Original Articles

Antiangiogenic compounds: well-established drugs *versus* emerging natural molecules

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ABSTRACT

Angiogenesis is the natural and physiologic process of growing blood vessels from pre-existing ones. Pathological angiogenesis occurs when the precise balance of all the molecular pathways that regulate angiogenesis is disrupted, and this process is a critical step in many diseases, including cancer. A limited number of antiangiogenic synthetic drugs have been developed. However, due to toxicity and side effects issues, the search for alternative to existing drugs is ongoing. In this sense, natural molecules obtained from plants or macrofungi, have demonstrated extraordinary potential in the treatment of angiogenesis-related pathologies, specially taking into consideration its absence or very low toxicity, when compared to synthetic drugs. Using natural compounds as potential angiogenesis modulators is thus a promising field of research, supporting the creation of novel therapies able to reduce the use of drugs and associated side effects. In this review, the current status of antiangiogenic drugs and the wide variety of natural extracts and molecules with antiangiogenic capacities, as well as the angiogenesis molecular pathways and therapeutic targets, are presented. Finally, the challenges that need to be overcome in order to increase the use of natural compounds for clinical purposes are discussed.

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1. An overview of angiogenesis

Angiogenesis is a biological process through which there is the formation of new blood vessels from pre-existing ones and occurs normally in the body under normal physiological conditions [1–3]. Angiogenesis naturally occurs during fetal development, tissue regeneration, wound healing and in the female reproductive cycle [1–4].

The trigger for normal angiogenesis is usually the detection of low levels of oxygen (hypoxia) by specific sensing mechanisms, in poorly perfused tissues, which stimulates the formation of new blood vessels to comply the cell metabolic requirements [5].

Alternatively, physiological angiogenesis is also triggered by mechanical tissue stretch [6].

Angiogenesis occurs in several steps, although some of these events may temporally overlap. The first step is the release of proteases that promote enzymatic degradation of the capillary basement membrane that triggers the migration of endothelial cells to the interstitial space and subsequent proliferation in cord-like form (sprout). The developing sprout elongates by proliferation of more endothelial cell and the two developing sprouts eventually fuse and form the lumen. Blood flow is then established and the newly formed blood capillary is stabilized through basement membrane deposition, pericyte recruitment and smooth muscle layer formation [7].

Although angiogenesis is a naturally occurring event, abnormal growth of new blood vessels is known to be involved in the development of various diseases including cancer, inflammation, eye illnesses, retinopathy, rheumatoid arthritis, among others [2,8]. Additionally, inadequate vessel preservation or growth may lead to ischemia causing myocardial infarction, stroke, and

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Abbreviations

AA-DLMs	Arachidonic Acid-derived Lipid
Ang-1	Angiopoietin
Akt	Protein Kinase B
ATP	Adenosine Triphosphate
BAEC	Bovine Aorta Endothelial Cells
CAM	Chick Chorioallantonic Membrane
Cdc37	Cell Division Cycle Protein 37
CDK4	Cyclin Dependent Kinase 4
CDK6	Cyclin Dependent Kinase 6
CDKs	Cyclin Dependent Kinases
CK2	Casein Kinase II
c-KIT	Tyrosine-Protein Kinase Kit
c-Met	Tyrosine-Protein Kinase Met
COX-2	Cyclooxygenase-2
CRC	Colorectal Cancer
DNA	Deoxyribonucleic Acid
EGCG	Epigallocatechin-3-gallate
EGFR	Epidermal growth factor receptor
eNOS	Endothelial Nitric Oxide Synthase
ERK	Extracellular Signal − Regulated kinase
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factors
GEJA	Gastro-Esophageal Junction Adenocarcinoma
GIST	Gastrointestinal Stromal Tumors
HCC	Hepatocellular Carcinoma
HIF-1	Hypoxia-inducible Factor
HMEC	Human Microvascular Endothelial Cells
Hsp90	Heat Shock Protein 90
HUVECs	Human Umbilical Vein Endothelial Cells
IFN	Interferon
IκB	Inhibitor of kappa B
IKK-β	Inhibitor of kappa B subunit β
IL-1	Interleukin - 1
IL-6	Interleukin - 6
iNOS	Inducible Nitric Oxide Synthase
LOX-5	5-Lipoxygenase
MAPK	Mitogen-Activated Protein Kinases
MMP	Matrix Metalloproteinases
MOLT-4	Human Leukemia Cells
MTC	Medullary Thyroid Cancer
NF-κB	Nuclear Factor kappa B
nNOS	Neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NSCL	Non-Small-Cell Lung Carcinoma
PDGF	Platelet Derived Growth Factor
PDGFR	Platelet Derived Growth Factor Receptor
PGA$_2$	Prostaglandin A2
PGD$_2$	Prostaglandin D2
PGE$_2$	Prostaglandin E2
PGF$_2$-α	Prostaglandin F2-α
PGI$_2$	Prostaglandin I2
PIK-3	Phosphoinositide 3-kinase
PKC	Protein Kinase C
PKC-α	Protein Kinase C α
RATEC	Rate Adipose Tissue Endothelial Cells
RCC	Renal Cell Carcinoma
RET|	Rearranged During Transfection
ROS	Reactive Oxygen Species
RTK	Receptor Tyrosine Kinase
STC	Soft Tissue Carcinoma
Tie	Angiopoietin receptor
TKI	Tyrosine Kinase Inhibitors
TNF-α	Tumor Necrosis Factor - α
TSP-1	Thrombospondin-1
VEGF	Vascular Endothelial Growth Factors
VEGFR-2	Vascular Endothelial Growth Factors Receptor - 2
YSM	Yolk Chic Sac Membrane

neurodegenerative diseases [1]. From a therapeutic point of view, in some diseases, including ischemic heart disease and peripheral arterial disease, the objective is to stimulate angiogenesis, while in other pathologies, including cancer, the goal is to inhibit abnormal angiogenesis.

The importance of angiogenesis in tumor development and metastases in cancer is well established. For tumor growth to occur, large amounts of nutrients and oxygen are necessary and, to overcome this situation, angiogenesis plays an important role in tumor development since it guarantees the survival of cells. Angiogenesis also facilitates the dissemination of tumor cells through the blood stream, achieving distant organs in the form of metastases [9,10]. Tumor angiogenesis occurs when tumor cells, as well as inflammatory cells aggregated to the tumor, produces angiogenesis factors that trigger the rapid development of angiogenesis [7,11]. Inhibition of tumor angiogenesis can thus decrease the blood flow, required for tumor development, and tumor cell growth would be ceased due to lack of nutrients and growth factors needed to support the formation of newly formed vessels [12].

Previous studies have identified and characterized numerous angiogenesis factors, both activators and inhibitors, which regulate angiogenesis. The most extensively studied angiogenesis regulators is vascular endothelial growth factor (VEGF) and the respective membrane receptors, mainly VEGFR-2, as they are recognized to play a major role in regulating physiological and pathological angiogenesis [13]. The first treatment that targeted tumor angiogenesis was monoclonal antibody bevacizumab, which acts by interacting and blocking VEGF interaction with its receptor. An alternative strategy to target VEGFR-2 is using small molecules like tyrosine kinase inhibitors (TKIs). This strategy resulted in the first clinically approved small molecule-like drugs that targeted tumoral angiogenesis: sunitinib and sorafenib [14,15]. VEGFR-2 inhibition is still being actively studied; it is considered an important strategy for angiogenesis inhibition [16] and towards the discovery of new anticancer drugs [17]. Many other angiogenesis therapeutic targets are currently being studied.

Natural compounds, present in medicinal and/or nutritional plants as well as in macrofungi sources, have stimulated a great interest from the pharmaceutical industry. Different natural compounds such as phenolic compounds, alkaloids, terpenoids among others, have shown strong antiangiogenic effects and can be considered as viable options to develop new strategies or drugs for targeting pathological angiogenesis. The low or even absent toxicity of these active compounds, make them an attractive alternative for human health maintenance. Chemoprevention is a promising anticancer approach with reduced secondary effects in comparison with synthetic drugs [18]. Chemoprevention consists in using other active molecules, such as naturally occurring anticancer agents, to inhibit or reverse some processes of carcinogenesis, including pathological angiogenesis [19]. The advent of diseases

can thus be substantially prevented through new dietary habits, and the increased consumption of natural products have long been known to have a chemopreventive effect.

In the next section (Section 2) a survey of selected angiogenesis pathways and therapeutic targets will be presented, with emphasis on molecular mechanisms that have been targeted by natural molecules or natural sources. Section 3 will then review the current status of drugs used against angiogenesis, while Section 4 will provide an extensive review on the state of the art of known natural sources with antiangiogenic activity. Finally, Section 5 will focus on the challenges that natural products face to be used at a wider scale for medicinal purposes, thus as potential substitutes for the existing drugs.

2. Angiogenesis molecular pathways and therapeutic targets

The formation of new blood vessels is controlled by various angiogenic factors that act by triggering the signaling pathways leading to blood vessels formation and repairing. Other angiogenic factors may act by promoting the inhibition of angiogenesis, thus interfering with the formation of new blood vessels. The activation and inhibition effects of these angiogenetic factors are normally balanced so that blood vessels only form when needed by the organism. These angiogenic factors may be classified in different groups including growth factors, matrix metalloproteinases (MMP-2 and MMP-9), cytokines, transcription factors, arachidonic acid derivatives and cell cycle related proteins, among others [1]. All of these angiogenic factors may be regarded as potential therapeutic targets, for treatment of conditions involving pathological angiogenesis. Some of the most widely studied angiogenic factors, as potential therapeutic targets, include vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), platelet derived growth factor (PDGF), matrix metalloproteinases, tumor necrosis factor alpha (TNF-α) and hypoxia-inducible factor (HIF-1), just to name a few [20]. Therapeutic treatments that target angiogenic factors have in fact already been developed, with the notable example of antibodies and small TKIs against VEGF and respective

receptors (Table 1). A brief description of some of the most studied angiogenic factors, and the respective molecular pathway, will be presented, highlighting the pathways that have already been targeted by natural compounds and sources. Fig. 1 presents an overview of the signaling pathways involved in angiogenesis, which were targeted by different natural molecules.

2.1. Receptor tyrosine kinase (RTK)-mediated growth factors

Growth factors like VEGF have received great attention, as well as their respective membrane receptor tyrosine kinase (RTKs): VEGFR-1, VEGFR-2 and VEGFR-3 [21]. Recent studies revealed that VEGF is the major mediator of endothelial cells angiogenesis signaling pathways, and is considered the main signal transducer in angiogenesis regulation [3,12]. VEGF acts by interacting with the extracellular domain of the respective RTKs, present in the membrane of endothelial cells. This interaction promotes VEGFR dimerization and activates the intracellular domain tyrosine kinase activity of VEGF receptors. The intracellular domain then phosphorylates and activates specific proteins involved in angiogenesis signaling pathways and this process eventually leads to stimulation of endothelial cell migration, proliferation and vascular formation [6]. For the development of new angiogenic inhibitors, the inhibition of VEGFR-2 has attracted great attention, since several monoclonal antibodies and TKIs have shown that it was possible to stop tumor angiogenesis, by blocking interaction between VEGF and his receptor VEGFR-2, present in the membrane of endothelial cells [12].

Another growth factor involved in angiogenesis is the platelet-derived growth factor (PDGF) that acts by activating specific RTKs proteins (PDGFRα and PDGFRβ), present in the membrane of endothelial cells. PDGF stimulates pericyte recruitment, a process that is fundamental on blood vessel maturation [22], resulting in the stabilization of the capillary wall [23]. Moreover, has been shown that PDGF and VEGF work symbiotically in order to stimulate formation and stabilization of the new blood vessels [22].

Table 1
Drugs currently in clinical use that affect angiogenesis.

Drug	Mode of action	Approved indications	Year of approval	References
Bevacizumab (Avastin)	VEGF Antibody	CRC, NSCLC, RCC, breast cancer	2004	[4]
Cabozantinib (Cabometyx)	RTK Inhibitor (VEGFR, c-Met)	MTC; RCC	2011	[174]
Lenalidomide (Revlimid)	VEGF expression inhibitor	Multiple Myeloma	2004	[114]
Pazopanib (Votrient)	RTK Inhibitor (c-KIT, FGFR, PDGFR and VEGFR)	RCC, STS	2009	[175]
Ramucirumab (Cyramza)	VEGFR Antibody	GEJA, NSCL	2014	[176]
Regorafenib (Stivarga)	RTK Inhibitor (VEGFR, Tie)	CRC, GIST	2012	[177]
Sorafenib (Nexavar)	RTK Inhibitor Multi-RTK inhibitor	RCC, HCC; MTC	2005	[14]
Sunitinib (Sutent)	RTK Inhibitor (Kit,VEGFR-2 and PDGFR inhibitor)	GIST, RCC	2006	[15]
Thalidomide (Immunoprin)	TNF-α and IL-6 expression inhibitor, NF-κB and COX-2 inhibitor	Multiple Myeloma	2006	[178]
Vandetanib (Caprelsa)	RTK Inhibitor (VEGFR-2, EGFR and RET)	MTC	2011	[179]

c-KIT — Tyrosine-Protein Kinase Kit; c-Met — Tyrosine-Protein Kinase Met; COX-2 — Cyclooxygenase-2; CRC — Colorectal Cancer; EGFR — Epidermal growth factor receptor; FGFR — Fibroblast Growth Factor Receptor; GEJA — Gastro-Esophageal Junction Adenocarcinoma; GIST — Gastrointestinal Stromal Tumors; HCC — Hepatocellular Carcinoma; IL-6 — Interleukin-6; MTC — Medullary Thyroid Cancer; NF-κB — Nuclear Factor Kappa B; NSCL — Non-Small-Cell Lung Carcinoma; PDGFR — Platelet Derived Growth Factor Receptor; RCC — Renal Cell Carcinoma; RET — Rearranged During Transfection; RTK — Receptor Tyrosine Kinase; STC — Soft Tissue Carcinoma; Tie — Angiopoietin receptor; TNF-α — Tumor Necrosis Factor — α; VEGF — Vascular endothelial Growth Factor; VEGFR — Vascular Endothelial Growth Factor Receptor.
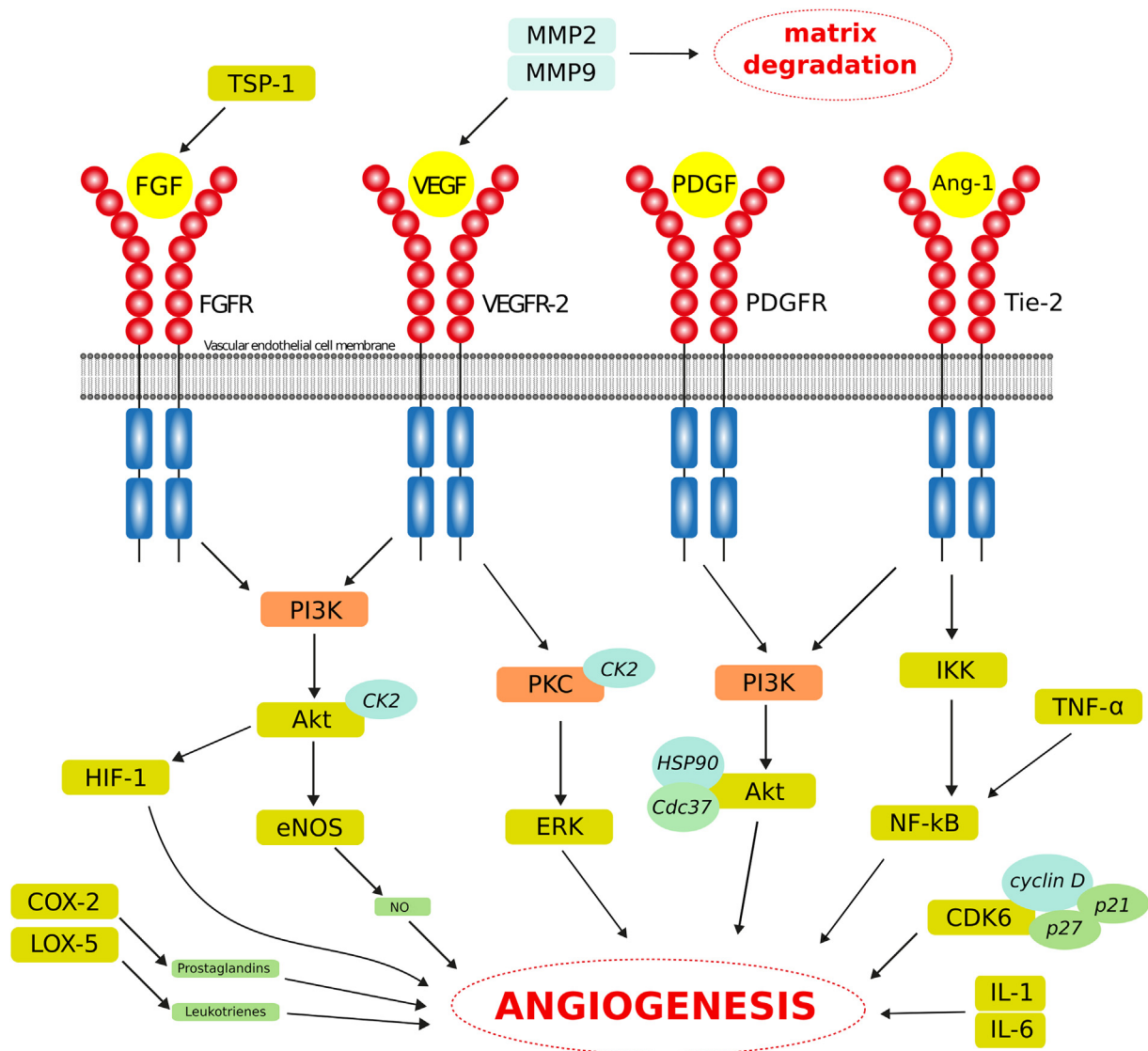
Fig. 1. Main molecular pathways involved in angiogenesis and that were targeted by natural molecules. Akt – Protein Kinase B; Ang-1 – Angiopoietin 1; CDK6 – Cyclin dependent kinase 6; Ck2 – Casein Kinase II; COX-2 – Cyclooxygenase-2; eNos – Endothelial nitric oxide synthase; ERK – Extracellular signal-regulated kinase; FGF – Fibroblast growth factor; FGFR – Fibroblast growth factor receptor; HIF-1 – Hypoxia-inducible factor; Hsp90 – Heat stock protein; IKK – Inhibitor of kappa B; IL-1 – Interleukin-1; IL-6 – Interleukin-6; LOX-5 – 5-Lipoxygenase; MMP2 – Matrix metalloproteinase 2; MMP9 – Matrix metalloproteinase 9; NF-kB – Nuclear factor kappa B; PDGF – Platelet derived growth factor; PI3K – Phosphoinositide 3-kinase; PKC – Protein kinase C; Tie – Angiopoietin receptor; TNF-α – Tumor necrosis factor-α; TSP-1 – Thrombospondin-1; VEGF – Vascular endothelial growth factor; VEGFR-2 – Vascular endothelial growth factor receptor 2.

Another RTK-mediated growth factor involved in angiogenesis is the fibroblast growth factor (FGF), known to be expressed by tumor cells [1]. FGF can be directly related with tumor cells proliferation, specifically the FGF-2 isoform, known to induce endothelial cell proliferation and migration by interacting with specific RTKs present in the membrane of endothelial cells [11,24]. Overall, FGF plays an important role in angiogenesis and evidence suggest the existence of cross talk and synergism between FGF and other growth factor pathways [25].

Finally, angiopoietin receptor-2 (Tie-2) is a transmembrane tyrosine kinase receptor, which binds to angiopoietins being also involved in regulating angiogenesis, among other cell activities. Angiopoietins are growth factors required for the formation of blood vessels, and Angiopoietin-1 (Ang-1) in known to down-regulate nuclear factor kappa B (NF-kB) complex, by binding to Tie-2 membrane receptor, via disruption of the IKK complex [26].

2.2. Matrix metalloproteinases

Matrix metalloproteinases (MMP) are proteinases participating in extracellular matrix degradation, a normal physiological process that is crucial in several biological events such as embryogenesis, cell proliferation, apoptosis, but also in angiogenesis [25]. Several MPPs were shown to be involved in pathological processes, for example in cancer development and metastasis, by promoting dysregulation of the basement membrane composition, thus facilitating apoptosis [27–30]. Specifically, MMP-2 and MMP-9 (also known as Gelatinase A and B, respectively) digest denatured collagens and were related to the cancer invasion process, as tumor cells must cross the collagen-rich basement membrane of blood vessel walls, in order to grow to distant locals from the primary tumor [27,28]. As an example of this process, the MMP-9 presents an important role in the pathological angiogenesis in malignant glioma [31] and diabetic retinopathy [30].

2.3. Cytokines

Cytokines are a diverse group of low molecular weight proteins that are involved in a number of cell signaling pathways that regulate as diverse cellular events as the immune response, inflammation and cancer, among others. It has been long recognized that the immune response is tightly associated with the endothelial process of angiogenesis, and that this association is implemented by way of cytokines that are produced during the immune response [32]. Endothelial cells have also been recognized for having the ability to generate abundantly cytokines [33]. These substances influence the intensity of the angiogenic response induced essentially during inflammation. The angiogenic effects attributed to cytokines has also been related with the ability to prime endothelial cells for the subsequent action of VEGF [34].

The protein cytokine interleukin-6 (IL-6) is involved in several biological activities, including hematopoiesis, immune responses and inflammation. This protein is secreted mainly by immune cells [35,36] and is hardly detectable under normal physiological conditions [36], although its induced biological responses are important in controlling inflammation and in maintenance of tissue homeostasis [35]. However, levels of IL-6 are significantly changed in pathological conditions; in particular, in inflammatory bowel disease, autoimmune acute phenomena, myeloma and arthritis [36], and part of IL-6 influence is by inducing leukocytosis and angiogenesis [37].

Other cytokine that also plays an important action in inflammatory diseases is interleukin-1 (IL-1), being a potent mediator in response to injury and infections [38]. IL-1 is mainly produced by myeloid cells and initiates and propagates inflammation mainly by inducing a local network of cytokines [30]. Pro-inflammatory mediators, including IL-1, have recently been shown to play an important role in tumor-mediated angiogenesis, and IL-1 inhibition is now considered as a potential target for anti-cancer therapy [39].

Tumor necrosis factor α (TNF-α) is an inflammatory cytokine, normally found in high concentrations in tissues subject to inflammation processes, being primarily produced by activated macrophages, T lymphocytes and natural killer cells [40]. Some studies reported that TNF-α is commonly found along the joints, leading to production of several pro-inflammatory effects, thus contributing to joint degradation [41,42]. Furthermore, TNF-α plays an important role the NF-κB signaling pathway initiation [43].

In general, in normal plasma concentrations, IL-1, IL-6 and TNF-α act together in promoting pathogens elimination, through increasing the body temperature (fever) and leukocytosis [36]. However, when found in high concentrations, they constitute activators of severe and acute inflammatory and immune responses, which have been associated with angiogenesis activation [39]. These cytokines have thus been recognized as potential targets for therapeutic antiangiogenic interventions [36,44].

2.4. Transcription factors

Transcription factors are proteins that are involved in gene expression regulation, by binding to specific deoxyribonucleic acid (DNA) sequences. Hypoxia-induced factor (HIF-1) is a transcription factor that plays an important role in the organism response to low oxygen concentrations scenarios (hypoxia), by regulating the expression of genes that facilitate adaptation and survival of cells in hypoxia situations [45,46]. In developing embryos, angiogenesis is a key process that is largely controlled by HIF-1 mediated hypoxia. The release of HIF-1 stimulates the expression of angiogenic factors, including VEGF. However, HIF-1 is also the main factor responsible for increasing the vascularization of hypoxic areas, which occur in ischemia situations and in tumor growth [46]. Although HIF-1 is

essential for the regulation of angiogenesis, it also promotes survival and proliferation of cancer cells, due to its angiogenic properties [47].

Nuclear factor kappa B (NF-kB) is a protein complex that acts as a transcription factor that is involved in several physiological processes including immune and inflammatory responses [48]. The NF-kB family is constituted by p65, RelB, c-Rel, p50 and p52 subunits, which act as homo or hetero-dimers [49]. Typically, the NF-kB complex remains inactive in the cytosol, by forming a protein complex with IkB (inhibitor of kappa B). By external stimulation, IkB is phosphorylated and targeted for degradation, thus freeing and enabling NF-kB gene expression activity [49,50]. However, dysregulation of NF-kB activity, plays a critical role in angiogenic, inflammatory and autoimmune diseases as well as in the cancer process [30]. NF-kB is involved in oncogenesis and tumor cell resistance, due to inadequate gene expression of several factors involved in apoptosis suppression, cell adhesion and proliferation [49]. The kinase responsible for the phosphorylation of IkB is IκB kinase-β (IKK-β), which is part of the IKK complex [51]. IKK-β is thus considered an angiogenesis inducer and is also regarded as a potential antiangiogenic target [51,52].

2.5. Cyclooxygenase 2 (COX-2) and 5-lipoxygenase (LOX-5)

Arachidonic acid-derived lipid mediators (AA-DLMs) are involved in the inflammation process and are biosynthesized by pathways dependent on cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. COX-2 is a key enzyme in the biosynthesis of prostaglandins, a family of AA-DLMs that include Prostaglandin E2 (PGE$_2$), Prostaglandin D2 (PGD$_2$), Prostaglandin F2α (PGF2α), Prostaglandin I2 (PGI$_2$) and prostaglandin A2 (PGA$_2$), [53,54]. Additionally, 5-lipoxygenase (LOX-5) participates in the conversion of arachidonic acid to leukotrienes, the second largest family of AA-DLMs [55]. COX2 and LOX-5 mediated biosynthesis of AA-DLMs, plays an important role in the inflammation process, which occur in different conditions including rheumatoid arthritis, neuro-inflammation and psoriasis [53–55]. Due to the contribution of COX-2 and LOX-5 in the inflammatory process, there is a large interest in the use of new drugs as inhibitors of these oxygenase enzymes [56,57]. Recently, the upregulation of COX-2 was reported in situations where antiangiogenic therapies were applied, specifically in treatment with anti-VEGFR-2 antibodies and sunitinib. When COX-2 is inhibited, the production of PGE2 levels diminish and the anti-VEGFR2 therapy efficiency improves. Following COX-2 inhibition, a reduction of tumors infiltration by cancer-associated fibroblasts is observed. Clinical investigations are ongoing to investigate the cooperative inhibition of COX-2 and VEGF-signaling capable to block tumor angiogenesis [58].

2.6. Cell cycle related proteins

The complexity of angiogenesis provides many targets for therapeutic intervention and a number of proteins, which are involved in the cell cycle complex machinery, have been studied as angiogenic modulators. Cyclin dependent kinases (CDKs) are serine/threonine kinases, which belong to the core cell cycle machinery, and exert their kinase activity when bounded to cyclins [59]. Cyclin D1 is an important cycle progression regulation and can also function as a co-transcriptional regulator by forming a complex with CDK6 kinase [60]. Overexpression of cyclin D1 has been shown to lead to accelerated G1 progression and chromosome instability in several cell types [61], and some studies relate the amount of cyclin D1 with cancer manifestation [62]. CDK6-cyclin D1 complex was also shown to be involved in tumor angiogenesis, through regulation of VEGF synthesis [62]. Also, cell cycle inhibitor proteins,

namely p21 and p27, were shown to block cell cycle progression by binding and inhibiting CDK-cyclin complexes [63], thus promoting cell cycle arrest, growth arrest and differentiation or senescence, in response to various stimuli [64]. Besides its ability to inhibit the activity of cyclin-dependent kinase, p21 also operates as a mediator of p53 tumor suppressor activity. Also, expression of p53 in cells can induce cell growth arrest through transcriptional activation of p21 [65]. Both p21 and p53 up-regulation can thus be viewed as potential therapeutic routes for tumor angiogenesis inhibition [66].

Heat shock protein 90 (Hsp90) is an essential adenosine triphosphate (ATP) dependent molecular chaperone, and is abundantly expressed in eukaryotic cells [67,68]. Hsp90 plays an important role in various cellular processes, among which cell cycle control, cell survival and different signaling pathways can be cited [69]. Hsp90 overexpression has been related to tumor cells survival, in adverse conditions such as lack of nutrients, hypoxia and acidosis [68]. Hsp90 has also been related to tumor angiogenesis, and recent studies have suggested that Hsp90 inhibitors promote angiogenesis inhibition, by affecting the PI3K/Akt/eNOS (phosphoinositide 3-kinase/protein kinase B/endothelial nitric oxide) signal transduction pathway in endothelial cells, as well as through down-regulation of VEGFR-2 expression [70].

Akt (also known as protein kinase B) is another serine/theronine kinase that has been recognized to be involved in the signaling pathways leading to cell proliferation, cell growth and survival [71], and the dysregulation of this kinase is related with various human diseases including diabetes, cancer and cardiovascular diseases [72]. Akt is activated by interacting with Hsp90, thus it is also recognized as a potential target in abnormal angiogenesis [71]. Cell division cycle 37 (Cdc37) protein has shown significant influence in cell proliferation, mainly in cancer cells [73]. Cdc37 promotes its function by forming complexes with oncogenic protein, including Hsp90, Raf1 and cyclin dependent kinase 4 (CDK4) [73]. Thereby, several authors have indicated Cdc37 as being involved in Hsp90 activation and subsequent tumor angiogenesis induction through Akt activation [74,75].

Extracellular signal-regulated kinase (ERK) is another serine/threonine kinase, which is a member of the mitogen-activated protein kinases (MAPK) kinase family that is known to be involved in various cellular functions, and in different cell types [76]. ERK is activated by different growth factors and cytokines, and have been reported to play pivotal roles in many aspects of cell function such as proliferation, differentiation and survival [77]. Phosphorylation of the ERK is induced by VEGF and, in this phosphorylated form, ERK is known to induce angiogenesis in endothelial cells. Inhibition of ERK was shown to prevent endothelial sprouting, although not initial artery differentiation. These studies implicate ERK as a specific effector of VEGFR signaling pathway, in the induction of angiogenic genes during sprouting [78].

2.7. Other intracellular angiogenic modulators

The most antique antiangiogenic factor to be identified was thrombospondin-1 (TSP-1). TSP-1 is an endogenous inhibitor and its antiangiogenic ability was related to the capability of interacting with FGF-2, thus preventing interaction between FGF-2 and the soluble heparin or endothelial cells heparin sulfate proteoglycans [79], thereby avoiding the progression of the angiogenic process. Angiostatin and endostatin were subsequently identified and both participate in antiangiogenic processes. Angiostatin is polypeptide that occur naturally in various animal species, including humans. It is classified as endogenous angiogenesis inhibitor and your capacity is related with downregulating VEGF expression blocking one the major vascular growth factors [80,81]. Like angiostatin, endostatin is also a polypeptide. Endostatin is derived from

collagen XVIII (created by digestion of the C terminal fragment of collagen) [82,83], it participates in inhibition of endothelial cells proliferation inhibiting many steps of angiogenesis [82,84]. The inhibition of VEGF, metalloproteinases and cyclin D1 is the most important ways that endostatin act for block the angiogenesis process [85]. Both proteins, angiostatin and endostatin, are expressed in pathological situations, such as pathological angiogenesis, and plays a critical role in inhibition of primary metastatic tumor growth [83].

The interferons are another molecules that act as angiogenesis inhibitor and can be classified in two classes: interferon-alpha (IFN-α) and interferon-beta (IFN-β) and both are cytokines. These interferons were one of the first to be used in association with chemotherapeutic agents in clinical trials of human tumors [86]. Thus, the IFN-α has been recognized as powerful angiogenic inhibitor [87] and though that IFN-α potential in angiogenic processes is mainly attributed to inhibition of FGF, decrease VEGF gene expression and downregulation of interleukin-8 production [87,88]. Additionally, the IFN-α has also direct effects on EC avoiding of their proliferation and migration [87]. Relatively to the IFN-β is described with capacities to decrease MMP-2 production through suppressing gene expression and down relate FGF expression [86].

Integrins belongs to heterodimeric transmembrane receptors (composed by an α- and a β-subunit) mediated cell-extracellular matrix adhesion [89] and coordinate a large amount of cellular activities in response to the extracellular environment [89]. Integrins receptors are important in angiogenic development [90] and, actuality, integrins represent an important target for pharmaceutical agents in order to create innovative ways for angiogenesis and metastatic control [91].

Neovastat is a product derived from shark cartilage (Æ-941) [92] and the main functionality is related with inhibition of two main mechanism of angiogenesis activation, in specific, VEGF (competes with VEGF for binding to VEGFR and inhibit the receptor activation) and MMP [92,93]. Additionally, the neovastat also shows a significant anti-tumor and anti-metastatic properties [93] and more recently the neovastat was also described with anti-inflammatory properties [94]. Furthermore, neovastat not revealed adverse side effects when applied in clinical uses.

Nitric oxide (NO) belongs to reactive oxygen species (ROS) and is catalyzed by the nitric oxide synthase (NOS) enzyme family [95,96]. Three NOS isoforms were identified including neuronal (nNOS), endothelial (eNOS) and inducible (iNOS) [96,97] and all isoforms play important biological functions. However, accumulated evidence suggests that NO production by eNOS, may play an important role in ischemic disorders by promoting neovascularization, and in tumor angiogenesis through Akt/eNOS signaling pathway activation. eNOS is thus regarded as a potential therapeutic target, either through activation in ischemic angiogenesis or through inactivation in tumor angiogenesis [70,98].

Casein Kinase II (CK2) is a serine/threonine kinase, which catalyzes the phosphorylation of several cytoplasmic and nuclear proteins [99]. CK2 participates in the regulation of multiple biological process including, survival, proliferation and cellular differentiation [100]. There is an increasing evidence pointing out that CK2 also plays an essential role in angiogenesis, either by interaction or phosphorylation of growth factors or proteins involved in angiogenesis signaling cascades [101]. Moreover, in tumor cells, the expression and activity of CK2 is frequently high to ensure cell growth [102]. CK2 inhibitors used for cancer treatment have found to be also angiogenesis inhibitors, and CK2 is widely regarded as a therapeutic target for cancer treatment and tumor angiogenesis [101].
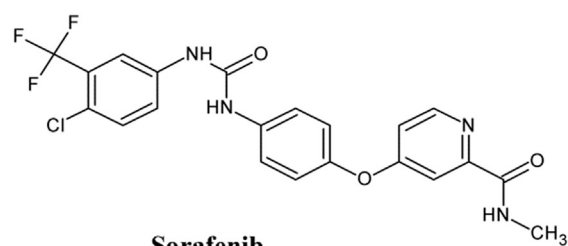
Protein kinase C (PKC) is another serine/threonine kinase that acts as an intracellular messenger, with important roles in

proliferation and migration of endothelial cells [79]. PKC is also known to be involved in RTKs-mediated angiogenesis signaling pathways, and its inhibition was shown to promote angiogenesis. The inhibition of PKC is thus regarded as a novel strategy for therapeutic angiogenesis, in cases of ischemic cardiovascular diseases [103].
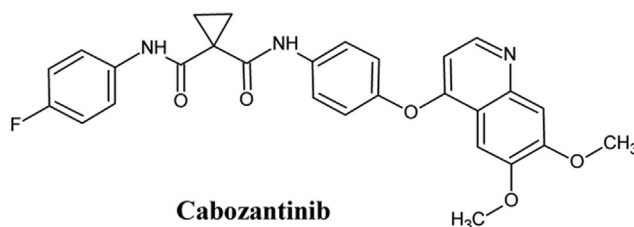
3. Antiangiogenic drugs

The development of drugs that act as angiogenic inhibitors has become essential for the treatment of various types of cancer (Table 1). The main objective of these antiangiogenic drugs is to deprive tumor cells of oxygen and nutrients, thus preventing the formation of new blood vessels and therefore limiting tumor growth [104]. An extensive, yet non-exhaustive, account of angiogenesis molecular pathways and targets was presented in chapter 2 (Fig. 1). Still, the majority of drugs in clinical use where developed, either as RTK inhibitors or as growth factor inhibitors, that activates the respective RTK (Fig. 2) [104,105]. The explanation for this lack of
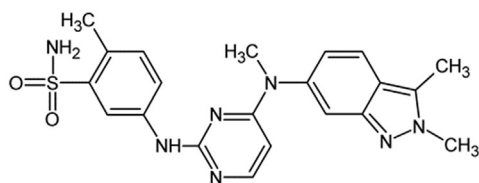
therapeutic targets diversity is probably due to the fact that anti-angiogenic drugs in clinical use are relatively recent. In fact, it was only in 2004 that bevacizumab (Avastin) was approved as the first antiangiogenic drug cancer treatment, by the USA Food and Drug Administration (FDA) [106,107]. Bevacizumab is a monoclonal antibody that specifically binds to VEGF, thus preventing it to interact and activate their RTK receptors [108]. Initially it was approved as a first-line treatment in metastatic colorectal cancer (CRC) and subsequently for treatment in cervical, non-small cell lung (NSCL), renal cell and glioblastoma cancers [106,109,110]. With the increased interest in antiangiogenic drugs, other compounds were developed over the years (Table 1). These compounds can be essentially divided in three families: antibodies targeting VEGF or his membrane RTKs (Bevacizumab and Ramucirumab); small molecule inhibitors of RTKs (Cabozatinib, Pazopanib, Regorafenib, Sorafenib, Sunitinib and Vandetanib) and small molecule inhibitors targeting proteins involved in angiogenesis signaling pathways, downstream membrane RTKs activation, either directly or by
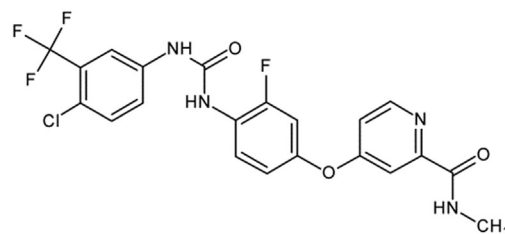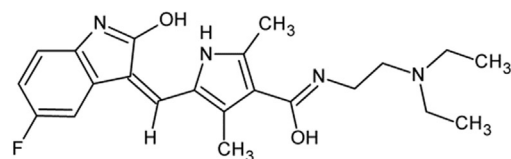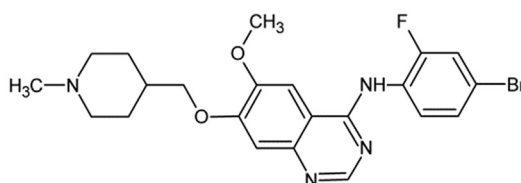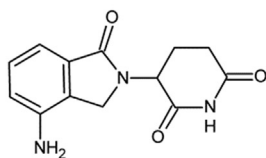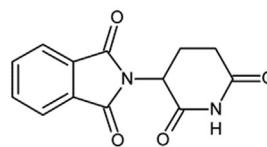

Fig. 2. Antiangiogenic drugs in clinical use.

inhibiting its expression (Lenalidomide and Thalidomide) [104,106].

Sorafenib was the first small RTK inhibitor drug to be developed and was initially approved against renal cell carcinoma, then against hepatocellular carcinoma (HCC) and more recently for differentiated thyroid treatment [111]. Sunitinib soon followed, being approved for gastrointestinal stromal tumors, rare stomach cancers and renal cell carcinoma [106,112]. Other RTK inhibitors approved for antiangiogenic clinical use includes: pazopanib, approved against advanced renal cell carcinoma and soft tissue sarcoma; vandetanib, approved against advanced medullary thyroid cancer situations that cannot be removed by surgery; carbozoantinib also approved against medullary thyroid cancer and renal cell carcinoma and vandetanib, approved against medullary thyroid cancer [107].

Thalidomide is a drug used for several decades for the treatment of various diseases, but was only approved as an anticancer drug in 2006, being approved against multiple myeloma. The precise mechanism of its antiangiogenic activity was not yet fully elucidated, although several activities that probably account for its activity, including TNF-α, IL-6 expression inhibition and NF-κB and COX-2 direct inhibition, were observed [113]. Lenalodomide belongs to the same type of inhibitors as thalidomine, being also used against multiple myeloma by inhibiting VEGF expression (Table 1) [114].

Despite the various molecules involved in the angiogenic process, most of these drugs have greater affinity for acting on tyrosine kinases, particularly the VEGF and respective receptor [104,105]. For example, bevacizumab is a monoclonal antibody that specifically recognize and binds to VEGF, making this growth factor unable to activate the receptor [108]. Other inhibitors bind to receptors, at the surface of endothelial cells, or to other proteins in the downstream signaling pathways that block their activities [112].

A common problem when using antiangiogenic drugs is the common situation of drug resistance. Although initially there is a positive response to the drugs, and the tumor angiogenesis is blocked, eventually the tumor acquires resistance and circumvents the pathway that is blocked, normally the VEGF/VEGFR2 target pair. Resistance is usually acquired when the tumor is able to growth, by enabling VEGF/VEGFR-2 independent pathways, thus promoting tumor angiogenesis [112]. An alternative to overcome the antiangiogenic drugs resistance is by their combination with other conventional therapies, including chemotherapy or radiation [19]. Combined therapies may have a synergistic effect when compared to the single drug therapies [115]. For example, bevacizumab sometimes is used with other drugs such as 5-fluorouracil or chemotherapy, to enhance treatment against various types of cancers [116].

Another factor to highlight is the toxicity that antiangiogenic drugs have in the body, contributing to side effects and leading sometimes to serious injuries [112]. The more common effects experienced by patients are hypertension, diarrhea, decrease of white blood cells, fatigue, taste modification and appetite reduction, weight loss, nausea, abdominal pain, skin reactions and hypocalcemia [110,112,117], and more frequent complications include hepatic toxicity, arterial and venous thrombotic events, gastric cancer and stroke [110,112]. Still, each drug is administered to different types of cancer and at distinct doses among patients, they result in more or fewer side effects in the body. In this sense, it becomes essential to develop new drugs with lower or no toxicity, and with the ability to prevent pathological angiogenesis [19]. Researchers have thus focused in antiangiogenic molecules that occur naturally in plants. These compounds are accessible, have low or minimal toxicity, and have been traditionally used for many years in the treatment of various diseases [47].

4. Natural sources of antiangiogenic compounds

Since primitive societies, plants, herbs and seeds, rich in phytochemicals, were used due to their benefits in human health. These molecules were shown to present a diverse array of action mechanisms, including antioxidant activity, enzyme stimulation, hormones mimicking and by interfering with DNA replication [115]. Phytochemicals have thus demonstrated positive effects in health, especially in cancer prevention [118]. Thereby, secondary plant metabolites have been considered as potential candidates for inhibition of pathological angiogenesis [47,119,120]. In some situations, in order to increase the benefits/properties of plants, extractions are conducted. Extractions allow the isolation of active ingredients, which may subsequently be administered at higher dosage, in order to obtain higher therapeutic effects [47]. Also, extracts may contain various phenolic compounds in natural proportions that, through synergistic interactions between them, complement each other's biological activity [19].

4.1. Antiangiogenic potential of extracts from plant and macrofungi origin

The information regarding the antiangiogenic potential of bioactive extracts, obtained from different natural sources, is summarized in Table 2, as well as the test/cell/model used, and their mechanism of action. Of note, is that methanolic and ethanolic extractions were the predominantly use methods with natural sources. The extracts have diverse mechanisms of action, and the same extract may have different pathways to inhibit angiogenesis. Different bioactive compounds may present distinct activities at different molecular levels [19].

In the work developed by Zhu et al. [121], artemisinin was isolated from an ethanolic extraction of *Arteminisia annua* L. and evaluated for its angiogenesis inhibition potential. Artemisinin contributed to a significant reduction of PGE$_2$ production in rat peritoneal cells and human peripheral blood mononuclear cells. Ghalib et al. [122] studied the antiangiogenic activity in HUVEC's of aspfalcolide, a compound isolated from a chloroform extract obtained from *Asparagus falcatus* L. leaves. The results showed a remarkable inhibitory effect of aspfalcolide on the proliferation (IC$_{50}$ 1.82 μM), migration and tube formation of human umbilical vein endothelial cells (HUVECs). Guimarães et al. [123] evaluated the potential of *Chamaemelum nobile* L. methanolic and aqueous extracts as angiogenesis inhibitors, through VEGFR-2 inhibition. The methanolic extract showed superior VEGFR-2 inhibition, when compared with the aqueous. Huang et al. [124] observed that a supercritical fluid extract of *Croton crassifolius* had potent antiangiogenic activity on the zebrafish model. They verified that cyperenoic acid is the active component present in the extract, and that this compound interferes with multiple molecular targets related to angiogenesis, including the growth factors VEGF and angiopoitein (Ang), and their respective RTKs (VEGFR and Tie-2). The antiangiogenic potential of *Eurycoma longifolia* methanol extract was studied by Al-Salahi et al. [125], using CAM (Chick chorioallantonic membrane), rat aortic, and HUVEC's assay models. They observed several angiogenesis inhibition related phenomena, including inhibition of neovascularization, suppression in sprouting of microvessels and inhibition of proliferation, migration and differentiation of HUVEC cells. Ahn et al. [95] investigated the antiangiogenic potential of ethanol extract and subsequent BuOH fraction of *Gastrodia elata Blume,* in CAM assay and murine

Table 2
Antiangiogenic extracts from plant and macrofungi origin.

Species	Extract type	Bioactive compounds	Assay/Cells/Model	Mechanisms/effects of antiangiogenic action	References
Plants					
Artemisia annua L.	Ethanol extract	Artemisinin (sesquiterpene lactone)	Rat peritoneal cells; PBMC	Inhibition of PGE2 production	[121]
Asparagus falcatus Linn	Chloroform extract	Aspfalcolide (sesquiterpene lactone)	HUVECs	Inhibition of VEGF-induced HUVECs proliferation, migration and tube formation	[122]
Chamaemelum nobile L.	Methanol extract and aqueous extract	–	Z'-Lyte^{TM} Kinase assay Kit	Inhibition of VEGFR-2 activity	[123]
Croton crassifolius Geiseler	Supercritical fluid extract (CO_2)	Cyperenoic acid (terpenes)	Zebrafish	Effects on VEGF-A, Ang and respective receptors	[124]
Eurycoma longifolia Jack	Methanol extract	–	CAM Rat aortic HUVECs	Inhibition of neovascularization Suppression in sprouting of microvessels Inhibition of proliferation, migration and differentiation	[125]
Gastrodia elata Blume	Ethanol extract Fraction: n-butanol	–	Murine macrophage cell line CAM	Inhibition of NO production and COX-2 Inhibition of vascular permeability	[95]
Origanum onites L.	Essential oil	–	5RP7 RATEC	Inhibition of cell viability and induction of apoptosis; May block tube formation and migration	[126]
Pinus halepensis Mill.	Lipid fraction (chloroform/methanol, 2:1)	Neutral lipids, glycolipids, and phospholipids	EC CAM	Inhibition of cells tubes formation Inhibition of blood vessels growth	[127]
Mushrooms					
Ganoderma lucidum (Curtis) P. Karst.	Methanol extract	Ganoderic acid F (lanostane triterpenoid)	HUVECs	Inhibition of capillary-like structures formation	[128]
Phellinus linteus (Berkeley & Curtis) Teng	Methanol extract Fractions: methylene chloride, ethyl acetate, n-butanol	–	HUVECs; Mice	Inhibition of proliferation, migration, tube formation and VEGFR-2 phosphorylation	[129]
Pleurotus tuber-regium (Rumph. ex Fr.) Singer	Ethanol extract Fraction: ethyl acetate	Chlorogenic acid and syringic acid	HUVECs Zebrafish	Inhibition of VEGF Decrease of blood vessels development	[130]

5RP7 – c-H-*ras* transformed rat embryonic cells; Ang – Angiopoietin; CAM – Chorioallantoic Membrane Assay; COX-2 – Cyclooxygenase-2; EC – Endothelial Cells; Flt-1 or VEGFR-1 – Vascular Endothelial Growth Factor Receptor 1; HUVEC – Human Umbilical Vein Endothelial cells; NO – Nitric Oxide; PBMC – Human Peripheral Blood Mononuclear Cells; RATEC – Rate Adipose Tissue Endothelial Cells; VEGF – Vascular Endothelial Growth Factor; VEGF-A – Vascular Endothelial Growth Factor A; VEGFR-2 – Vascular Endothelial Growth Factor Receptor 2. – Not specified or described.

macrophage cell line. The results suggested inhibition of vascular permeability and promotion of NO and COX-2 production. The antiangiogenic aptitude of the essential oil obtained from *Origanum onites* L. was evaluated by Bostancıoğlu et al. [126]. The results show that this essential oil could markedly inhibit cell viability and induce apoptosis in 5RP7 cells and block formation and migration in rate adipose tissue endothelial cells (RATEC). Additionally, the oil demonstrated a higher toxicity against cancer cell (5RP7), comparatively with healthy cells. In the work developed by Kadria et al. [127], the antiangiogenic activity of neutral lipids, glycolipids and phospholipids, obtained from *Pinus halepensis* Mill. seeds, was evaluated *in vitro* using endothelial cells and *in vivo* using the CAM assay. Both assays pointed out for strong antiangiogenic activity through significant inhibition of blood vessels growth.

Some studies with mushroom extracts also reveal anti-angiogenic properties. Nguyen et al. [128] studied ganoderic acid F, present in a methanolic extract of *Ganoderma lucidum,* and observed that ganoderic acid F have a potent inhibitory effect in the formation of capillary-like structures in HUVEC cells. Lee et al. [129] evaluated different fractions, obtained from *Phellinus linteus* methanolic extract. The results reveal several antiangiogenic related inhibitory effects, including inhibition of HUVEC cells pro-liferation, migration and assembly into capillary-like structures. They observed that the mechanism of action of the extracts occurred through inhibition of VEGFR-2 phosphorylation. Lin et al. [130] also studied an ethyl acetate fraction, obtained from the

mushroom *Pleurotus tuber-regium* ethanolic extract. The ethyl acetate fraction demonstrated to be rich in phenolics, mainly chlorogenic and syringic acids. Using the zebrafish model, the ethyl acetate fraction was shown to inhibit blood vessels development and, using the HUVEC cells model, this fraction revealed ability to inhibit VEGF.

Some studies evaluated the anticancer effects of combined phenolic rich extracts or combined individual phenolic compounds, in order to overcome pathological angiogenesis. Mertens-Talcott et al. [131] combined quercetin with ellagic acid and the results showed a synergistic effect on proliferation reduction, viability and apoptosis activation in human leukemia cells (MOLT-4). Mertens-Talcott & Percival [132] investigated the interactions of ellagic acid, quercetin and resveratrol and the results showed a high synergistic effect for the ellagic acid/resveratrol combination, in the induction of apoptosis and reduction of cell growth in MOLT-4 cells. Bagchi et al. [133] evaluated the *in vitro* and *in vivo* efficacy of a formulation composed by six anthocyanin-rich extracts (fruits of wild blueberry, bilberry, cranberry, elderberry, and strawberry, and from raspberry seeds) in antiangiogenic activity. In both *in vitro* and *in vivo*, the combined extracts suppressed important key regulators of angiogenesis such as TNF-α and VEGF in human keratinocytes, and significantly inhibited NF-kB in mouse hemangioendothelioma endothelial cells. Other studies developed by Zhou et al. [134] and Zhou et al. [135], evaluated *in vivo* the blend between tea and soy extracts observing the inhibition of angiogenesis, in prostate and

breast cancer. A combined extract of clove, oregano, thyme, walnuts and coffee, proved to be a potent modulator of NF-kB signaling, both *in vitro* in a monocytic cell line, and *in vivo* in transgenic mice [136].

4.2. Antiangiogenic potential of phenolic compounds

Recently, many studies about phenolic compounds have been published and have portrayed a picture where they were shown to interfere, at a molecular level, with a large number of biological mechanisms [1]. Phenolic compounds were shown to have high affinity to molecular targets, as diverse as membrane receptors, protein transporters, transcriptions factors or through gene expression modulation [53]. Table 3 and Fig. 3 present an overview of the phenolic compounds that have been reported in the literature with antiangiogenic activities, through different mechanism/effects of action.

Kim et al. [65,137], studied the antiangiogenic ability of two phenolic acids, caffeic and rosmarinic acids, in human retinal endothelial. The results showed that caffeic acid promotes inhibition of VEGF-induced proliferation, migration and tube formation, while rosmarinic acid showed cell cycle related inhibition of cell proliferation, related to increased levels of p21. Labrecque et al. [23] studied ellagic acid, having concluded that this phenolic acid inhibits phosphorylation of VEGFR-2 and PDGFR, in endothelial and smooth muscle cells, respectively.

Flavonoids are another group of phenolic compounds that have been extensively studied as potential chemopreventive agents. Acacetin was studied by Liu et al. [138] in ovarian cancer cells and showed a decrease in VEGF activation, through HIF-1α inhibition and Akt activation; indicating that Akt and HIF-1α are the essential downstream targets of acacetin for angiogenesis inhibition.

Apigenin is another flavonoid that has been extensively studied. A study performed by Zhao et al. [102], proved that apigenin exhibits cytotoxicity against human multiple myeloma cells, but not against normal peripheral blood mononuclear cells. These activities were related to proliferation inhibition and apoptosis induction in human multiple myeloma cells, through CK2 inhibition, Cdc37 reduction and Hsp90 phosphorylation. In a study performed by Banerjee and Mandal [139], two colorectal cell lines (HT-29 and HCT-15), were treated with apigenin and the results showed anti-proliferative and apoptotic effects, together with the increase of

Table 3
Phenolic compounds from commercial sources with antiangiogenic activity.

Phenolic compound		Assay/Cells/Model	Mechanisms/effects of antiangiogenic action	References
Phenolic acids	Caffeic acid	Human retinal endothelial cells	Inhibition of VEGF-induced proliferation, migration and tube formation	[137]
	Ellagic acid	BAECs	InhibitionVEGFR-2 phosphorylation	[23]
		Smooth muscle cells	Inhibition of VEGF and PDGF receptors phosphorylation	
	Rosmarinic acid	Human retinal endothelial cells	Inhibition of proliferation	[65]
			G$_2$/M phase cell cycle arrest with increase of p21^{WAF1}	
Flavonoids	Acacetin	Ovarian cancer cells	Decrease of VEGF transcriptional activation through HIF-1α inhibition and Akt activation	[138]
	Apigenin	Human multiple myeloma cells	Inhibition of CK2 kinase activity and reduction of Cdc37 and Hsp90 phosphorylation	[102]
		Human colorectal cancer cells	Anti-proliferative and apoptotic effects	[139]
			Increase in p21 levels through a p53 independent pathway and inhibition of cyclins E expression due to large amounts of the active p21and activation of p16 down-regulated cyclin D1	
		Human pancreatic cells	Induction of cell apoptosis and inhibition of IKK-β-mediated NF-κB activation	[140]
		Human pancreatic cancer cells	Inhibition of the proliferation and migration through inhibition of HSP90/Cdc37 interaction	[68]
		Z′-Lyte^{TM} Kinase assay Kit	Inhibition of VEGFR-2 activity	[123]
	Casticin and chrysosplenol D	Rat peritoneal cells; PBMC	Suppression of NO, PGE$_2$, and cytokines (VEGF, IL-1β, IL-6 and TNF-α) (*)	[121]
	Epigallocatechin-3-gallate (EGCG)	HUVECs	Interference with formation of VEGFR-2 complex	[141]
		Human fibrosarcoma cell line	Inhibition of MMP-2 and MMP-9	[27]
	Genistein	Zebrafish	Reduction of VEGF expression	[143]
		Retinal cells	Reduction of HIF-1α expression	[142]
		Intestinal epithelium	Inhibition of the activation of NF-κB and Akt signaling pathways	[43]
	Kushecarpin D	HUVECs	Inhibition of cell proliferation, migration, adhesion, and tube formation; Ability to induce cell cycle arrest at the G$_2$/M phase (*)	[144]
	Luteolin	Human pancreatic cancer cells	Anti-proliferative and apoptotic effects with significantly decreased protein expression of nuclear GSK-3β and NF-κB	[145]
		Z′-Lyte^{TM} Kinase assay Kit	Inhibition of VEGFR-2 activity	[123]
	Quercetin	HUVECs;	Inhibition of the VEGFR-2 expression; cell viability and tube formation	[146]
		Zebrafish	Disrupt formation of intersegmental vessels	
		Human lymphocytes	Inhibition of COX-2	[53]
Phenylethanoid	Hydroxytyrosol	EC	Inhibition of endothelial cell proliferation, migration and tube formation	[147]
			Increase subG1 subpopulation	
			Decrease MMP2 expression	
Stilbenes	Resveratrol	Capillary endothelial cells	Inhibition of VEGF and FGF receptors	[148]
		BAECs	Inhibition of proliferation, migration and tube formation	[149]
		Human adipose tissue	Inhibition of VEGF expression	[151]
		Retinal pigment epithelium	Inhibition of HIF-1α and VEGF expression	[150]

Akt — Serine-Threonine Kinase; BAECs — Bovine Aorta Endothelial Cells; CK2 — Casein Kinase 2; COX-2 — Cyclooxygenase 2; EC — Endothelial Cells; ECRF-24 — Human Vein Endothelial Cells; FGF-2 — Fibroblast Growth Factor 2; GSK-3β — Glycogen Synthase Kinase 3 beta; HIF-1α — Hypoxia Inducible Factor 1α; HMEC — Human Microvascular Endothelial; HSP90/Cdc37 — Heat Shock Protein 90/Cell Division Cycle 37; HUVECs — Human Umbilical Vein Endothelial Cells; IL-6 — Interleukin 6; IL-1β — Interleukin 1β; LOX-5 — 5-Lipoxygenase; MMP-2 — Matrix Metalloproteinase-2; MMP-9 — Matrix Metallopeptidase 9; NF-κB — Nuclear Factor Kappa B; NO — Nitric Oxide; p21^{WAF1} — Cyclin-Dependent Kinase Inhibitor 1; PBMC — Human Peripheral Blood Mononuclear Cells; PDGF — Platelet-Derived Growth Factor; PGE$_2$ — Prostaglandin E$_2$; TNF-α — Tumor Necrosis Factor α; VEGF — Vascular Endothelial Growth Factor; VEGFR-2 — Vascular Endothelial Growth Factor Receptor-2. *** assay without cells, (*) — From natural sources.

Caffeic acid

Ellagic acid

Rosmarinic acid

Acacetin

Apigenin

Casticin

Chrysosplenol D

Epigallocatechin-3-gallate

Genistein

Kushecarpin D

Luteolin

Quercetin

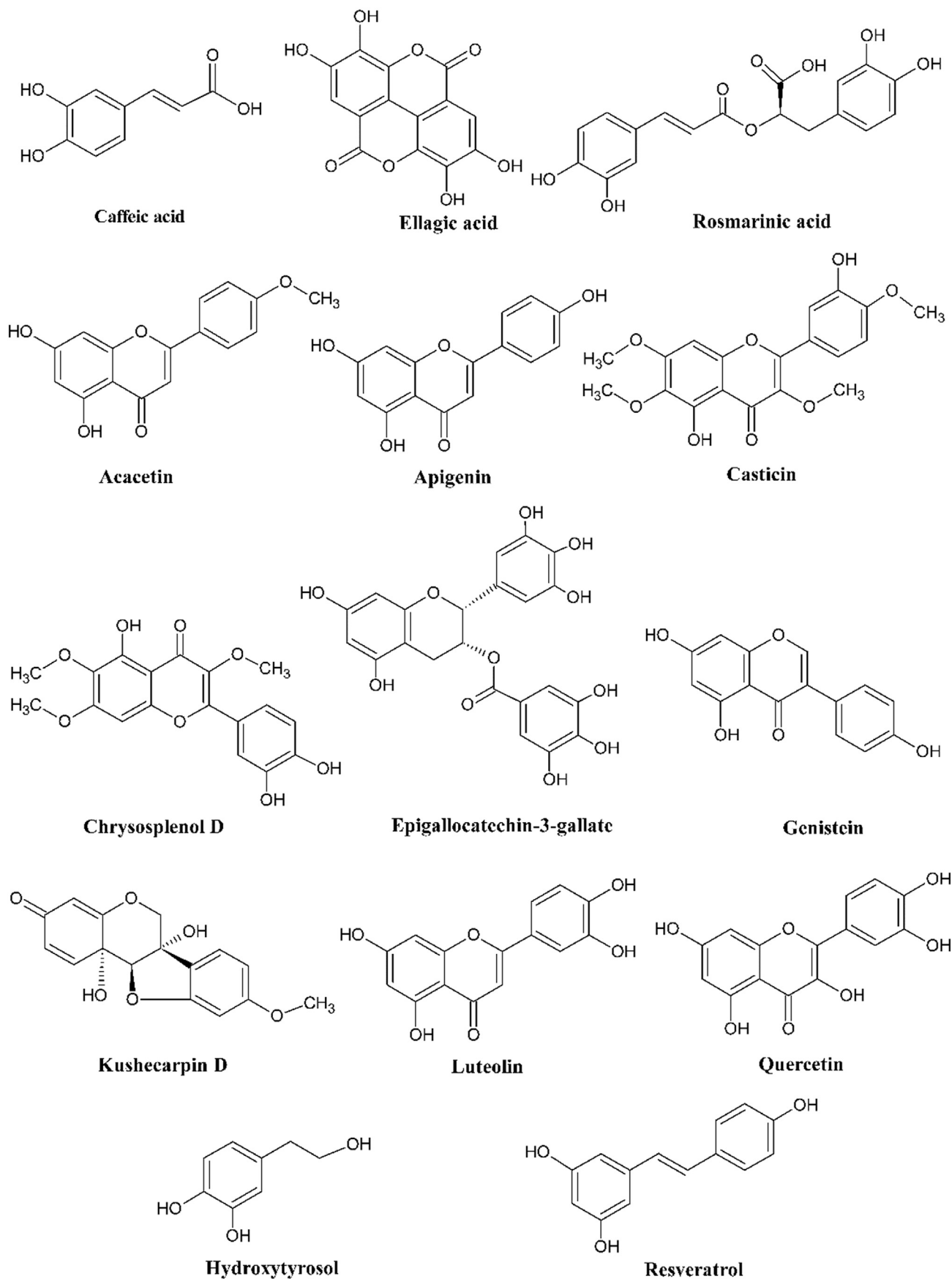**Hydroxytyrosol**

Resveratrol

Fig. 3. Phenolic compounds with antiangiogenic activity.

p21 levels and inhibition of cyclins E and D1. In pancreatic cells, different targets of apigenin were observed and this flavonoid was shown to interfere with cell proliferation, apoptosis and migration effects through different mechanism, including inhibition of IKK-β, NF-κB activation [140] and by HSP90/Cdc37 inhibition [68]. Finally, Guimarães et al. [123] demonstrated, by using an enzymatic assay, that apigenin was able to inhibit VEGFR-2.

Two flavonoids, casticin and chrysosplenol D, were extracted from *Arteminisia annua* L. and studied for their antiangiogenic proprieties by Zhu et al. [121]. This study showed that these flavonoids are involved in the suppression of various molecules associated to the angiogenesis process, including NO, PGE2, VEGF, IL-1β, IL-6 and TNF-α, both in rat peritoneal cells and human peripheral blood mononuclear cells.

Epigallocatechin-3-gallate (EGCG) is a flavonoid abundantly found in green tea, that has shown significant antioxidant and anticancer activity. Rodriguez et al. [141] reported that ECGC inhibits the formation of the VEGFR dimer, a process that is essential in VEGF angiogenesis signaling. Maeda-Yamamoto et al. [27] reported another effect of EGCG, in human fibrosarcoma cells, where metastasis development was inhibited by EGCG binding to the matrix metalloenzymes MMP-2 and MMP-9.

Wang et al. [142], Rathinasamy et al. [143] and Ruiz and Haller [43] studied the effects of genistein in angiogenesis and verified, respectively, a decrease in VEGF expression and consequent inhibition of regenerative caudal find in zebrafish, a decrease in HIF-1α expression in retinal cells and an inhibition of NF-κB and Akt signaling pathways in intestinal epithelium.

Kushecarpin D is a recently discovered flavonoid, isolated from the dried root of *Sophora flavescens* A., a plant known as a medicinal herb. In a study developed by Pu et al. [144], the antiangiogenic properties of Kushecarpin D were examined *in vitro* using HUVEC cells. The results indicate that this flavonoid showed antiangiogenic activity, via inhibitory effects on cell proliferation, cell migration, cell adhesion, and tube formation and the ability to induce cell cycle arrest at G2/M phase.

Luteolin is another flavonoid abundantly found in various food sources, its antiangiogenic properties were studied by Johnson and Mejia [145] and Guimarães et al. [123]. These works revealed interference in the angiogenesis at a molecular level, including, inhibition of the NF-kB signaling pathway in human pancreatic cancer cells, and VEGFR-2 activity inhibition.

To finalize the flavonoid group, Zhao et al. [146] investigated the antiangiogenic activity of quercetin, both with zebrafish model and HUVEC cells. Quercetin was shown to disrupt the formation of the intersegmental vessels, the dorsal aorta and the posterior cardinal vein in transgenic zebrafish model; and was shown to inhibit cell viability, VEGFR-2 expression and tube formation in HUVEC cells. Thus, quercetin was shown to be involved in suppressing, both *in vivo* and *in vitro*, the extracellular signal-regulated VEGFR-2 signaling pathway. Inflammation is a process that is tightly linked with angiogenesis, especially in conditions like rheumatoid arthritis. Pascual-Teresa et al. [53] studied the potential of quercetin to stagnate inflammation, by inhibition of COX-2 transcription, and demonstrated that quercetin metabolites were able to downgrade COX-2 expression.

Fortes et al. [147] investigated the antiangiogenic potential of hydroxytyrosol, a phenolic compound found in virgin olive oil, in three different types of endothelial cells including, bovine aorta endothelial cells (BAEC), umbilical vein endothelial cells (ECRF-24) and human microvascular endothelial cells (HMEC). This phenolic compound displayed a diverse set of action mechanisms related to angiogenesis inhibition. Hydroxytyrosol was shown to inhibit proliferation, migration and tube formation in the studied endothelial cells; it affects cell cycle by a remarkable increase in the subG1 subpopulation, which is indicative of apoptotic cells; and also decreases the MMP-2 mediated invasive potential of endothelial cells.

Resveratrol is the best studied phenolic compound from the stilbenes group. Bråkenhielm et al. [148] demonstrated the ability of resveratrol to inhibit capillary endothelial cell growth and this inhibition was related to the inhibition of both FGFR and VEGFR angiogenesis signaling pathway, thru suppression of MAP Kinase phosphorylation. In a work developed by Igura et al. [149], resveratrol was shown to inhibit proliferation, migration and tube formation in BAECs, although the exact molecular mechanism of action was not studied. Zhang et al. [150] verified that resveratrol significantly inhibited HIF-1α and VEGF expression, under hypoxia conditions. Another study performed by Cullberg et al. [151] also verified the ability of resveratrol to inhibit key factors in hypoxia conditions in human adipose tissue, specifically it was observed that resveratrol inhibited VEGF expression.

In general, the phenolic compounds have shown significant antiangiogenic properties, and are certainly worth a closer look for the possible development of new therapies against pathological and tumor angiogenesis.

4.3. Antiangiogenic potential of other natural compounds

Phenolic compounds are the most extensively studied natural compounds for their antiangiogenic properties. However, other compounds, obtained from natural sources, have demonstrated effectiveness as angiogenesis inhibitors, including alkaloids and terpenoids (Table 4 and Figs. 4–6), and have also become important topics of study concerning cancer prevention through inhibition of angiogenesis.

Pterogynidine is an alkaloid that showed strong antiangiogenic effects in HUVEC cells. The results demonstrated that this alkaloid drastically reduced capillary-like structures formation and its activity was related to NF-kB inhibition [152]. Punarnavine is another alkaloid that was shown to inhibit neovascularization in sponge implant model, using Ehrlich ascites carcinoma model, by suppressing VEGF expression. Using HUVECs cells, punarnavine also demonstrated inhibition ability of MMP-2 and MMP-9 expression [153]. In another study, Manu & Kuttan [77] proved the antiangiogenic properties of punarnavine in B16F-10 melanoma cells in mice, by supressing or down regulating the expression of MMP-2, MMP-9, ERK and VEGF. Zhao et al. [154] studied the antiangiogenic potential of total alkaloids present *in Rubus alceifolius* poir extract; briefly, the study demonstrated that these compounds inhibit pathological angiogenesis, through suppression of microvessel, via reducing VEGF expression; and HUVECs cell replication, by blocking cell cycle G1 to S progression. The results were confirmed *in vivo* using the CAM model.

In the terpenoid group, various compounds showed antiangiogenic potential. Aescin or β-escin (see Fig. 5), a major active compound in horse chestnut extract, was able to inhibit angiogenesis, using the HUVEC cell model and the CAM assay. At a molecular level, aescin was shown to inhibit angiogenesis by increasing expression of thrombospondin-1 (TSP-1) and by decreasing expression of protein kinase C-α (PKC-α) [79].

Other class of terpenoids with antiangiogenic potential are carotenoids (see Fig. 6). Ganesan et al. [155] studied the antiangiogenic potential, and the mechanism of action, of two algal carotenoids (fucoxanthin and siphonaxanthin), using the HUVEC cell model. This study showed that both carotenoids suppress FGF-2 expression. Furthermore, the antiangiogenic inhibition ability of total carotenoids (β-carotene, β-cryptoxanthin, lutein, zeaxanthin and retinoic acid), present in maize extract, was established, using

Table 4
Other natural compounds with antiangiogenic potential.

Natural compound		Assay/Cell/Model	Mechanism/effects of antiangiogenic action	Reference
Alkaloids	Pterogynidine	HUVECs	Reduction of NF-kB activity	[152]
	Punarnavine	HUVECs	Inhibition of MMP-2 and MMP-9 expression	[153]
		Ehrlich ascites carcinoma tumor	Downregulation of VEGF expression	
		B16F-10 melanoma cells	Downregulation of MMP-2 and MMP-9, ERK, VEGF expression	[77]
	–	HUVECs and CAM	Blocking of cell cycle G1/S and inhibition of VEGF	[154]
Terpenoids	Aescin	HUVECs and CAM	Increase expression of TSP-1, and decrease expression of PKC-α	[79]
	Carotenoids	HUVECs	Suppression of FGF-2 expression	[155]
		YSM and CAM	–	[156]
	Celastrol	Human glioma cells	Suppression of VEGFR expression	[157]
		Human lung carcinoma (H1299), human embryonic kidney (A293), human multiple myeloma (U266) and bladder cancer (253JBV) cell line	Inhibition of TNF-induced and NF-kB activation	[158]
	Escins Ia, Ib, IIa and IIb	In mice models	–	[159]
	Furanodiene	HUVECs and zebrafish embryos	Inhibition of VEGF and suppression of Akt	[160]
	Polyphyllin D	Human microvascular endothelial cell line (HMEC-1) and Zebrafish embryos	–	[161]
	Withaferin A	Caski human cervical cancer cell line and human hepatoma (SK-Hep1) cells	Inhibition of MMP-9 activity	[163]
		HUVECs and CAM	Suppression of VEGF expression	[162]
		#	Inhibition of VEGF	[164]
		HUVECs	Inhibition of NF-kB	[165]
	Withanone and Withaferin A	HUVECs and nude mice	Downregulation of VEGF and MMP	[166]

Akt – Serine-Threonine Kinase; CAM – Chick Chorioallantonic Membrane; ERK – Extracellular Signal-Regulated Kinases; FGF-2 – Fibroblast Growth Factor-2; HUVECs – Human Umbilical Vein Endothelial Cells; MMP-2 – Matrix Metalloproteinase-2; MMP-9 – Matrix Metalloproteinase-9; NF-kB – Nuclear Factor Kappa B; PKC-α – Protein Kinase C-α; TNF – Tumor Necrosis Factor; TSP-1 – Thrombospondin-1; VEGF – Vascular Endothelial Growth Factor; VEGFR – Vascular Endothelial Growth Factor Receptor; YSM – Chick Yolk Sac Membrane; – Not specified or described; # – not used cells, only molecular docking studies.

the chick yolk sac membrane (YSM) and CAM assays [156]. The results showed that this extract was an interesting source of carotenoids, which effectively inhibited the formation of new vessels. Celastrol (see Fig. 4) is a terpenoid that demonstrated antiangiogenic effects, by suppression of VEGFR expression in human glioma cells, consequently reducing the signal transduction between VEGF and VEGFR, thus inhibiting endothelial cell proliferation, migration and differentiation [157]. Other studies proved that celastrol inhibits angiogenesis through an alternative mechanism, by inhibiting TNF-α-induced activation of the NF-kB complex [158]. Escins Ia, Ib, IIa and IIb (see Fig. 5), obtained from natural sources, proved their potential to inhibit the increase of vascular permeability in mice models [159]. Furanodiene (see Fig. 4) is an active ingredient found in various plants, which was shown to inhibit angiogenesis in HUVEC cells model, through inhibition of VEGF. These results were confirmed using the zebrafish model. Furanodiene was also shown to suppress expression of Akt kinase [160].

Polyphyllin D was another terpenoid studied for its antiangiogenic potential. This compound displayed *in vitro* angiogenesis inhibition, by suppressing cell proliferation, migration and tube formation; and *in vivo* angiogenesis inhibition by the ability to impair intersegmental vessels formation in zebrafish embryos [161].

An extensive study was performed on the antiangiogenic potential of withaferin A [162]. This terpenoid showed ability to block cell invasion and migration in Caski human cervical cells and in hepatoma SK-Hep1 cells. This activity was linked to the ability of withaferin A to decrease MMP-9 activity [163]. Withaferin A also demonstrated ability to block tube formation in HUVEC cells and in the CAM assay. This angiogenesis inhibition ability was related to direct inhibition of VEGF [162]. The hypotheses that withaferin A promotes angiogenesis inhibition, thru VEGF direct inhibition, was further demonstrated using a molecular docking approach. In this study, a rational interaction mode between withaferin A and VEGF

was presented [164]. An alternative mechanism of action of withaferin A, obtained from *Withania somnifera,* was also presented by another study, where withaferin A was shown to inhibit NF-kB activity in HUVEC cells [165]. Additionally, Gao et al. [166], studied the combination of withanone and withaferin A, verifying that this combination showed significant antimigratory and antiangiogenic activities, both *in vitro* or *in vivo* assays. Furthermore, the authors demonstrated, by using bioinformatic and biochemical approaches, that withanone and withaferin A caused downregulation of VEGF and MMPs.

Taken together, all the reviewed studies demonstrate that there are several compounds, obtained from natural sources, which can be considered for antiangiogenic therapy, or as new drugs for the development of chemically-related and even more potent antiangiogenic compounds. As so, this review synopsizes important knowledge based on the current state of the art of naturally occurring angiogenesis inhibitors.

5. Future challenges

Due to their remarkable chemical variety, natural compounds have attracted considerable attention as potential candidates for therapeutic use against different pathologies. Special attention has been payed to naturally occurring anticancer agents, and respective derivatives, and in the study of the multiple pathways involved in cancer development [167]. Angiogenesis is an essential process involved in several diseases, including tumor-associated angiogenesis. Although angiogenesis is considered a relevant target for the prevention and treatment of many disorders, the bulk of the research done so far is focused on tumor angiogenesis, and, as a consequence, clinically available antiangiogenic drugs are all targeted to tumor angiogenesis [47,168]. Current antiangiogenic drugs are limited in number, expensive and have shown to induce serious side effects (Table 1 and Fig. 2). The search for natural products and natural molecules as potential antiangiogenics, with less toxicity
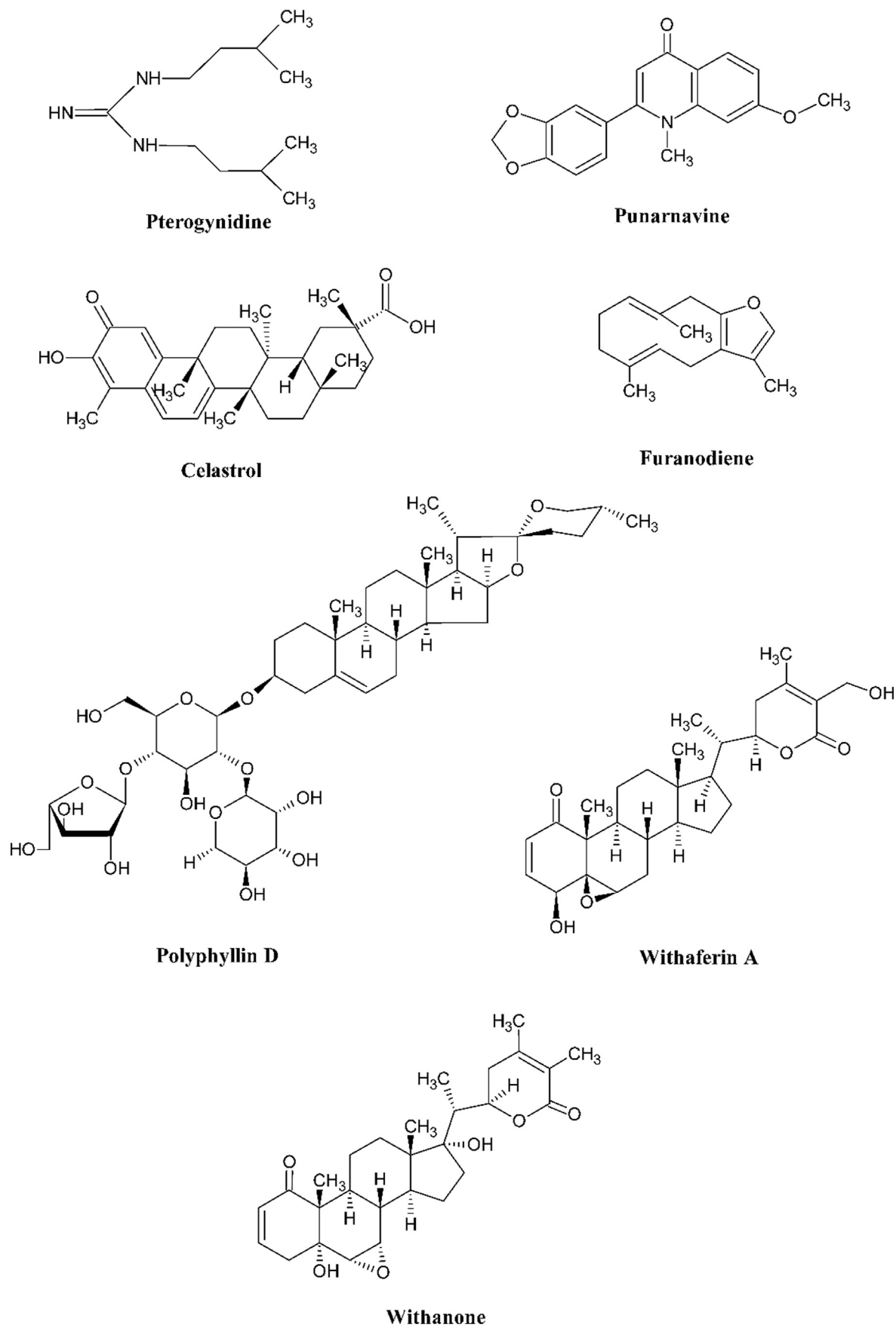
Pterogynidine

Punarnavine

Celastrol

Furanodiene

Polyphyllin D

Withaferin A

Withanone

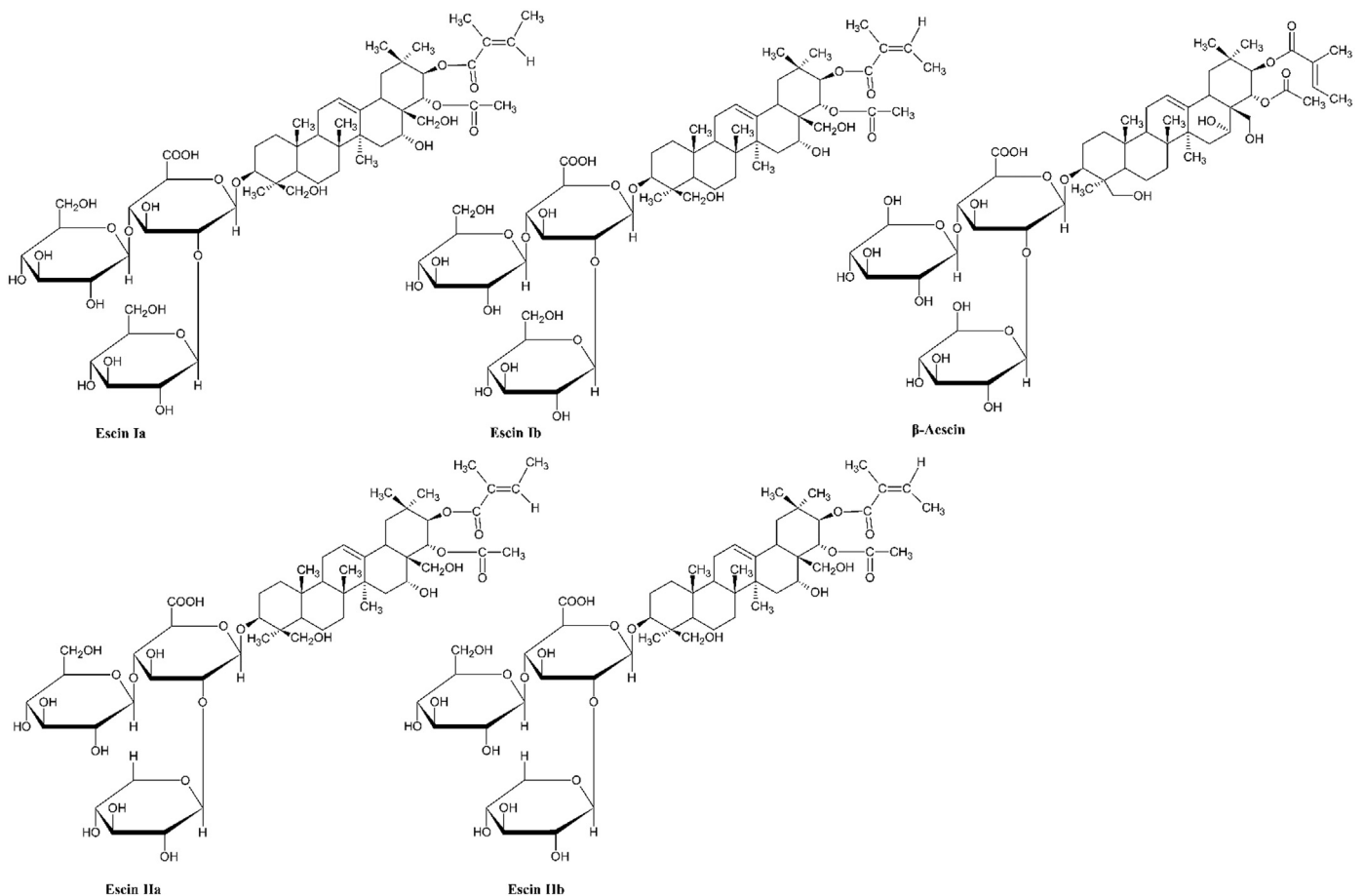Fig. 4. Alkaloids and terpenoids with antiangiogenic activity.

Fig. 5. Different escins (terpenoids) with antiangiogenic activity.

and at competitive prices, is thus the obvious next step in anti-angiogenic therapy [115]. This review describes a wide variety of natural extracts and molecules (Tables 2–4 and Figs. 3–6) with angiogenic modulation ability and, when relevant information is available, the molecular mechanisms underlying the respective activity are discussed. When comparing the small number of proteins targeted by current antiangiogenic drugs, with the large number of molecular pathways involved in the complex mechanism of angiogenesis, it is clear to draw the conclusion that there is still considerable work to be done in order to find better and more diverse antiangiogenic drugs, and natural sources urge to be explored due to their chemical diversity [47].

The main advantage of natural products, relies on their ability to be more acceptable to patients, thus more adequate to be administered orally. As shown in Tables 2–4, natural compounds present various mechanisms in order to target angiogenesis. Furthermore, these natural molecules exhibit antiangiogenic activity identical to the synthetically drugs currently in clinical use [47]. In this sense, Chatterjee & Bhattacharjee [167] compared the performance of epigallocatechin gallate and the drug pazopanib, as VEGFR-2 inhibitors. The results showed similar effectiveness of the two compounds. Furthermore, the use of phenolic compounds individually, or combined, has shown to diminish synthetic drugs resistance and may have therapeutic potential for a broader range of tumor diseases [47].

In spite of the current context, there are still problems that need to be overcome, to generalize the use of natural compounds in clinical practice against different pathologies [115]. The main

problems are related to bioavailability, bioefficacy and biostability issues, since many natural compounds exhibit low solubility and low absorption rates. Therefore, only a small amount of the ingested dose reaches the circulation and the desired target location [115]. Microencapsulation constitutes a possible technique that may help to surpass these constraints, ensuring a better deliver of natural compounds to the desired tissue target. Through microencapsulation, natural compounds are incorporated into polymer matrices enabling better protection [169]. Such processes help to guarantee the activity of the natural compounds, and to improve targeting to the desired location [170]. Several studies, conducted to microencapsulate phenolic compounds, showed enhanced antiangiogenic effects of these forms [170–172]. Another strategy to increase the bioavailability, efficacy and stability is discussed by Wang et al. [47] and Lu et al. [115] consisting on chemical derivatization. Chemical derivatization also called as chemical modification correspond at a transformation of chemical compound in another compound by changing one or more functional groups in order to modify the specific characteristics. In this sense, the main objective is altering reactivity or properties such as solubility, thermal stability, among others. Thus, with this approach, functional groups are added or removed to the phenolic compounds, improving its pharmacokinetic profile [47]. The principal objective of these modifications is increasing the bioactivity of the phenolic compounds and consequently problems, such as absorption, can be overcome and thus favoring their interaction with the specific molecules of pathological angiogenesis blocking the reaction chain. However, these technologies such as microencapsulation or
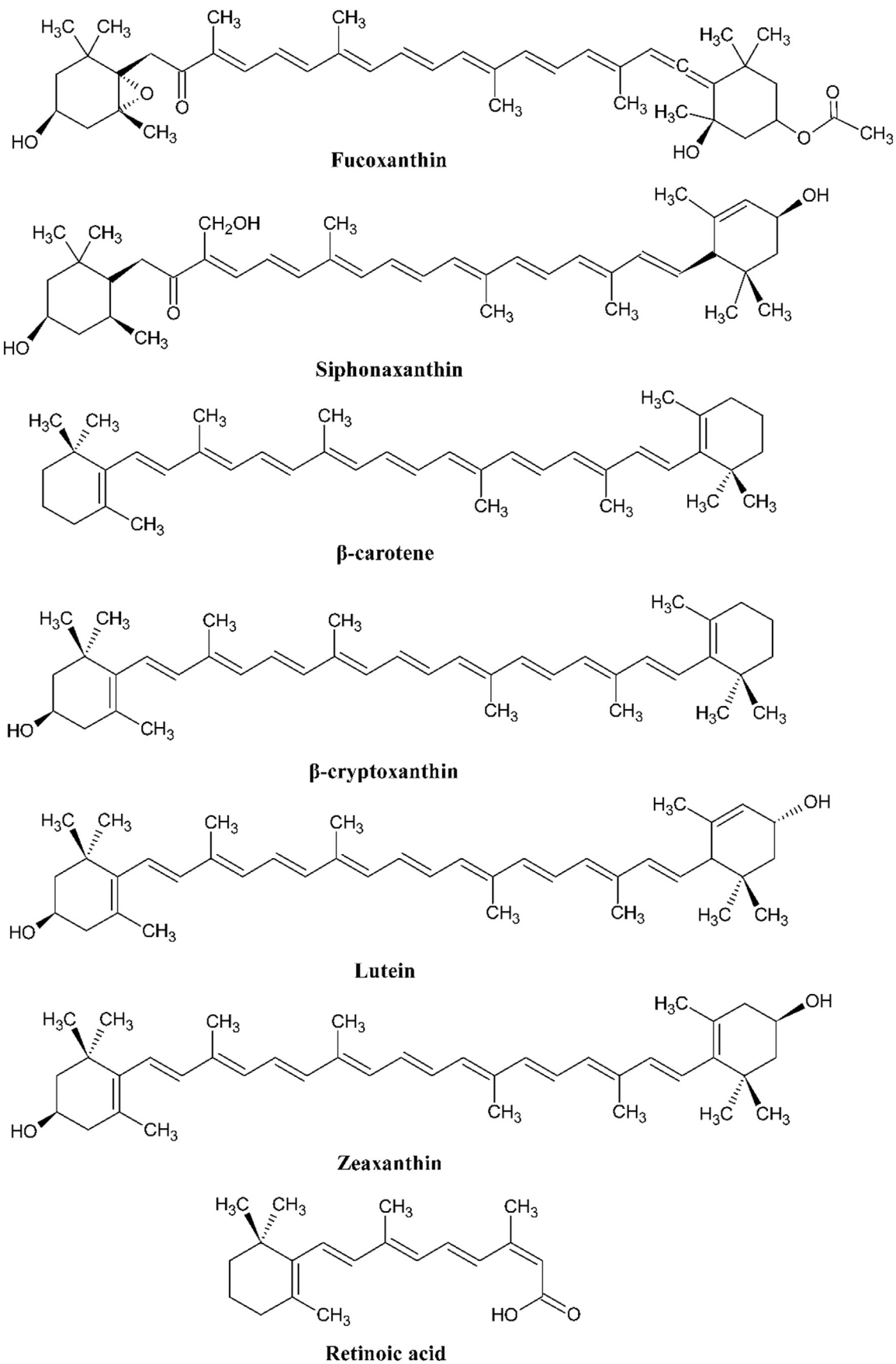
Fig. 6. Different carotenoids (terpenoids) with antiangiogenic activity.

chemical derivations applied in natural compounds require further studies in order to optimize the antiangiogenic effect.

Pathological angiogenesis occurs when an imbalance of endogenous proangiogenic and antiangiogenic factors occurs. Although the focus of angiogenesis-related drug development has been geared to the discovery of antiangiogenic compounds for use in pathologies where excessive angiogenesis occurs (cancer, rheumatoid arthritis, retinopathy to name a few), an increase interest has been directed towards the development of proangiogenic drugs for use in pathologies were insufficient angiogenesis occurs (coronary heart disease, stroke, chronic wounds to name a few) [173]. Given that a number of natural compounds have exhibited proangiogenic activity, the approach of explore these compounds in such applications configures a promising field of research [115].

6. Concluding remarks

All cells need a steady supply of oxygen, nutrients and a way to remove waste materials, and this is accomplished by an efficient network by blood vessels. Angiogenesis is a biological process through which new blood vessels are formed and is essential for various biological processes. Pathological angiogenesis is related with the development of various and serious diseases, particularly cancer. In this case, the angiogenesis is very important for development, survival and metastases formation. Angiogenesis is very complex and involves different and numerous angiogenic factors and signaling pathways, including growth factors, MMP, cytokines, arachidonic acid derivatives, transcription factors and cell cycle related proteins among others. VEGF and his membrane receptor is the most studied growth factor. Several antiangiogenic drugs have been developed, and bevacizumab was the first one to be used in therapies applied in vivo to tumor angiogenesis. Still, due to toxicity and cost constraints of these drugs, the development of new treatments is becoming highly important. In this context, natural bioactive compounds, present in various natural products, have shown high antiangiogenic capacity together with well-being effects. Compared with currently available antiangiogenic drugs, plant-derived products may not only have similar therapeutic potential, presenting also clear advantages due to their lower toxicity and ease way of administration. Also, they can be regarded as inexpensive solutions, when compared with synthetic counterparts. The approach of applying natural compounds in the treatment to angiogenesis-related pathologies is, therefore, a promising field of research. However, novel and effective strategies are necessary to improve their bioavailability for clinical use.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

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