2019) Cysteine cathepsins in extracellular matrix remodeling: extracellular matrix degradation and beyond. Matrix Biology 75–76:141–159. https://doi.org/10.1016/j.matbio.2018.01.024

Walker C, Mojares E, del Río Hernández A (2018) Role of extracellular matrix in development and cancer progression. International Journal of Molecular Sciences 19:3028. https://doi.org/10.3390/ijms19103028

Walma DAC, Yamada KM (2020) The extracellular matrix in development. Development 147:dev175596. https://doi.org/10.1242/dev.175596

Wang M, Xu Y, Wen G-Z, et al (2019) Rapamycin suppresses angiogenesis and lymphangiogenesis in melanoma by downregulating VEGF-A/VEGFR-2 and VEGF-C/VEGFR-3 expression. OncoTargets and Therapy 12:4643–4654. https://doi.org/10.2147/OTT.S205160

Wetzel S, Seipold L, Saftig P (2017) The metalloproteinase ADAM10: a useful therapeutic target? Biochimica et Biophysica Acta (BBA) - Molecular Cell Research 1864:2071–2081. https://doi.org/10.1016/j.bbamcr.2017.06.005

Winer A, Adams S, Mignatti P (2018) Matrix metalloproteinase inhibitors in cancer therapy: turning past failures into future successes. Molecular Cancer Therapeutics 17:1147–1155. https://doi.org/10.1158/1535-7163.MCT-17-0646

Wing Ying Cheung C, Gibbons N, Wayne Johnson D, Lawrence Nicol D (2010) Silibinin – A promising new treatment for cancer. Anti-Cancer Agents in Medicinal Chemistry 10:186–195. https://doi.org/10.2174/1871520611009030186

Winkler J, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z (2020) Concepts of extracellular matrix remodelling in tumour progression and metastasis. Nature Communications 11:5120. https://doi.org/10.1038/s41467-020-18794-x

Wittenauer J, Mäckle S, Sußmann D, et al (2015) Inhibitory effects of polyphenols from grape pomace extract on collagenase and elastase activity. Fitoterapia 101:179–187. https://doi.org/10.1016/j.fitote.2015.01.005

Wroblewski M, Bauer R, Cubas Córdova M, et al (2017) Mast cells decrease efficacy of anti-angiogenic therapy by secreting matrix-degrading granzyme B. Nature Communications 8:269. https://doi.org/10.1038/s41467-017-00327-8

Wu W, Xie Z, Zhang Q, et al (2020) Hyperoside ameliorates diabetic retinopathy via anti-oxidation, inhibiting cell damage and apoptosis induced by high glucose. Frontiers in Pharmacology 11:797. https://doi.org/10.3389/fphar.2020.00797

Xiaokaiti Y, Wu H, Chen Y, et al (2015) EGCG reverses human neutrophil elastase-induced migration in A549 cells by directly binding to HNE and by regulating α1-AT. Scientific Reports 5:11494. https://doi.org/10.1038/srep11494

Xu H, Becker CM, Lui WT, et al (2011) Green tea epigallocatechin-3-gallate inhibits angiogenesis and suppresses vascular endothelial growth factor C/vascular endothelial growth factor receptor 2 expression and signaling in experimental endometriosis in vivo. Fertility and Sterility 96:1021-1028.e1. https://doi.org/10.1016/j.fertnstert.2011.07.008

Yamada KM, Collins JW, Cruz Walma DA, et al (2019) Extracellular matrix dynamics in cell migration, invasion and tissue morphogenesis. International Journal of Experimental Pathology 100:144–152. https://doi.org/10.1111/iep.12329

Yao Z, Wu H, Zhang S, Du Y (2014) Enzymatic preparation of κ-carrageenan oligosaccharides and their anti-angiogenic activity. Carbohydrate Polymers 101:359–367. https://doi.org/10.1016/j.carbpol.2013.09.055

Yee EMH, Brandl MB, Pasquier E, et al (2017) Dextran-catechin inhibits angiogenesis by disrupting copper homeostasis in endothelial cells. Scientific Reports 7:7638. https://doi.org/10.1038/s41598-017-07452-w

Ying QL, Rinehart AR, Simon SR, Cheronis JC (1991) Inhibition of human leucocyte elastase by ursolic acid. Evidence for a binding site for pentacyclic triterpenes. Biochemical Journal 277:521–526. https://doi.org/10.1042/bj2770521

Yodkeeree S, Chaiwangyen W, Garbisa S, Limtrakul P (2009) Curcumin, demethoxycurcumin and bisdemethoxycurcumin differentially inhibit cancer cell invasion through the down-regulation of MMPs and uPA. The Journal of Nutritional Biochemistry 20:87–95. https://doi.org/10.1016/j.jnutbio.2007.12.003

Yu X, Zhu J, Mi M, et al (2012) Anti-angiogenic genistein inhibits VEGF-induced endothelial cell activation by decreasing PTK activity and MAPK activation. Medical Oncology 29:349–357. https://doi.org/10.1007/s12032-010-9770-2

Zhao D, Qin C, Fan X, et al (2014) Inhibitory effects of quercetin on angiogenesis in larval zebrafish and human umbilical vein endothelial cells. European Journal of Pharmacology 723:360–367. https://doi.org/10.1016/j.ejphar.2013.10.069

Zhong S, Khalil RA (2019) A Disintegrin and Metalloproteinase (ADAM) and ADAM with thrombospondin motifs (ADAMTS) family in vascular biology and disease. Biochemical Pharmacology 164:188–204. https://doi.org/10.1016/j.bcp.2019.03.033

Zhou Y-X, Xia W, Yue W, et al (2015) Rhein: a review of pharmacological activities. Evidence-Based Complementary and Alternative Medicine 2015:1–10. https://doi.org/10.1155/2015/578107

Zou G, Zhang X, Wang L, et al (2020) Herb-sourced emodin inhibits angiogenesis of breast cancer by targeting VEGFA transcription. Theranostics 10:6839–6853. https://doi.org/10.7150/thno.43622

References Related To Table 1

Anwar S, Speciale A, Fratantonio D, et al (2014) Cyanidin-3-O-glucoside modulates intracellular redox status and prevents HIF-1 stabilization in endothelial cells in vitro exposed to chronic hypoxia. Toxicology Letters 226:206–213. https://doi.org/10.1016/j.toxlet.2014.01.048

Baici A, Gyger-Marazzi M (1982) The slow, tight-binding inhibition of cathepsin b by leupeptin. a hysteretic effect. European Journal of Biochemistry 129:33–41. https://doi.org/10.1111/j.1432-1033.1982.tb07017.x

Barash U, Lapidot M, Zohar Y, et al (2018) Involvement of heparanase in the pathogenesis of mesothelioma: basic aspects and clinical applications. Journal of the National Cancer Institute 110. https://doi.org/10.1093/jnci/djy032

Bertl E, Bartsch H, Gerhäuser C (2006) Inhibition of angiogenesis and endothelial cell functions are novel sulforaphane-mediated mechanisms in chemoprevention. Molecular Cancer Therapeutics 5:575-85. https://doi.org/10.1158/1535-7163.MCT-05-0324

Bhat TA, Nambiar D, Tailor D, et al (2013) Acacetin inhibits in vitro and in vivo angiogenesis and downregulates stat signaling and vegf expression. Cancer Prevention Research 6:1128–1139. https://doi.org/10.1158/1940-6207.CAPR-13-0209

Boreddy SR, Sahu RP, Srivastava SK (2011) Benzyl isothiocyanate suppresses pancreatic tumor angiogenesis and invasion by inhibiting HIF-α/VEGF/Rho-GTPases: pivotal role of STAT-3. PLoS ONE 6:e25799. https://doi.org/10.1371/journal.pone.0025799

Cale JM, Li S-H, Warnock M, et al (2010) Characterization of a novel class of polyphenolic inhibitors of plasminogen activator inhibitor-1. Journal of Biological Chemistry 285:7892–7902. https://doi.org/10.1074/jbc.M109.067967

Cao Y, Fu Z-D, Wang F, et al (2005) Anti-angiogenic activity of resveratrol, a natural compound from medicinal plants. Journal of Asian Natural Products Research 7:205–213. https://doi.org/10.1080/10286020410001690190

Cárdenas C, Quesada AR, Medina MA (2006) Evaluation of the anti-angiogenic effect of aloe-emodin. Cellular and Molecular Life Sciences 63:3083–3089. https://doi.org/10.1007/s00018-006-6399-6

Cárdenas C, Quesada AR, Medina MA (2011) Anti-angiogenic and anti-inflammatory properties of kahweol, a coffee diterpene. PLoS ONE 6:e23407. https://doi.org/10.1371/journal.pone.0023407

Cárdenas C, Quesada AR, Medina MÁ (2004) Effects of ursolic acid on different steps of the angiogenic process. Biochemical and Biophysical Research Communications 320:402–408. https://doi.org/10.1016/j.bbrc.2004.05.183

Chen M-L, Lin Y-H, Yang C-M, Hu M-L (2012) Lycopene inhibits angiogenesis both in vitro and in vivo by inhibiting MMP-2/uPA system through VEGFR2-mediated PI3K-Akt and ERK/p38 signaling pathways. Molecular Nutrition & Food Research 56:889–899. https://doi.org/10.1002/mnfr.201100683

Donà M, Dell'Aica I, Calabrese F, et al (2003) Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. The

Journal of Immunology 170:4335–4341. https://doi.org/10.4049/jimmunol.170.8.4335

Elkin M, Miao H-Q, Nagler A, et al (2000) Halofuginone: a potent inhibitor of critical steps in angiogenesis progression. The FASEB Journal 14:2477–2485. https://doi.org/10.1096/fj.00-0292com

Fajardo I, Quesada AR, Castro IN de, et al (1999) A comparative study of the effects of genistein and 2-methoxyestradiol on the proteolytic balance and tumour cell proliferation. British Journal of Cancer 80:17-24. https://doi.org/10.1038/sj.bjc.6690315

Fortes C, García-Vilas JA, Quesada AR, Medina MÁ (2012) Evaluation of the anti-angiogenic potential of hydroxytyrosol and tyrosol, two bio-active phenolic compounds of extra virgin olive oil, in endothelial cell cultures. Food Chemistry 134:134–140. https://doi.org/10.1016/j.foodchem.2012.02.079

García-Caballero M, Cañedo L, Fernández-Medarde A, et al (2014) The marine fungal metabolite, AD0157, inhibits angiogenesis by targeting the akt signaling pathway. Marine Drugs 12:279–299. https://doi.org/10.3390/md12010279

García-Caballero M, Marí-Beffa M, Cañedo L, et al (2013) Toluquinol, a marine fungus metabolite, is a new angiosuppresor that interferes the Akt pathway. Biochemical Pharmacology 85:1727–1740. https://doi.org/10.1016/j.bcp.2013.04.007

García-Vilas JA, Pino-Ángeles A, Martínez-Poveda B, et al (2017a) The noni anthraquinone damnacanthal is a multi-kinase inhibitor with potent anti-angiogenic effects. Cancer Letters 385:1–11. https://doi.org/10.1016/j.canlet.2016.10.037

García-Vilas JA, Quesada AR, Medina MÁ (2013) 4-Methylumbelliferone Inhibits Angiogenesis in Vitro and in Vivo. Journal of Agricultural and Food Chemistry 61:4063–4071. https://doi.org/10.1021/jf303062h

García-Vilas JA, Quesada AR, Medina MÁ (2017b) Hydroxytyrosol targets extracellular matrix remodeling by endothelial cells and inhibits both ex vivo and in vivo angiogenesis. Food Chemistry 221:1741–1746. https://doi.org/10.1016/j.foodchem.2016.10.111

Gho Y, Shin S-S, Choi YH, et al (2019) Hydrangenol suppresses VEGF-stimulated angiogenesis by targeting p27KIP1-dependent G1-cell cycle arrest, VEGFR-2-mediated signaling, and MMP-2 expression. Animal Cells and Systems 23:72–81. https://doi.org/10.1080/19768354.2019.1578262

Guruvayoorappan C, Kuttan G (2007) β-Carotene Inhibits Tumor-Specific Angiogenesis by Altering the Cytokine Profile and Inhibits the Nuclear Translocation of Transcription Factors in B16F-10 Melanoma Cells. Integrative Cancer Therapies 6:258–270. https://doi.org/10.1177/1534735407305978

Hamsa TP, Kuttan G (2010) Harmine inhibits tumour specific neo-vessel formation by regulating VEGF, MMP, TIMP and pro-inflammatory mediators both in vivo and in vitro. European Journal of Pharmacology 649:64–73. https://doi.org/10.1016/j.ejphar.2010.09.010

Hamsa TP, Kuttan G (2011) Anti-angiogenic activity of Ipomoea obscura extract and Ipobscurine-A. Immunopharmacology and Immunotoxicology 33:488-97. https://doi.org/10.3109/08923973.2010.531277

Hossain A, Heron D, Davenport I, et al (2016) Protective effects of bestatin in the retina of streptozotocin-induced diabetic mice. Experimental Eye Research 149:100–106. https://doi.org/10.1016/j.exer.2016.06.016

Hseu Y-C, Chen S-C, Lin W-H, et al (2011) Toona sinensis (leaf extracts) inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis in vascular endothelial cells. Journal of Ethnopharmacology 134:111–121. https://doi.org/10.1016/j.jep.2010.11.058

Hsiao Y-H, Hsieh M-J, Yang S-F, et al (2019) Phloretin suppresses metastasis by targeting protease and inhibits cancer stemness and angiogenesis in human cervical cancer cells. Phytomedicine 62:152964. https://doi.org/10.1016/j.phymed.2019.152964

Hu J, Lin S, Huang JJ, Cheung PCK (2018) Mechanistic study of the in vitro and in vivo inhibitory effects of protocatechuic acid and syringic acid on vegf-induced angiogenesis. Journal of Agricultural and Food Chemistry 66:6742–6751. https://doi.org/10.1021/acs.jafc.8b01534

Huang M, Tang S-N, Upadhyay G, et al (2014) Embelin suppresses growth of human pancreatic cancer xenografts, and pancreatic cancer cells isolated from krasg12d mice by inhibiting akt and sonic hedgehog pathways. PLoS ONE 9:e92161. https://doi.org/10.1371/journal.pone.0092161

Huang S-T, Wang C-Y, Yang R-C, et al (2011a) Ellagic acid, the active compound of phyllanthus urinaria , exerts in vivo anti-angiogenic effect and inhibits MMP-2 activity. Evidence-Based Complementary and Alternative Medicine 2011:1–10. https://doi.org/10.1093/ecam/nep207

Huang S-T, Yang R-C, Wu H-T, et al (2011b) Zinc-chelation contributes to the anti-angiogenic effect of ellagic acid on inhibiting MMP-2 activity, cell migration and tube formation. PLoS ONE 6:e18986. https://doi.org/10.1371/journal.pone.0018986

Ishai-Michaeli R, Eldor A, Vlodavsky I (1990) Heparanase activity expressed by platelets, neutrophils, and lymphoma cells releases active fibroblast growth factor from extracellular matrix. Cell Regulation 1:833–842. https://doi.org/10.1091/mbc.1.11.833

Jankun J (2011) Diverse inhibition of plasminogen activator inhibitor type 1 by theaflavins of black tea. International Journal of Molecular Medicine 27:525–529. https://doi.org/10.3892/ijmm.2011.615

Jankun J, Selman SH, Swiercz R, Skrzypczak-Jankun E (1997) Why drinking green tea could prevent cancer. Nature 387:561–561. https://doi.org/10.1038/42381

Jedinák A, Maliar T, Grančai D, Nagy M (2006a) Inhibition activities of natural products on serine proteases. Phytotherapy Research 20:214–217. https://doi.org/10.1002/ptr.1836

Jedinák A, Mučková M, Košt'álová D, et al (2006b) Antiprotease and antimetastatic activity of ursolic acid isolated from salvia officinalis. Zeitschrift für Naturforschung C 61:777–782. https://doi.org/10.1515/znc-2006-11-1203

Jiang C, Agarwal R, Lü J (2000) Anti-angiogenic potential of a cancer chemopreventive flavonoid antioxidant, silymarin: inhibition of key attributes of vascular endothelial cells and angiogenic cytokine secretion by cancer epithelial cells. Biochemical and Biophysical Research Communications 276:371–378. https://doi.org/10.1006/bbrc.2000.3474

Kanashiro A, Souza JG, Kabeya LM, et al (2007) Elastase release by stimulated neutrophils inhibited by flavonoids: importance of the catechol group. Zeitschrift für Naturforschung C 62:357–361. https://doi.org/10.1515/znc-2007-5-607

Kang S-W, Choi J-S, Choi Y-J, et al (2010) Licorice isoliquiritigenin dampens angiogenic activity via inhibition of MAPK-responsive signaling pathways leading to induction of matrix metalloproteinases. The Journal of Nutritional Biochemistry 21:55–65. https://doi.org/10.1016/j.jnutbio.2008.10.004

Kanjoormana M, Kuttan G (2010) Antiangiogenic activity of ursolic acid. Integrative Cancer Therapies 9:224–235. https://doi.org/10.1177/1534735410367647

Kim A, Ma JY (2019) Piceatannol-3-O-β-D-glucopyranoside (PG) exhibits in vitro anti-metastatic and anti-angiogenic activities in HT1080 malignant fibrosarcoma cells. Phytomedicine 57:95–104. https://doi.org/10.1016/j.phymed.2018.12.017

Kim A, Ma JY (2018) Rhaponticin decreases the metastatic and angiogenic abilities of cancer cells via suppression of the HIF-1α pathway. International Journal of Oncology 53(3):1160-1170. https://doi.org/10.3892/ijo.2018.4479

Kim JH, Byun JC, Hyun CG, Lee NH (2009) Compounds with elastase inhibition and free radical scavenging activities from Callistemon lanceolatus. Journal of Medicinal Plants Research 3:914–920

Kim JH, Shim JS, Lee S-K, et al (2002) Microarray-based analysis of anti-angiogenic activity of demethoxycurcumin on human umbilical vein endothelial cells: crucial involvement of the down-regulation of matrix metalloproteinase. Japanese Journal of Cancer Research 93:1378–1385. https://doi.org/10.1111/j.1349-7006.2002.tb01247.x

Kim MH (2003) Flavonoids inhibit VEGF/bFGF-induced angiogenesis in vitro by inhibiting the matrix-degrading proteases. Journal of Cellular Biochemistry 89:529–538. https://doi.org/10.1002/jcb.10543

Kumar A, Sunita P, Jha S, Pattanayak SP (2016) Daphnetin inhibits TNF-α and VEGF-induced angiogenesis through inhibition of the IKKs/IκBα/NF-κB, Src/FAK/ERK1/2 and Akt signalling pathways. Clinical and Experimental Pharmacology and Physiology 43:939–950. https://doi.org/10.1111/1440-1681.12608

Kumar S, Agnihotri N (2021) Piperlongumine targets NF-κB and its downstream signaling pathways to suppress tumor growth and metastatic potential in experimental colon cancer. Molecular and Cellular Biochemistry 476:1765–1781. https://doi.org/10.1007/s11010-020-04044-7

Kunimasa K, Ikekita M, Sato M, et al (2010) Nobiletin, a citrus polymethoxyflavonoid, suppresses multiple angiogenesis-related endothelial cell functions and angiogenesis in vivo. Cancer Science 101: 2462-9 . https://doi.org/10.1111/j.1349-7006.2010.01668.x

Kvestad H, Evensen L, Lorens JB, et al (2014) In vitro characterization of valproic acid, atra, and cytarabine used for disease-stabilization in human acute myeloid leukemia: antiproliferative effects of drugs on endothelial and osteoblastic cells and altered release of angioregulatory mediators by endothelial cells. Leukemia Research and Treatment 2014:1–12. https://doi.org/10.1155/2014/143479

Kwak H-J, Park M-J, Park C-M, et al (2006) Emodin inhibits vascular endothelial growth factor-A-induced angiogenesis by blocking receptor-2 (KDR/Flk-1) phosphorylation. International Journal of Cancer 118:2711–2720. https://doi.org/10.1002/ijc.21641

Lai K, Hsu S, Yang J, et al (2015) Diallyl trisulfide inhibits migration, invasion and angiogenesis of human colon cancer HT-29 cells and umbilical vein endothelial cells, and suppresses murine xenograft tumour growth. Journal of Cellular and Molecular Medicine 19: 474-84. https://doi.org/10.1111/jcmm.12486

Lai S-L, Cheah S-C, Wong P-F, et al (2012) In vitro and in vivo anti-angiogenic activities of panduratin A. PLoS ONE 7:e38103. https://doi.org/10.1371/journal.pone.0038103

Lamy S, Akla N, Ouanouki A, et al (2012) Diet-derived polyphenols inhibit angiogenesis by modulating the interleukin-6/STAT3 pathway. Experimental Cell Research 318:1586–1596. https://doi.org/10.1016/j.yexcr.2012.04.004

Laschke MW, Vorsterman Van Oijen AE, Scheuer C, et al (2011) In vitro and in vivo evaluation of the anti-angiogenic actions of 4-hydroxybenzyl alcohol. British Journal of Pharmacology, 163(4): 835-844. https://doi.org/10.1111/j.1476-5381.2011.01292.x

Lavie G, Mandel M, Hazan S, et al (2005) Anti-angiogenic activities of hypericin in vivo: potential for ophthalmologic applications. Angiogenesis 8:35–42. https://doi.org/10.1007/s10456-005-3828-3

Lee J-H, Choi S, Lee Y, et al (2010) Herbal compound farnesiferol c exerts antiangiogenic and antitumor activity and targets multiple aspects of VEGFR1 (Flt1) or VEGFR2 (Flk1) signaling cascades. Molecular Cancer Therapeutics 9:389–399. https://doi.org/10.1158/1535-7163.MCT-09-0775

Leu SJ, Lin YP, Lin RD, et al (2006) Phenolic constituents of Malus doumeri var. formosana in the field of skin care. Biological & Pharmaceutical Bulletin 29:740–745. https://doi.org/10.1248/bpb.29.740

Li W, Yu J, Xiao X, et al (2021) Imperatorin reduces the inflammatory response of atherosclerosis by regulating MAPKs signaling pathway in vivo and in vitro. International Immunopharmacology 90:107170. https://doi.org/10.1016/j.intimp.2020.107170

Li Y, Sun W-G, Liu H-K, et al (2011) γ-Tocotrienol inhibits angiogenesis of human umbilical vein endothelial cell induced by cancer cell. The Journal of Nutritional Biochemistry 22:1127–1136. https://doi.org/10.1016/j.jnutbio.2010.09.012

Li Z, Yao L, Li J, et al (2012) Celastrol nanoparticles inhibit corneal neovascularization induced by suturing in rats. International Journal of Nanomedicine 7:1163–1173. https://doi.org/10.2147/IJN.S27860

Lim H, Jang J-P, Han J, et al (2018) Antiangiogenic potential of microbial metabolite elaiophylin for targeting tumor angiogenesis. Molecules 23:563. https://doi.org/10.3390/molecules23030563

Lin Z, Jensen JK, Hong Z, et al (2013) structural insight into inactivation of plasminogen activator inhibitor-1 by a small-molecule antagonist. Chemistry & Biology 20:253–261. https://doi.org/10.1016/j.chembiol.2013.01.002

Liu C-T, Bi K-W, Huang C-C, et al (2017) Davallia bilabiata exhibits anti-angiogenic effect with modified MMP-2/TIMP-2 secretion and inhibited VEGF ligand/receptors expression in vascular endothelial cells. Journal of Ethnopharmacology 196:213–224. https://doi.org/10.1016/j.jep.2016.12.019

Liu G, Liu M, Wei J, et al (2014) CS5931, a novel polypeptide in ciona savignyi, represses angiogenesis via inhibiting vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). Marine Drugs 12:1530–1544. https://doi.org/10.3390/md12031530

Liu J-J, Huang T-S, Cheng W-F, Lu F-J (2003) Baicalein and baicalin are potent inhibitors of angiogenesis: Inhibition of endothelial cell proliferation, migration and differentiation. International Journal of Cancer 106:559–565. https://doi.org/10.1002/ijc.11267

Liu Y, Liu G, Mei J, Wang J (2016) The preventive effects of hyperoside on lung cancer in vitro by inducing apoptosis and inhibiting proliferation through Caspase-3 and P53 signaling pathway. Biomedicine & Pharmacotherapy 83:381–391. https://doi.org/10.1016/j.biopha.2016.06.035

López-Jiménez A, García-Caballero M, Medina MÁ, Quesada AR (2013) Anti-angiogenic properties of carnosol and carnosic acid, two major dietary compounds from rosemary. European Journal of Nutrition 52:85–95. https://doi.org/10.1007/s00394-011-0289-x

Lou C, Zhu Z, Xu X, et al (2019) Picroside II, an iridoid glycoside from Picrorhiza kurroa, suppresses tumor migration, invasion, and angiogenesis in vitro and in vivo. Biomedicine & Pharmacotherapy 120:109494. https://doi.org/10.1016/j.biopha.2019.109494

Lou C, Zhu Z, Zhao Y, et al (2017) Arctigenin, a lignan from Arctium lappa L., inhibits metastasis of human breast cancer cells through the downregulation of MMP-2/−9 and heparanase in MDA-MB-231 cells. Oncology Reports 37:179–184. https://doi.org/10.3892/or.2016.5269

Madhan B, Krishnamoorthy G, Rao JR, Nair BU (2007) Role of green tea polyphenols in the inhibition of collagenolytic activity by collagenase. International Journal of Biological Macromolecules 41:16–22. https://doi.org/10.1016/j.ijbiomac.2006.11.013

Martínez-Poveda B, García-Vilas JA, Cárdenas C, et al (2013) The brominated compound aeroplysinin-1 inhibits proliferation and the expression of key pro-inflammatory molecules in human endothelial and monocyte cells. PLoS ONE 8:e55203. https://doi.org/10.1371/journal.pone.0055203

Martínez-Poveda B, Quesada AR, Medina MÁ (2005a) Hyperforin, a bio-active compound of St. John’s Wort, is a new inhibitor of angiogenesis targeting several key steps of the process. International Journal of Cancer 117:775–780. https://doi.org/10.1002/ijc.21246

Martínez-Poveda B, Quesada AR, Medina MÁ (2005b) Hypericin in the dark inhibits key steps of angiogenesis in vitro. European Journal of Pharmacology 516:97–103. https://doi.org/10.1016/j.ejphar.2005.03.047

Masola V, Onisto M, Zaza G, et al (2012) A new mechanism of action of sulodexide in diabetic nephropathy: inhibits heparanase-1 and prevents FGF-2-induced renal

epithelial-mesenchymal transition. Journal of Translational Medicine 10:213. https://doi.org/10.1186/1479-5876-10-213
Meyer K, Ueberham E, Gebhardt R (2004) Influence of organosulphur compounds from garlic on the secretion of matrix metalloproteinases and their Inhibitor TIMP-1 by cultured HUVEC cells. Cell Biology and Toxicology 20:253–260. https://doi.org/10.1023/B:CBTO.0000038463.55930.79
Midorikawa S, Sanada H, Hashimoto S, Watanabe T (2000) Enhancement by homocysteine of plasminogen activator inhibitor-1 gene expression and secretion from vascular endothelial and smooth muscle cells. Biochemical and Biophysical Research Communications 272:182–185. https://doi.org/10.1006/bbrc.2000.2753
Mitaine-Offer A-C, Hornebeck W, Sauvain M, Zèches-Hanrot M (2002) Triterpenes and phytosterols as human leucocyte elastase inhibitors. Planta Medica 68:930–2. https://doi.org/10.1055/s-2002-34929
Moncada-Pazos A, Obaya AJ, Viloria CG, et al (2011) The nutraceutical flavonoid luteolin inhibits ADAMTS-4 and ADAMTS-5 aggrecanase activities. Journal of Molecular Medicine 89:611–619. https://doi.org/10.1007/s00109-011-0741-7
Murata RM, Yatsuda R, dos Santos MH, et al (2010) Antiproliferative effect of benzophenones and their influence on cathepsin activity. Phytotherapy Research 24:379–383. https://doi.org/10.1002/ptr.2954
Niu T-T, Zhang D-S, Chen H-M, Yan X-J (2015) Modulation of the binding of basic fibroblast growth factor and heparanase activity by purified λ-carrageenan oligosaccharides. Carbohydrate Polymers 125:76–84. https://doi.org/10.1016/j.carbpol.2015.02.069
Oku N, Matsukawa M, Yamakawa S, et al (2003) Inhibitory effect of green tea polyphenols on membrane-type 1 matrix metalloproteinase, MT1-MMP1. Biological and Pharmaceutical Bulletin 26:1235–1238. https://doi.org/10.1248/bpb.26.1235
Park SL, Won SY, Song J-H, et al (2016) Esculetin inhibits VEGF-induced angiogenesis both in vitro and in vivo. The American Journal of Chinese Medicine 44:61–76. https://doi.org/10.1142/S0192415X1650004X
Pilátová M, Stupáková V, Varinská L, et al (2010) Effect of selected flavones on cancer and endothelial cells. General Physiology and Biophysics 29:134–143. https://doi.org/10.4149/gpb_2010_02_134
Pratheeshkumar P, Kuttan G (2011) Andrographolide inhibits human umbilical vein endothelial cell invasion and migration by regulating MMP-2 and MMP-9 during angiogenesis. Journal of Environmental Pathology, Toxicology and Oncology 30:33–41. https://doi.org/10.1615/JEnvironPatholToxicolOncol.v30.i1.40
Pratheeshkumar P, Son Y-O, Budhraja A, et al (2012) Luteolin inhibits human prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. PLoS ONE 7:e52279. https://doi.org/10.1371/journal.pone.0052279
Rasouli H, Parvaneh S, Mahnam A, et al (2017) Anti-angiogenic potential of trypsin inhibitor purified from Cucumis melo seeds: Homology modeling and molecular docking perspective. International Journal of Biological Macromolecules 96:118–128. https://doi.org/10.1016/j.ijbiomac.2016.12.027

Rodríguez-Nieto S, González-Iriarte M, Carmona R, et al (2002) Antiangiogenic activity of aeroplysinin-1, a brominated compound isolated from a marine sponge. The FASEB Journal 16:1–27. https://doi.org/10.1096/fj.01-0427fje

Rodríguez-Nieto S, Chavarría T, Martínez-Poveda B, et al (2002) Anti-angiogenic effects of homocysteine on cultured endothelial cells. Biochemical and Biophysical Research Communications 293:497–500. https://doi.org/10.1016/S0006-291X(02)00232-2

Samad NA, Abdul AB, Rahman HS, et al (2018) Zerumbone suppresses angiogenesis in hepg2 cells through inhibition of matrix metalloproteinase-9, vascular endothelial growth factor, and vascular endothelial growth factor receptor expressions. Pharmacognosy magazine 13: S731-S736. https://doi.org/10.4103/pm.pm_18_17

Saraswati S, Alhaider AA, Agrawal SS (2013a) Punarnavine, an alkaloid from Boerhaavia diffusa exhibits anti-angiogenic activity via downregulation of VEGF in vitro and in vivo. Chemico-Biological Interactions 206:204–213. https://doi.org/10.1016/j.cbi.2013.09.007

Saraswati S, Kanaujia PK, Kumar S, et al (2013b) Tylophorine, a phenanthraindolizidine alkaloid isolated from Tylophora indica exerts antiangiogenic and antitumor activity by targeting vascular endothelial growth factor receptor 2–mediated angiogenesis. Molecular Cancer 12:82. https://doi.org/10.1186/1476-4598-12-82

Sartor L, Pezzato E, Dell'Aica I, et al (2002) Inhibition of matrix-proteases by polyphenols: chemical insights for anti-inflammatory and anti-invasion drug design. Biochemical Pharmacology 64:229–237. https://doi.org/10.1016/S0006-2952(02)01069-9

Scoditti E, Calabriso N, Massaro M, et al (2012) Mediterranean diet polyphenols reduce inflammatory angiogenesis through MMP-9 and COX-2 inhibition in human vascular endothelial cells: A potentially protective mechanism in atherosclerotic vascular disease and cancer. Archives of Biochemistry and Biophysics 527:81–89. https://doi.org/10.1016/j.abb.2012.05.003

Shi G, Zhou L (2018) Emodin suppresses angiogenesis and metastasis in anaplastic thyroid cancer by affecting TRAF6-mediated pathways in vivo and in vitro. Molecular Medicine Reports 18:5191–5197. https://doi.org/10.3892/mmr.2018.9510

Shin K-O, Seo C-H, Cho H-H, et al (2014) Ginsenoside compound K inhibits angiogenesis via regulation of sphingosine kinase-1 in human umbilical vein endothelial cells. Archives of Pharmacal Research 37: 1183-92. https://doi.org/10.1007/s12272-014-0340-6

Siedle B, Hrenn A, Merfort I (2007) Natural compounds as inhibitors of human neutrophil elastase. Planta Medica 73:401–420. https://doi.org/10.1055/s-2007-967183

Singh RP, Dhanalakshmi S, Agarwal C, Agarwal R (2005) Silibinin strongly inhibits growth and survival of human endothelial cells via cell cycle arrest and downregulation of survivin, Akt and NF-κB: implications for angioprevention and antiangiogenic therapy. Oncogene 24:1188–1202. https://doi.org/10.1038/sj.onc.1208276

Sinha S, Khan S, Shukla S, et al (2016) Cucurbitacin B inhibits breast cancer metastasis and angiogenesis through VEGF-mediated suppression of FAK/MMP-9 signaling axis. The International Journal of Biochemistry & Cell Biology 77:41–56. https://doi.org/10.1016/j.biocel.2016.05.014

Soundararajan R, Sayat R, Robertson GS, Marignani PA (2009) Triptolide: an inhibitor of a disintegrin and metalloproteinase 10 (ADAM10) in cancer cells. Cancer Biology & Therapy 8:2054–2062. https://doi.org/10.4161/cbt.8.21.9803

Tan W, Lin L, Li M, et al (2003) Quercetin, a dietary-derived flavonoid, possesses antiangiogenic potential. European Journal of Pharmacology 459:255–262. https://doi.org/10.1016/S0014-2999(02)02848-0

Taraboletti G, Poli M, Dossi R, et al (2004) Antiangiogenic activity of aplidine, a new agent of marine origin. British Journal of Cancer 90:2418–2424. https://doi.org/10.1038/sj.bjc.6601864

Thaloor D, Singh AK, Sidhu GS, et al (1998) Inhibition of angiogenic differentiation of human umbilical vein endothelial cells by curcumin. Cell growth & differentiation 9:305–12

Thejass P, Kuttan G (2007a) Inhibition of endothelial cell differentiation and proinflammatory cytokine production during angiogenesis by allyl isothiocyanate and phenyl isothiocyanate. Integrative Cancer Therapies 6:389–399. https://doi.org/10.1177/1534735407309084

Thejass P, Kuttan G (2007b) Inhibition of angiogenic differentiation of human umbilical vein endothelial cells by diallyl disulfide (DADS). Life Sciences 80:515–521. https://doi.org/10.1016/j.lfs.2006.09.045

Tsai M-Y, Yang R-C, Wu H-T, et al (2011) Anti-angiogenic effect of tanshinone IIA involves inhibition of matrix invasion and modification of MMP-2/TIMP-2 secretion in vascular endothelial cells. Cancer Letters 310:198–206. https://doi.org/10.1016/j.canlet.2011.06.031

Umezawa H, Aoyagi T, Morishima H, et al (1970) Chymostatin, a new chymotrypsin inhibitor produced by actinomycetes. The Journal of Antibiotics 23:425–427. https://doi.org/10.7164/antibiotics.23.425

Vidal-Albalat A, González F v. (2016) Natural products as cathepsin inhibitors. Studies in Natural Products Chemistry 50:179–213

Vijay Avin BR, Prabhu T, Ramesh CK, et al (2014) New role of lupeol in reticence of angiogenesis, the cellular parameter of neoplastic progression in tumorigenesis models through altered gene expression. Biochemical and Biophysical Research Communications 448:139–144. https://doi.org/10.1016/j.bbrc.2014.04.090

Wang L, Lan X-Y, Ji J, et al (2018) Anti-inflammatory and anti-angiogenic activities in vitro of eight diterpenes from Daphne genkwa based on hierarchical cluster and principal component analysis. Journal of Natural Medicines 72:675–685. https://doi.org/10.1007/s11418-018-1202-1

Wang N, Wang Z-Y, Mo S-L, et al (2012) Ellagic acid, a phenolic compound, exerts anti-angiogenesis effects via VEGFR-2 signaling pathway in breast cancer. Breast Cancer Research and Treatment 134:943–955. https://doi.org/10.1007/s10549-012-1977-9

Wang S-J, Sun B, Cheng Z-X, et al (2011) Dihydroartemisinin inhibits angiogenesis in pancreatic cancer by targeting the NF-κB pathway. Cancer Chemotherapy and Pharmacology 68:1421–1430. https://doi.org/10.1007/s00280-011-1643-7

Wang Z, Wang N, Han S, et al (2013) Dietary compound isoliquiritigenin inhibits breast cancer neoangiogenesis via VEGF/VEGFR-2 signaling pathway. PLoS ONE 8:e68566. https://doi.org/10.1371/journal.pone.0068566

Wittenauer J, Mäckle S, Sußmann D, et al (2015) Inhibitory effects of polyphenols from grape pomace extract on collagenase and elastase activity. Fitoterapia 101:179–187. https://doi.org/10.1016/j.fitote.2015.01.005

Wu W, Xie Z, Zhang Q, et al (2020) Hyperoside ameliorates diabetic retinopathy via anti-oxidation, inhibiting cell damage and apoptosis induced by high glucose. Frontiers in Pharmacology 11:797. https://doi.org/10.3389/fphar.2020.00797

Wu XY, Xu H, Wu ZF, et al (2015) Formononetin, a novel FGFR2 inhibitor, potently inhibits angiogenesis and tumor growth in preclinical models. Oncotarget 6:44563–44578. https://doi.org/10.18632/oncotarget.6310

Yamakawa S, Asai T, Uchida T, et al (2004) (−)-Epigallocatechin gallate inhibits membrane-type 1 matrix metalloproteinase, MT1-MMP, and tumor angiogenesis. Cancer Letters 210:47–55. https://doi.org/10.1016/j.canlet.2004.03.008

Yan M, Wang H, Gu Y, et al (2021) Melatonin exerts protective effects on diabetic retinopathy via inhibition of Wnt/β-catenin pathway as revealed by quantitative proteomics. Experimental Eye Research 205:108521. https://doi.org/10.1016/j.exer.2021.108521

Yang G-W, Jiang J-S, Lu W-Q (2015) Ferulic acid exerts anti-angiogenic and anti-tumor activity by targeting fibroblast growth factor receptor 1-mediated angiogenesis. International Journal of Molecular Sciences 16:24011–24031. https://doi.org/10.3390/ijms161024011

Yang J, Jiang M, Zhen Y (2003) Novobiocin inhibits angiogenesis and shows synergistic effect with vincristine. Yao xue xue bao = Acta pharmaceutica Sinica 38: 731-734

Ying QL, Rinehart AR, Simon SR, Cheronis JC (1991) Inhibition of human leucocyte elastase by ursolic acid. Evidence for a binding site for pentacyclic triterpenes. Biochemical Journal 277:521–526. https://doi.org/10.1042/bj2770521

Yodkeeree S, Chaiwangyen W, Garbisa S, Limtrakul P (2009) Curcumin, demethoxycurcumin and bisdemethoxycurcumin differentially inhibit cancer cell invasion through the down-regulation of MMPs and uPA. The Journal of Nutritional Biochemistry 20:87–95. https://doi.org/10.1016/j.jnutbio.2007.12.003

Yu X, Zhu J, Mi M, et al (2012) Anti-angiogenic genistein inhibits VEGF-induced endothelial cell activation by decreasing PTK activity and MAPK activation. Medical Oncology 29:349–357. https://doi.org/10.1007/s12032-010-9770-2

Yue PYK, Wong DYL, Wu PK, et al (2006) The angiosuppressive effects of 20(R)-ginsenoside Rg3. Biochemical Pharmacology 72:437–445. https://doi.org/10.1016/j.bcp.2006.04.034

Zhang L, Chen C, Duanmu J, et al (2018) Cryptotanshinone inhibits the growth and invasion of colon cancer by suppressing inflammation and tumor angiogenesis through modulating MMP/TIMP system, PI3K/Akt/mTOR signaling and HIF-1α nuclear translocation. International Immunopharmacology 65:429–437. https://doi.org/10.1016/j.intimp.2018.10.035

Zhang L, Chen L, Lu Y, et al (2010a) Danshensu has anti-tumor activity in B16F10 melanoma by inhibiting angiogenesis and tumor cell invasion. European Journal of Pharmacology 643:195–201. https://doi.org/10.1016/j.ejphar.2010.06.045

Zhang S, Salemi J, Hou H, et al (2010b) Rapamycin promotes β-amyloid production via ADAM-10 inhibition. Biochemical and Biophysical Research Communications 398:337–341. https://doi.org/10.1016/j.bbrc.2010.06.017

Zhang W, Lu Y, Xu B, et al (2009) Acidic mucopolysaccharide from holothuria leucospilota has antitumor effect by inhibiting angiogenesis and tumor cell invasion in vivo and in vitro. Cancer Biology & Therapy 8:1489–1499. https://doi.org/10.4161/cbt.8.15.8948

Zhou D-C, Zheng G, Jia L-Y, et al (2021) Comprehensive evaluation on anti-inflammatory and anti-angiogenic activities in vitro of fourteen flavonoids from Daphne Genkwa based on the combination of efficacy coefficient method and principal component analysis. Journal of Ethnopharmacology 268:113683. https://doi.org/10.1016/j.jep.2020.113683