REVIEW

# Natural products against cancer angiogenesis

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**Abstract** The process of angiogenesis is quite well-known nowadays. Some medicines and extracts affecting this process are already used routinely in supporting the conventional treatment of many diseases that are considered angiogenic such as cancer. However, we must be aware that the area of currently used drugs of this type is much narrower than the theoretical possibilities existing in therapeutic angiogenesis. Plant substances are a large and diverse group of compounds that are found naturally in fruits, vegetables, spices, and medicinal plants. They also have different anticancer properties. The aim of this literature review article is to present the current state of knowledge concerning the molecular targets of tumor angiogenesis and the active substances (polyphenols, alkaloids, phytohormones, carbohydrates, and terpenes) derived from natural sources, whose activity against cancer angiogenesis has been confirmed.

**Keywords** Natural products · Angiogenesis · Targets · Chemoprevention · Cancer

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**Abbreviations**

| | |
|---|---|
| AFGF | Acidic fibroblast growth factor |
| AP-1 | Activator protein 1 |
| AIF | Apoptosis-inducing factor |
| Akt | Ak strain thymoma |
| $\alpha$-DFMO | $\alpha$-Difluoromethylornithine |
| Ang | Angiogenin |
| ANGPT | Angiopoietin |
| APAF | Apoptotic protease-activating factor |
| ATF-4 | Activating transcription factor 4 |
| BAP | 6-Benzylaminopurine |
| Bax | Bcl-2-associated X protein |
| Bcl-2 | B cell lymphoma 2 |
| bFGF | Basic fibroblast growth factor |
| CAM | Chorioallantoic membrane |
| CD151 | Cluster of differentiation 151 |
| Cdc42 | Cell division control protein 42 homolog |
| CDK | Cyclin-dependent kinase |
| clAP | Calf-intestinal alkaline phosphatase |
| COX-2 | Cyclooxygenase-2 |
| CYP4F3 | Leukotriene-B(4) omega-hydroxylase 2 |
| Diablo | Direct IAP-binding protein with low pI |
| DLL4 | Delta-like ligand 4 |
| DMXAA | Dimethyl xanthenyl acetic acid |
| DNA | Deoxyribonucleic acid |

| E$_2$(PGE$_2$) | Prostaglandin E2 |
| ECs | Endothelial cells |
| EGF | Epidermal growth factor |
| EGFL7 | EGF-like domain-containing protein 7 |
| ERK | Extracellular signal-regulated kinases |
| FasL | Fas ligand |
| FGF | Fibroblast growth factor |
| GM-CSF | Granulocyte-macrophage colony-stimulating factor |
| GSH | Glutathione |
| ROS | Reactive oxygen species |
| HER2 | Human epidermal receptor 2 |
| HGF | Hepatocyte growth factor |
| HIF | Hypoxia-inducible factor |
| IL-8 | Interleukin-8 |
| JAK | Janus kinase |
| JNK | c-Jun N-terminal kinases |
| LOX | Lipoxygenase |
| MAP | Mitogen-activated protein |
| MCP-1 | Monocyte chemoattractant protein 1 |
| MRI | Magnetic resonance imaging |
| mTOR | Mammalian target of rapamycin |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NRPs | Neuropilins |
| pAK | p21 activated kinase |
| PARP | Poly ADP ribose polymerase |
| PDGF | Platelet-derived growth factor |
| PEDF | Pigment epithelium-derived factor |
| PERK | PKR-like endoplasmic reticulum kinase |
| PI3K | Phosphatidylinositol-3-kinase |
| PIGF | Phosphatidylinositol-glycan biosynthesis class F protein |
| PLGF | Placental growth factor |
| PTN | Pleiotrophin |
| Sema3 | Semaphorin-3 |
| SLC7A11 | Sodium-independent glutamate transporter |
| GCLC | Glutamate-cysteine ligase catalytic subunit |
| NRF-2 | Nuclear factor (erythroid-derived 2)-like 2 |
| Smac | Second mitochondria-derived activator of caspases |
| STING | Stimulator of interferon genes |
| TGF-β | Transforming growth factor-β |
| TNF-α | Tumor necrosis factor-α |
| TSP-1 | Thrombospondin-1 |
| uPA | Urokinase-type plasminogen activator |
| VEGF | Vascular endothelial growth factor |

# Introduction

The global burden of cancer is projected to have more than doubled over the next two decades, raising the prospect of a significant investment in health systems, thus posing a real medical problem [1]. Changes in risk factor distributions and an aging population are both contributing to the growing prevalence and incidence of cancer around the world despite global trends towards lower cancer incidence and mortality rates for a number of cancer types in developed countries [2, 3]. Based on GLOBOCAN data [2], the International Agency for Research on Cancer (IARC) estimated that 14.1 million new cancer cases were diagnosed and that 8.2 million patients died from this disease worldwide in 2012 alone. The increasing number of people with cancer highlights the need for more cancer prevention efforts.

Complementary and alternative medicines, which cover a large spectrum of old to new strategies that purport to extend options to prevent and to treat diseases such as cancer, are gaining more attention in oncology management [4–6]. The emergence of natural bioactive compounds represents a natural experiment, as millions of Americans have begun self-medicating with these products [7]. Natural products have been valuable sources of new therapeutic agents [8]; the number of chemotherapeutic agents and their sources indicates that 80 % of approved drugs are derived from natural compounds [9]. With the new high-throughput screening technologies, natural products are likely to provide many of the lead structures for the modelization of novel substances with enhanced anticancer activities that have high selectivity [5]. One of the most involved factors in cancer invasion and metastasis is angiogenesis; this term was introduced and used for the first time by John Hunter in 1787 [10]. It was described and considered a therapeutic target in cancer therapy by Judah Folkman [11]. It is defined as being the process of creating new thin-walled capillaries based on the existing blood vessel network in the life of an adult organism which should be distinguished from another process of creating vessels—which runs only during the fetal period [12–14]. Furthermore, the process of angiogenesis should be distinguished from arteriogenesis, which is a remodeling of small vessels by the activity of various factors, including the physical ones. Thus, angiogenesis is a complex, multi-stage process during which many changes must occur [15, 16]. Until now, usually five basic stages of angiogenesis have been distinguished. The factors that stimulate angiogenesis are usually hypoxia, ischemia, or inflammation that acts on cytokines, as well as the basic pro-angiogenic factors of vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) type [17, 18].

The initial signal is the flaccidity of the existing vessels caused by nitric oxide (NO). NO provokes the launch of proteolytic enzymes that activate the production of the new vascular structures by the degradation of the basement membrane. Then, the integrins facilitate and regulate the adhesion and migration of endothelial cells (ECs). The stimulation of ECs (especially their mobility and proliferation) is caused by the molecules released from the same cell matrix such us the

fibroblast growth factors, commonly known as FGF. The proliferation of ECs determines the genesis of the new tubular structures, which will mature and be stabilized under the effect of angiopoietins and their corresponding receptors [19]. Neovascularization is also important during the process of natural wound healing, initiating the repair processes and contributing to the development of granulation tissue and the limitation of the necrosis area [12, 20]. This process is also the base of the proper maturation of bones and hair growth [21].

The physiological angiogenesis is part of the pathological picture of chronic inflammatory changes associated with asthma, rheumatoid arthritis, and gastrointestinal diseases, such as Crohn's disease or ulcerative colitis. It can cause blindness as a result of chronic changes in the retina or cornea (diabetic retinopathy, macular degeneration), it plays a role in the development of obesity (adipose tissue development) or endometriosis, and it is added to the production of alveoli, typically at an early postnatal stage. Hypoxia is a powerful stimulus of vessel formation in the cardiovascular system, occurring in ischemic heart disease, atherosclerosis, stroke, and ischemia of the lower limbs (peripheral vascular impairment) [22–24]. In the pathological conditions, the angiogenesis process gets out of control which results in the development and growth of primary tumors and also increases the risk of metastasis [13, 16, 25].

### Tumor angiogenesis—the study of new medicines

Intensive research to develop drugs similar to angiostatin (e.g., bevacizumab (Avastin®)) has proved to be disappointing when applied to humans. These medicines might slow the progression of certain types of cancer and might be known for the effective regression of tumors in some cases, but the results achieved tend to be and their action must be supported by other means. There are two methods of inhibiting tumor angiogenesis:

1. Classical angiogenesis inhibitors (targeted therapy), which inhibit the proliferation and formation of new blood vessels
2. Substances which destroy the existing vessels, leading to necrosis within the tumor, and drugs that inhibit angiogenesis in the tumor, leading to its death by cutting off the life-giving blood.

In practice, the antiangiogenic drugs are effective but can only be used in combination with other cytostatics. It is not enough to impair the development of the network of blood vessels to cure the tumor. It is important to remove cancer cells that survive malnutrition, a lack of oxygen, and attacks of immune cells. Tumor cells with time can immunize to the action of lock mechanisms—creating substitute mechanisms.

Antiangiogenic molecules are used as monotherapy in situations when it comes to the longest restraint of the development of the tumor classified as incurable. Their relatively low toxicity allows for the long-term use, but such treatment is very expensive. Cancer is a multidimensional disease, which unfortunately very rarely surrenders under the influence of a single agent. However, it is a fact that the control of angiogenesis is essential for the treatment of cancer [26, 27].

There are natural methods, which strongly affect angiogenesis without causing side effects and which can be combined with conventional therapy. These are as follows:

– A specific diet rich in food products that inhibit angiogenesis, e.g., some types of green tea, roots, and herbs
– Anything that contributes to the elimination of inflammations which are the direct cause of the development of new blood vessels

In this work, we will focus on recent advances in understanding the pathogenesis of tumor angiogenesis through potential therapeutic targets and the use of natural products as potential prospects in the chemoprevention of cancer.

## Angiogenesis: focus on mechanisms and molecular targets

The formation of the vascular system is a complex process, which requires the interaction of some factors and molecular signals. In the developing embryo, elementary blood vessels appear through a procedure known as vasculogenesis, in which blood vessels form de novo by differentiation and adhesion of individual progenitor cells [28]. These progenitors can generate angioblasts in response to growth factor VEGF [26]. These angioblasts produce blood islands which can fuse and remodel to generate the first primitive plexus of vessels. After the formation of the immature plexus, pericytes (mural cells) that interact with the outer surface of the vessel are recruited. During adult life, neovascularization happens through angiogenesis; the growth of vessels from already present capillaries passes by the multistep process and can be represented as a process in two stages. First, the tube formation is observed, in which ECs react to a growth factor which leads to migrating, proliferating, and producing the new sprout. Second, vascular maturation occurs, during which budding vessels are settled by enlisting pericytes or vascular smooth muscle cells and by generating an extracellular matrix [29].

Hellstrom et al. (2001) [30] reported that a lack of pericytes causes endothelial cell hyperplasia associated with an abnormal shape and morphological signs of increased permeability. The regulation function of pericytes on ECs takes place through the cell–cell contact and the secreted factors. Recent

studies identified several signaling pathways controlling arterial and venous identities, such as VEGF, complex Eph-Ephrin system, Notch, angiopoietins (ANGPT1 and ANGPT2), placental growth factor (PLGF), platelet-derived growth factor (PDGF), TGF, FGF, interleukin-8 (IL-8), and HGF [31, 32]. The most important pro-angiogenic factors are listed in Table 1.

Angiogenesis is a complex process, directed by the balance between pro- and antiangiogenic molecules expressed by different cell types. It obviously includes more than a simple upregulation of angiogenic activity, and it is postulated to be the result of a balance of positive and negative regulators. When pro-angiogenic factors copy the effect of angiostatic molecules, the tumor gets an angiogenic phenotype that leads to the formation of new blood vessels [33].VEGF is one of the most angiogenic players in the process of the vascular system. It is involved in mitogenesis, in endothelial cell migration, as well as in sprouting and lumen formation. It is known as tumor angiogenic factor or as vascular permeability factor. It also regulates molecules that are involved in endothelial proliferation. And its upregulation is important in physiological processes [31].

## FGF

FGFs (pro-angiogenic growth factors) are a family of heparin-binding proteins which are stored in the vascular basal lamina and act both as a reservoir supply and as an upregulator during active angiogenesis. The common forms are FGF-1 or acidic FGF (aFGF) and FGF-2 or basic FGF (bFGF). FGF-1 and FGF-2 induce EC proliferation and differentiation of epiblast cells into ECs. Moreover, FGF-2 induces the production of collagenases and urinary plasminogen activator which works as a chemoattractant for these cells [34, 35].

**Table 1** Factors stimulating and inhibiting angiogenesis

| Stimulators | Inhibitors |
| --- | --- |
| VEGF | Angiostatin |
| Angiopoietin-1 | Antiangiogenic antithrombin III |
| FGF | Endostatin (a fragment of collagen XIII) |
| Interleukin-8 | Heparin fragment |
| Leptin | Fibronectin |
| MCP-1 | Interferon-α, interferon-β, interferon-γ |
| MMPs | Interleukin 4 |
| NOS | Interleukin 12 |
| PDGF-BB | Interleukin 18 |
| TNF-α | Plasminogen activator inhibitor |
| Angiogenin | PEDF |
| TGF | Fragment of prolactin (16 kDa) |
| | TSP-1 |
| | Retinoids |

## Angiopoietins

The angiopoietins are a family (angiogenin (Ang)-1–Ang-4) of extracellular ligands that are bound to the ECs' specific Tie receptors. They are a group of receptor tyrosine kinases which act during vessel remodeling and angiogenesis. Among the four famed angiopoietins, Ang-1 and Ang-2 are the best-characterized cytokines. Their expressions are limited to the tumor cells and in the microvasculature, respectively [36]. Ang-1 boosts endothelial cell survival and sprouting and stabilizes vascular networks by enrolling pericytes to immature vessel segments. On the other hand, Ang-2, expressed at places of vascular remodeling, results in the loss of pericytes and exposes ECs to angiogenic factors [37–39].

## TGF-β

The transforming growth factor-β (TGF-β) superfamily is involved in more than 30 structurally identical growth factors and includes the three TGF-β isotypes 1–3 [40]. They are released in a latent structure, and under acidic conditions, they require a cleavage of the associated peptide domain. TGF-β promotes extracellular matrix deposition and integrin receptor upregulation [41]. It is one of the most important interleukins for modulation of the wound EC proliferation, the migration, and the lumen formation [39].

## TNF-α

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine, secreted mostly by activated macrophages during inflammation and immune response. It has many functions including the motivation of GM-CSF and IL-1 and has been argued to work on ECs both directly, by inducing cell differentiation, and indirectly by producing other angiogenic factors from other cells [42, 43].

## Notch

The Notch signaling, a cell membrane receptor; is the pathway that plays multiple roles in physiological processes both in the development and in adult life [44]. There are four receptors (Notch 1–4) and five ligands of Notch family, and it has a mechanism of signal transduction that requires cell–cell contact. It initiates when a ligand, expressed on the surface of a cell (signal-sending cell), physically interacts with a receptor, expressed on the surface of another cell (signal-receiving cell). Upon cell–cell contact and the ligand binding, the receptor undergoes two proteolytic cleavages operated by proteases of the disintegrin and metalloproteinase family [(ADAM)/tumor necrosis factor-α (TACE) converting enzyme] and γ-secretase enzyme, respectively. The first split results in a conformational convert, while the other is responsible for the

production and the release of the Notch intracellular domain (NICD) [45–47].

## Semaphorins

One of the latest regulators of angiogenesis is class 3 semaphorins, a family of secreted proteins. It has a role in pathophysiological angiogenesis [48–50]. Both the antiangiogenic semaphorin-3 (Sema3)A and Sema3F are expressed by ECs, suggesting an autocrine function, while Sema3C is argued to be a pro-angiogenic factor. A loss of Sema3A expression in favor of VEGF may result in the angiogenic switch in some cancers [51].

## RhoJ

RhoJ is another signaling protein, an endothelial-specific member of the Cdc42 that controls endothelial motility, tubulogenesis, and lumen formation in vitro depicts [52]. RhoJ plays an important role in endothelial biology and in angiogenesis. Manipulation of RhoJ expression exhibits that it amends the actin cytoskeleton and focal adhesions, crucial elements of endothelial migration during angiogenesis.

## CD151

Cluster of differentiation 151 (CD151) is one of the 33 human tetraspanins. They constitute a family of membrane proteins expressed in the endothelium. They function as organizers of the cell surface by allowing the regulation of processes such as cell adhesion, signaling, and intracellular trafficking. CD151 is essential for pathological angiogenesis which is indispensable for endothelial tubulogenesis, perhaps by aiding endothelial cell–cell adhesion [53].

## Mechanisms of vessel formation

Egginton [54] reported that the local physical environment may play a distinctive role in response to altered tissue request. Previous studies had reported two different forms of capillary formation: splitting and sprouting angiogenesis. Cellular components involve the glycocalyx (disruption of a vasculoprotective layer), nitric oxide synthase [endothelial nitric oxide synthase (eNOS) is important for vasodilatation], and CD31 (as part of a mechanosensory complex that existed in intercellular junctions).

There are many genes (~600 genes) whose expression is controlled by their environment identified by Serial analysis of gene expression libraries that appear to be organized by shear stress, a lot of which are involved in EC migration, adhesion, and angiogenesis, while low shear stress is found at sites of vascular obstruction (e.g., thrombosis or embolism) [55]. New blood vessel formation happens either by angiogenesis or by vasculogenesis. Vasculogenesis is the formation of new blood vessels de novo from progenitor cells, such as angioblasts, which differentiate into ECs, form tubes, and create primitive vessels. In contrast, angiogenesis is the formation of new vessels from the preexisting blood vessels. It consists of a complex multistep process involving extracellular matrix components. It starts with an enlargement of the original vessel, which then sprouts by intussusception and then splits into individual capillaries. This process is divided into four phases: proteolytic degradation of the basement membrane and enclosing extracellular matrix, EC proliferation and migration, lumen formation, and reorganization [22].

## Endothelial cell sprouting

In a normal blood vessel, a basement membrane (BM) rests deep to the EC monolayer in the arterial intima, the BM must be degraded before EC invasion into the surrounding extracellular matrix [56]. ECs, in response to specific pro-angiogenesis signals, change from a quiet to a synthetically active phenotype distinguished by a high mitotic index and raised capacity for migration and matrix proteolysis, such as VEGF. The first event occurring is the detachment of pericytes from the vessel wall and the loosening of endothelial cell junctions. Meanwhile, matrix metalloproteases (MMPs) mediate the proteolytic degradation of the basement membrane and some ECs acquire a motile and invasive phenotype, necessary for the initiation of vessel sprouting. These activated ECs are able to disrupt the tight junctions, adherens junctions, and gap junctions which exist between neighboring intimal ECs and perivascular cells and invade into the basal lamina and surrounding extracellular matrix [57, 58]. Hence, loosed from the capillary intima and in the extravascular area, ECs proliferate and migrate towards chemotactic and angiogenic initiation in a 3-D extracellular environment and sorting of new angiogenic sprouts [59].

This process in which the capillaries expand within itself (way of vessel growth) is called intussusceptive angiogenesis (and subsequent tube formation); it is the capacity of ECs to establish luminal compartments within multicellular chains which allow for the flow of blood from the preexisting vasculature to the neovasculature. Without those new capillary networks, the ability to execute their function of oxygen and nutrient transport to normal or pathologic areas would be disabled [60, 61].

Inoculation is the anastomosis of two luminal parts to form one persistent lumen which resembles a later step of angiogenesis, in which a quiescent vessel senses an angiogenic signal, such as VEGF, VEGF-C, ANG-2, FGFs, or chemokines, released by hypoxia, inflammatory tumor stroma, or a cancer cell. Pericytes first separate from the vessel wall (in response to ANG-2) and release themselves from the basement membrane by proteolytic decadence, which is interposed by metalloproteinases. ECs disconnect their junctions

and the new vessel. VEGF increases the permeability of the EC strata, leads plasma proteins to extravasate, and lays down a temporary extracellular matrix (ECM) scaffold [62].

In the case of integrin signaling, ECs migrate onto this ECM surface. Proteases liberate angiogenic signals stored in the ECM like VEGF and FGF and remodel the ECM into angio-competent surroundings. To construct a perfused tube and prevent ECs from moving all together across the angiogenic signal, one endothelial cell, the tip cell, is chosen to lead the tip in the existence of factors such as VEGF receptors, NRPs, and the NOTCH ligands DLL4 and JAGGED1. The neighbors of the tip cell suppose subsidiary postures as stalk cells, which split to extend the stalk (stimulated by Notch signaling pathway, PLGF, and FGFs) and set the lumen. Tip cells are equipped with filopodia to sense environmental instruction cues such as ephrins and semaphorins, while stalk cells liberate molecules such as EGFL7 into the ECM to convey locative information about the position of their neighbors so that the stalk elongates [63]. A hypoxia-inducible program, driven by hypoxia-inducible factor (HIF-1$\alpha$), renders ECs' interaction to angiogenic signs. Myeloid bridge cells help in fusion with another vessel branch and let the initiation of blood flow. For a vessel to become efficient, it must become mature and stable. ECs continue their quiet state, and signals such as PDGF-B, ANG-1, TGF-$\beta$, ephrin-B2, and NOTCH lead the cells to be wrapped by pericytes. Protease inhibitors known as tissue inhibitors of metalloproteinases and plasminogen activator inhibitor-1 (PAI-1) lead to the precipitation of a basement membrane, and junctions are reestablished to ensure flux distribution [64].

## Inhibition of angiogenesis by bioactive compounds

### Plant angiogenesis inhibitors

During the past decade, intensive studies in plant material have led to the confirmation of antiangiogenic properties and antitumor activity of a number of commonly used medicinal plants [65–71]. Plant-derived substances are characterized by expected properties in terms of antitumor activity, gaining considerable interest among many synthetic chemotherapeutic agents used in oncology [72–75]. Both untreated plant extracts and purified individual substances are used, which through a number of specific arteries in tumor cells can and lead to their death (through either apoptotic or necrotic activity) as well as by induction of aging [76–80].

Induction of programmed cell death, particularly apoptosis in cancer cells, plays an important role in chemoprevention. Apoptosis, which is an organized process, may be induced by external factors, including the natural substances of plant origin. Until now, various substances that can initiate cell death by apoptosis in multiple tumor types have been identified [26,

81, 82]. These substances have a diverse chemical structure, and their presence was confirmed in vegetables, fruits, spices, and herbs [83–89]. Compounds such as curcumin in turmeric [90–92], naringenin in citrus [93], capsaicin in pepper [94], diallyl trisulphide and allin in garlic [95], carnosic acid in rosemary [96, 97], betulinic acid in almond hull [98], humulone in beer hop [99], and resveratrol in grapes [100, 101] were reported to inhibit angiogenesis by targeting the cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) pathways. Inhibition of the COX-2 pathway, for example, was shown to reduce prostaglandin $E_2(PGE_2)$ production [102], which may suppress vascular endothelial growth factor (VEGF) expression [103, 104], a key mediator of in vitro angiogenesis [105, 106].

Large-scale world research is focused on the search for new properties of already known natural compounds of plant origin, in order to improve health and the quality and length of life. As a result, they provide knowledge about the most effective substances. The most attractive are those that exhibit pleiotropic activity and those that can also be used against cancer cells [107–109]. The resistance of tumor cells to factors that could be completely eliminated from the organism led to the use of two strategies to fight them. The first is to reduce cell division. The second one, which may be carried out in conjunction with the first, is the induction of cell death. Until now in both cases, the most commonly used were synthetic drugs, so-called antiinfective drugs, and radiotherapy treatment. However, the effectiveness of these treatments is variable and depends on many factors, primarily on the type of cancer and its stage of development. Therefore, substances of plant origin are very important, because they support treatment and stop the development of cancer, protecting healthy cells against malignant transformation [110, 111].

### Plants as a source of antiangiogenic drugs: experimental studies

Some plant metabolites are compounds that inhibit angiogenesis. Substances showing anticancer properties can be found in the plants used in herbal medicine as well as in those that are included in our diet. In the search for antiangiogenic drugs, a number of bioactive plant substances and dietary products have been tested for their antiangiogenic potential [77, 112–114]. The evaluation of the performance of natural anticancer compounds and other substances potentially having antiangiogenic properties is done with the use of the chorioallantoic membrane (CAM) test on the chorioallantoic membrane of chicken embryos [115, 116].

In the antiangiogenic therapy, many compounds also found in natural products such as fruits, vegetables, spices, and green tea were used. Many compounds present in natural products such as fruits, vegetables, spices, and green tea are also being used in the antiangiogenic therapy. Medicinal substances are

present in the whole plants or in their particular organs (stems, leaves, roots, seeds). The most common plants in discussed area are *Selaginella tamariscina* Beauv [117], *Gleditsia sinensis* [118], *Acer tegmentosum* [119], *Viscum album* [110], *Strychnos nux-vomica* [68], *Apium graveolens* [120–122], *Rosmarinus officinalis* [123, 124], *Brucea javanica* [66], and *Hypericum perforatum* [125]. These and many other plants contain substances of a therapeutic use, including polyphenols and their derivatives (which are the most important group), anthracycline antibiotics and their quinone analogs, alkaloids, and other metabolites of the integrated nitrogen atom in the molecule, terpenoids, polysaccharides, polyamines, and cytokinins [78, 87, 110, 126–129]. Table 2 shows a list of medicinal plants with the bioactive substances extracted from them that directly inhibit angiogenesis. The advantages of antiangiogenic substances found in natural products include the following (see Fig. 1):

– General availability, as many of these substances are present in our daily diet
– The low price of products compared to other drugs
– The fact that they are effectively absorbed from the gastrointestinal tract
– They long-lasting effect, which can be used in long-term prevention and treatment
– They rarely have side effects

Studies have shown that antiangiogenic therapy was more effective in combining the inhibitors of angiogenesis with radiotherapy or chemotherapy [79, 130]. Due to a large number of substances used in the treatment and prevention of cancers, the article describes only selected substances of the above-described groups of compounds.

*Polyphenolic compounds*

Polyphenolic compounds are a group of plant secondary metabolites synthesized mainly from phenylalanine or tyrosine. In chemical terms, polyphenols are compounds having at least one aromatic ring substituted with one or more hydroxyl groups. Depending on the number of hydroxy aromatic rings and the type of functional groups of the phenolic compounds of the phenolic origin, we distinguish acids, polyphenols, and monophenols. Large numbers of derivatives of phenolic compounds are the simple polyphenols, phenylpropanoids, benzoic acid derivatives, flavonoids, stilbenes, and polymers of phenolic compounds such as tanning agents (proanthocyanidins) or lignans [131, 132]. The human diet consists of a mixture of plant polyphenols. It is estimated that the daily intake of plant polyphenols is approximately 1 g [110].

In terms of biology, polyphenolic compounds are strong antioxidants. They prevent dysfunctions of the organism resulting from an inefficient operation of the antioxidant mechanism or excessive production of oxidants, preventing the development of diseases known as civilization diseases (cancer, coronary heart disease, stroke, diabetes). Recent research confirms that the polyphenols show cytotoxic activity and inhibit tumor growth, metastasis, and angiogenesis [131].

*Curcumin* (Fig. 2a) is a polyphenol built of ferulic acid residues. It is one of the best-known compounds exhibiting angiogenesis inhibitory activity. It is the yellow pigment extracted from the rhizome of *Curcuma longa* L., characterized by a potent pleiotropic activity [133]. Curcumin is involved in the regulation of many cellular processes, such as keeping the redox balance in nerve cells. In these cells for example, curcumin limits the synthesis of β-amyloid, a key factor for the development of Alzheimer's disease, which is synthesized during oxidative stress. In addition, curcumin contributes to the reduction of the activity of transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and thus other proteins, including COX-2 and IL-8, and growth factor kinases, including kinases, type MAP, and JAK [134], are involved in the inflammatory reactions [135]. The pleiotropic effect of curcumin is also implicated in the inhibition of hepatic metastasis of tumor cells (CBO140C12) and rat hepatoma (AH109A).

In breast cancer cells (MDA-MB 231), it affects the functioning of estrogen receptors, among others, by reducing the activity of NF-κB/AP-1 factors dependent on metalloproteinases of the type MMP-1 and MMP-2 [131]. Moreover, analogs of curcumin, which is BDMC-A (dimethoxy curcumin) [136], stopping the cell cycle at the G2/M results in inhibition of proliferation of breast cancer cells (MCF-7), with simultaneous initiation of the internal and external apoptotic pathway by inhibiting the activity of B cell lymphoma 2 (Bcl-2) and activation of proteins: p53, Bcl-2-associated X protein (Bax), cytochrome c, apoptotic protease-activating factor (Apaf-1), FasL, and caspases 8, 9, and 3 (Fig. 3) [137]. Additionally, the metabolism products of curcumin, which are ferulic acid and vanillin, also exhibit cytotoxic properties towards ECs [78]. *Ferulic acid*, by removing free radicals, exhibits chemopreventive activity towards the healthy cells [138], while *vanillin* is involved in the repair of mutated deoxyribonucleic acid (DNA) of the cancer cells, including colon cancer cells (HT-29) [139], and also reducing the metastasis through angiogenesis of these cells [140].

*Epigallocatechin* (Fig.2b) is the main polyphenol found in tea leaves along with (−)-epigallocatechin gallate (the main component of green tea), (−)-gallate, (−)-epicatechin gallate, and (−)-epicatechin [141]. These polyphenols have the ability to inhibit the growth of lung cancer cell line PC-9 with high efficiency, and the most effective is the (−)-epicatechin gallate. In addition, the polyphenols activate processes leading to apoptosis in several types of cancer, such as prostate cancer, colon cancer, and lung cancer and inhibit angiogenesis. *Epicatechin*

**Table 2** Medicinal plants containing biologically active substances having direct antiangiogenic effects

| Plant | Active substance |
|---|---|
| *Allium sativum* L. | Diallyl trisulphide, allin |
| *Aloe vera* (L.) Burm. f. | Barbarodin, emodin |
| *Apium graveolens* L. | Apigenin, 3-*n*-butylphthalide |
| *Angelica sinensis* | *N*-butylidenephthalide, 4-hydroxyderricin |
| *Artemisia annua* L. | Artemisinin |
| *Berberis vulgaris* L. | Berberine |
| *Catharanthus roseus* L. | Alcaloids (vinblastine, vincristine) |
| *Capsicum frutescens* L. | Capsaicin |
| *Capsicum* spp. | Capsaicin |
| *Camellia sinensis* L. | Phenols: epigallocatechin |
| *Cambretum caffrum* Kuntz | Cambretastatin |
| *Camptotheca acuminata* Decne. | Alcaloids (derivative: irinotecan, topotecan, rubitecan) |
| *Chrysobalanus icaco* L. | Flavonoids, terpenoids |
| *Curcuma longa* L. | Curcumin, frulic acid |
| *Dysoxylum binectariferum* (Roxb.) Hook. f. ex.Bedd | Flavopiridol |
| *Ganoderma lucidum* L. | Triterpenoids |
| *Ginkgo biloba* L. | Ginkgolide B |
| *Gleditsia sinensis* | Alcaloids, flavonoids, phenols, saponins |
| *Glycine maxima* L. (Merr.) (soy) | Isoflavone**s:** genistein, daidzein |
| *Glycyrrhiza glabra* L. | Isoliquiritigenin: glabridin |
| *Hibiscus sabdariffa* L. | Protocatechuic acid |
| *Hippophae rhamnoides* L. | Isorhamnetin |
| *Hypericum perforatum* Thunb. | Floroglucin (derivative: hyperforin and adhyperforin) |
| *Juglans region* L. | Melatonin |
| *Magnoliae* spp. | Magnosalin |
| *Magnolia obovata* Tunb. | Honokiol, magnolol |
| *Matricaria chamomilla* L. | Flavonoids: apigenin, fisetin |
| *Ocimum sanctum* L. | Carnosol, ursolic acid |
| *Paeonia suffruticosa* Andrews | 1,2,3,4,6-Penta-*O*-galloyl-$\beta$-D-glucose (PGG) |
| *Panax ginseng* C.A. Meyer | Saponins: 20(R)- and 20(S)-ginsenoside-Rg3 |
| *Poria cocos* Wolf | 1–3-$\alpha$-D-glucan |
| *Polygonum cuspidatum* L. | Resveratrol |
| *Prunus dulcis* (Mill.) D.A. Webb | Betulinic acid |
| *Rabdosia rubescens*Hora | Ponicidin, oridonin |
| *Rheum palmatum* L. | Emodin |
| *Rosmarinus officinalis* L. | Carnosol, ursolic acid, carnosic acid |
| *Salvia miltiorrhiza* Bunge. | Cryptotanshinone |
| *Sanguinaria canadensis* L. | Sanguinarine |
| *Scutellaria baicalensis* Georgi. | Baicalin, baicalei |
| *Silybum marianum* L. | Silymarin (silybin) |
| *Tanacetum parthenium* L. | Parthenolide |
| *Tabebuia avellanedae* Lorentz ex Griseb | Glycosides, $\beta$-lapachone |
| *Taxus brevifolia* Nutt. | Taxoids |
| *Viscum album* L. | Lectins |
| *Zingiber officinale* L. | 6-Gingerol |
| *Prunus dulcis* (Mill.) D.A. Webb | Betulinic acid |

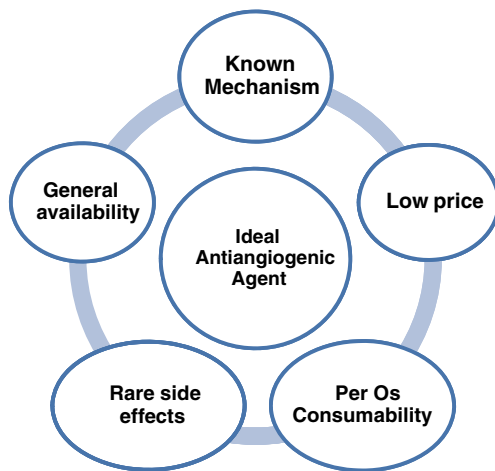On the basis of literature data and own studies cited in this article

Fig. 1 Qualities of an ideal antiangiogenic compound

*gallate* induces apoptosis in tumor cells by inhibiting the activity of TNF-$\alpha$ [110]. It also contributes to stopping the cell cycle in G0–G1 phase of the cells of Burkitt's lymphoma, initiating subsequently the classic signs of apoptosis such as DNA fragmentation, visible as a ladder, activation of caspases 9 and 3, inhibition of the activity of antiapoptotic proteins Bcl-2 and Mcl-1, mitochondrial membrane permeability, and the release of pro-apoptotic proteins (including cytochrome C, Smac/DIABLO, and AIF) from the mitochondria into the cytosol and the generation of reactive oxygen species [141].

*Carnosic acid* (CA) and *carnosol* (CS) are phenolic compounds existing in fresh and dried leaves of *Rosmarinus officinalis* L. It is believed that both compounds are responsible for the antioxidant, antiinflammatory, and cytotoxic properties of the raw material and extract [142–144]. CA (Fig.2c) is the major phenolic diterpene showing antioxidant, antibacterial, and antiobesity activity, inhibiting platelet aggregation and having antiangiogenic properties as well as showing the antitumor effect of P-glycoprotein [96, 145–147]. Figure 4 shows anticancer molecular mechanisms of CA.

CS inhibits induced expression of cytokines and adhesion molecules and adhesion of monocytes to ECs by a mechanism which involves NF-$\kappa$B. The latter mechanism can be associated with antiinflammatory properties of the compound [148]. CA can be subjected to oxidative degradation and rearrangement of the cascade, giving other antioxidant compounds of the rosemary like CS (Fig.2d) (namely, rosmanol, galdosol, and rosmariquinone).
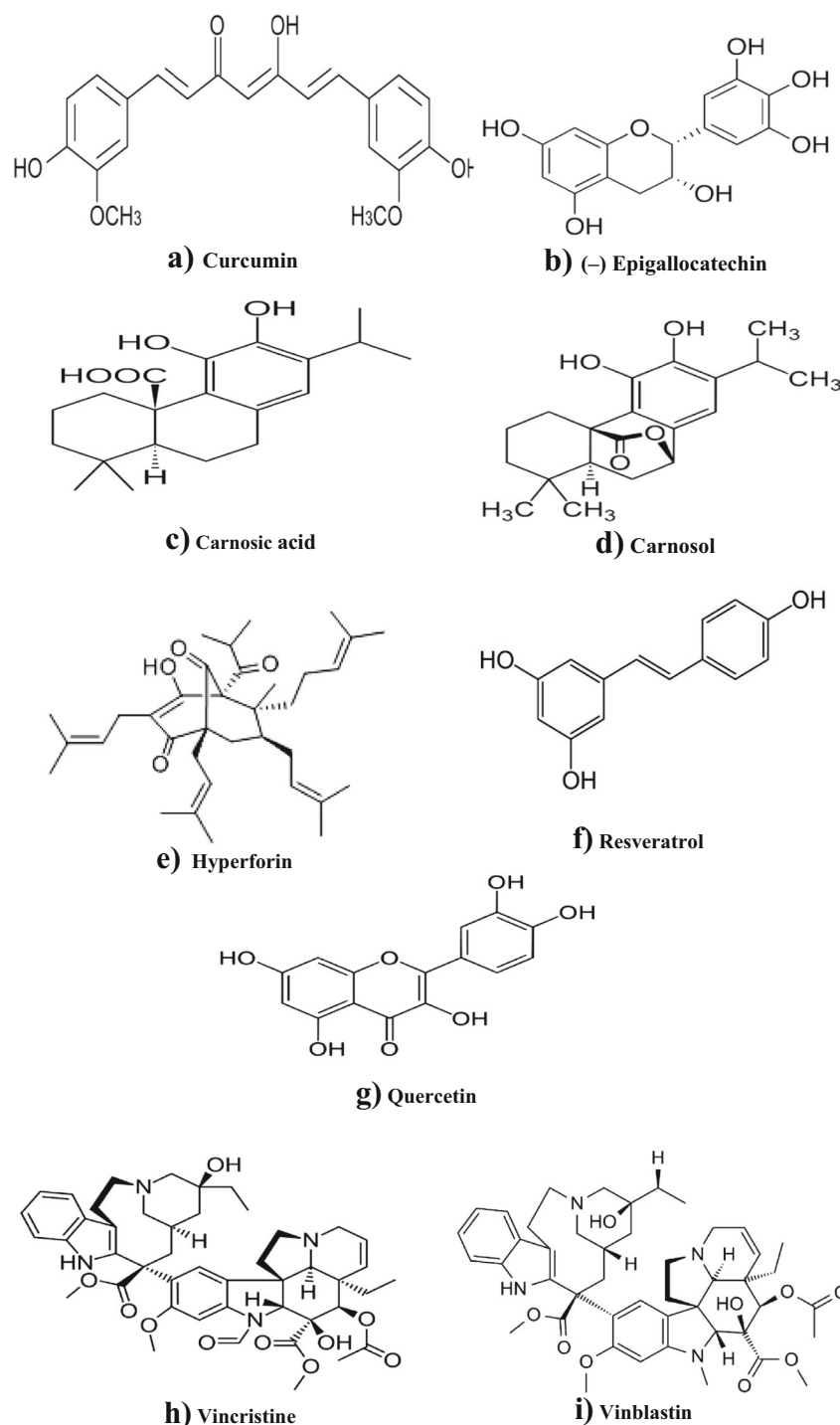
The biological activity of CS is similar to the activity of CA [149]. CA is able to inhibit certain functions of ECs (differentiation, proliferation, and migration and has proteolytic possibilities). Literature data indicates that the growth inhibitory effect exerted on the endothelial cell and tumor proliferation may be due to, at least in part, induction of apoptosis.

Inhibition of the mentioned production steps of the in vitro angiogenesis was confirmed by the observed inhibition of angiogenesis in vivo confirmed by a chicken chorioallantoic membrane test. Antiangiogenic activity of CS and CA may help to prevent cancer, and the antimetastatic effects of rosemary extract suggest their potential in the treatment of other cancers related to angiogenesis [150].

**Hyperforin and hyperforin derivatives of phloroglucin of acyl phloroglucinol** Numerous studies have confirmed that these substances inhibit the growth of cancer cells. Both hyperforin and adhyperforin are extracted from the herb *Hypericum perforatum* L. *Hyperforin* has been proposed as an innovative anticancer drug that induces apoptosis in cancer cells and inhibits angiogenesis in vivo [151, 152]. The inhibitory effect of hyperforin in neovascularization of experimental mouse tumor model was demonstrated by Dona et al. [153]. Hyperforin inhibits angiogenesis in vivo and is capable of inhibiting several key stages of angiogenesis in vitro, including endothelial cell proliferation, differentiation, and invasion, as well as the extracellular matrix degradation by MMP-2 and urokinase [154]. Therefore, the hyperforin seems to be a promising antiangiogenic compound. Determination of the molecular mechanisms related to its antiangiogenic effect is the next step in the evaluation of preclinical and clinical trials (Fig. 2e).

*Resveratrol* (3,5,4′-trihydroxystilbene) is a derivative of stilbene phytoalexin. First, it is isolated from the roots of veratrum (*Veratrum grandilorum*) [155]. Currently, it is known that resveratrol (Fig.2f) is present in fruit, grape leaves, berries, and peanuts [156]. It is also the active substance of wine. Resveratrol has proven to have antitumor and chemopreventive properties. It affects each phase of carcinogenesis (i.e., on the initiation, promotion, and progression of the process) by modulating the signal transduction pathways in cells that control cell growth and division, apoptosis, inflammation, angiogenesis, and metastasis. It is believed that this is one of the best factors that can be used in tumor therapy, in many types of cancer (breast, prostate, stomach, colon, pancreas) [100]. It has been shown that resveratrol in breast cancer cells (MCF-7, MDA-MB-231) and murine skin inhibits the cell cycle and induces apoptosis through the mitochondrial pathway releasing cytochrome c, Apaf-1, and activating the caspase and PARP [157, 158]. It also maintains the expression of p53 protein, which reduced activity, is one of the causes of carcinogenesis [159]. Antiangiogenic activity of resveratrol stems from its ability to inhibit the division of human umbilical EC (HUVEC) and reduction of the lytic activity of MMP-2 [160]. Resveratrol inhibits VEGF-induced angiogenesis by disruption of reactive oxygen species-dependent src kinase activation and subsequent VE-cadherin tyrosine

**Fig. 2** Bioactive compounds known as an antiangiogenics



a) **Curcumin**

b) **(−) Epigallocatechin**

c) **Carnosic acid**

d) **Carnosol**

e) **Hyperforin**

f) **Resveratrol**

g) **Quercetin**

h) **Vincristine**

i) **Vinblastin**

phosphorylation [161, 162]. Resveratrol given to rats inhibited the growth of glioma. By inhibiting angiogenesis [163, 164], RSV inhibited HIF-1$\alpha$ accumulation and VEGF secretion induced by cobalt chloride (CoCl2) through SIRT1 in human retinal pigment epithelial (hRPE) cells. Furthermore, resveratrol downregulated VEGFR2 phosphorylation and activation induced by VEGF in ECs via SIRT1. Thus, the inhibitory effect of RSV on the HIF-1$\alpha$/VEGF/VEGFR2 signaling axis is mediated, at least in part, through SIRT1. The results suggest that targeting SIRT1 could have therapeutic potential for the treatment of CNV (Fig.5) [165]. However, long-term intake of resveratrol-enriched wine products can produce side effects due to the alcohol content. Therefore, there must be a precaution not to encourage people to consume a large quantity of wine rather than a reasonable amount of red wine (two to three glasses per day). Other food products and non-alcoholic drinks could be considered to be alternative and optional resveratrol sources.
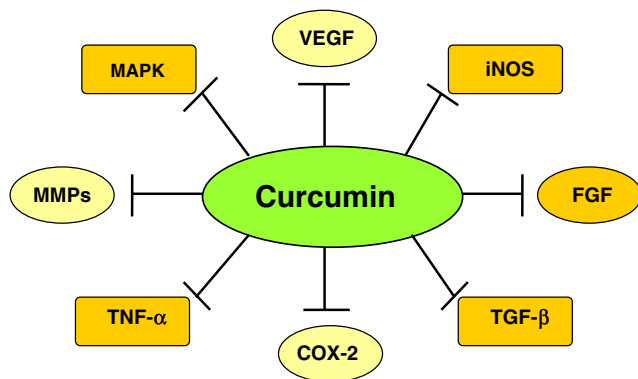
Fig. 3 Molecular targets of curcumin

*Isoflavones* are the chemical compounds structurally similar to steroid hormones though they are not derived from cholesterol [166]. The most known isoflavones are quercetin, luteolin, apigenin, kaempferol, and genistein. A large group of these compounds exerts different effects on the human body, showing antioxidant, cardioprotective, and anticancer activity. By blocking proteasome activity, they induce apoptosis in Jurkat T-leukemia cells. Yang et al. [167] have shown that the activity of isoflavones in relation to proteasome is as follows: apigenin ≥ luteolin > quercetin > kaempferol (apigenin acts the strongest). The differential activities of these compounds are due to the chemical structure of molecules in which hydrogen fourth (C4) in the ring C has the highest activity against substrates. In addition, computer
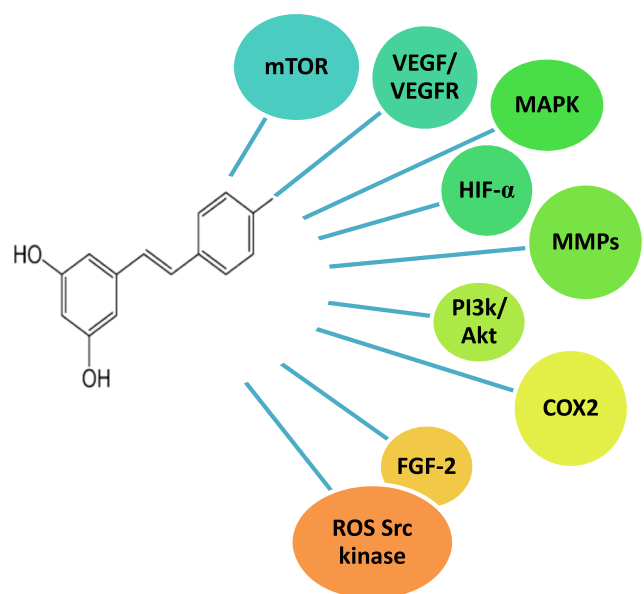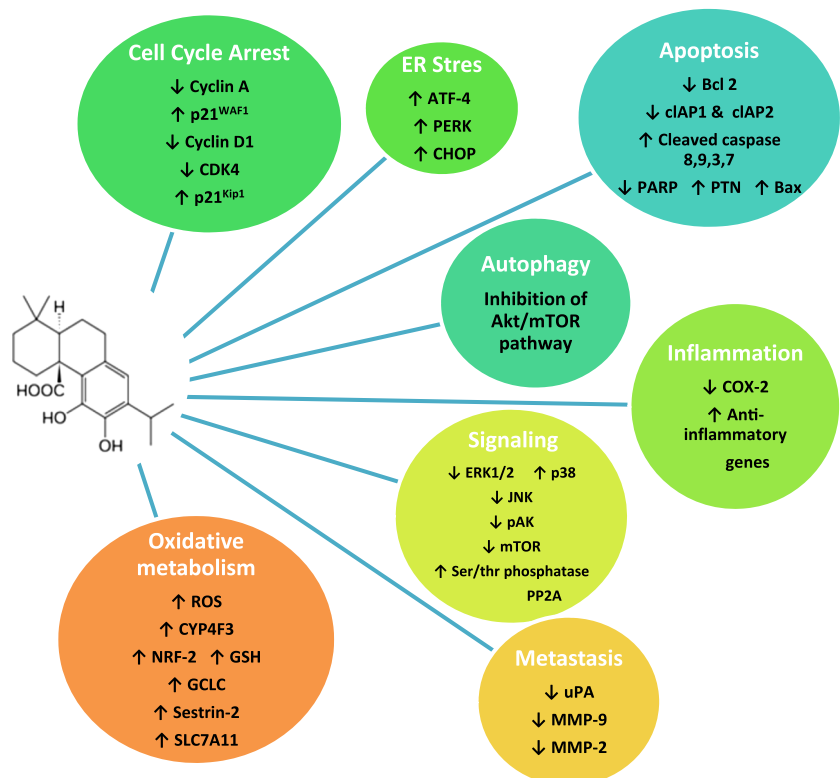


Fig. 5 Multiple targets triggered and inhibited by resveratrol in cancer angiogenesis

modeling has shown that the removal of the hydroxyl group at C3 also extends inhibition of the activity of the proteasome, while inducing apoptosis and inhibiting angiogenesis [168]. This is done by the interaction of specific processes responsible for regulation of apoptosis, such as the release of cytochrome c from mitochondria, activation of caspases 9 and 3, the stimulation of the synthesis of caspase-8 and tBid protein,

Fig. 4 Anticancer and antiangiogenic molecular mechanisms of carnosic acid

and the reduction of the expression of antiapoptotic proteins of the Bcl-2 family, such as Bcl-X(L), stimulation of the expression of proteins Bax and Bak as well as interaction with a nuclear factor NF-κB (Fig.6) [169].

*Quercetin* (3,3′,4′,5,7-pentahydroxyflavone) is a flavone found in onions, raspberries, red grapes, apples, cherries, broccoli, and leafy greens. Specifically, flavonoids and chalcones regulate expression of VEGF, MMPs, and EGFR and inhibit NF-κB, PI3-K/Akt, and ERK1/2 signaling pathways, thereby causing strong antiangiogenic effects. It has been reported that quercetin (Fig. 2g) showed significant antiangiogenic potential by inhibiting angiogenesis through multiple mechanisms. These include interaction with the COX-2 and LOX-5 enzymes, the EGF receptor, the HER-2 intracellular signaling pathway, and the NF-κB nuclear transcription protein [170–173]. Quercetin may enhance the anticancer effects of tamoxifen through antiangiogenesis [174, 175].

*Genistein* is an isoflavone isolated from soybean seeds (*Glycine maxima* L). When combined with cisplatin, it significantly decreases the proliferation of three BxPC cells of pancreatic cancer and their induced apoptosis. The reduction of tumor growth was also observed in vivo in a mouse xenograft model of the BxPC-3 cell [176]. Furthermore, tumor regression was observed in C57B16 mice with Lewis lung carcinoma cells [177]. It is worth mentioning that the pharmacotherapy with the use of genistein can be carried out in conjunction with radiation therapy. Depending on the endogenous estrogen concentrations and the target tissue, genistein and daidzein may interfere with ER signaling. Furthermore, several other ER-independent mechanisms of action, such as the inhibition of steroidogenic enzyme activities, modulation of growth factor action, downregulation of tyrosine and other

protein kinases, and the inhibition of angiogenesis, have been suggested for isoflavones on the basis of experiments with animal and cellular models [178]. However, the physiologic relevance of these effects in humans is unclear. *Delphinidin* is a specific flavonoid present in the skin of *Solanum melongena* showing cytotoxic activity against human tumor cells. It has been proved that the compound has inhibitory activity against the MMPs, degradation of extracellular matrix during the invasion of tumor cells [179].

## Secondary metabolites with integrated nitrogen

Plant secondary metabolites, the nitrogen atom in the molecule, include alkaloids, betalains, cyanogenic glycosides, and glucosinolates (a glucosinolate) [180]. Over 12,000 different alkaloids are known, which are mainly in the seeds, roots, leaves, and bark of plants. Most of the plant species containing alkaloids belong to the families Ranunculaceae, Solanaceae, and poppy. Examples of plants that contain alkaloids include barberry, coltsfoot, henbane, periwinkle pink, pomegranate bark, seeds, coffee, tea leaves, and cocoa [89].

*Vinblastine* and *vincristine* (Fig. 2h, i) obtained from *Catharanthus roseus* show properties valuable in anticancer therapy. Such compounds block the formation of microtubule and karyokinetic spindles, resulting in the inhibition of mitosis at metaphase, cell death, and inhibiting angiogenesis. In addition, they affect the microtubule involved in chemotaxis and migration of organelles and vesicles of the secretory cells and outside. They also affect the structural integrity of some cells [181]. Therefore, vinblastine and vincristine are used to treat leukemia, lymphoma, breast cancer, testicular cancer, lung cancer, and Kaposi's sarcoma [182]. Different vinca alkaloids have their own unique properties. *Vinblastine* inhibits angiogenesis or the process by which new blood vessels grow from preexisting ones. Vinblastine is most often applied to treat Hodgkin's disease, non-Hodgkin's lymphoma, breast cancer, and germ cell tumors. Side effects of vinblastine include toxicity to white blood cells, nausea, vomiting, constipation, dyspnea, chest or tumor pain, wheezing, and fever. Vinblastine is also occasionally associated with antidiuretic hormone secretion and angina. An antiangiogenic effect of vinblastine was then plainly shown by Vacca et al. [183], who studied multiple events in HUVECs related to angiogenesis in vitro. They also reported the relation dose–response antiangiogenic activity by vinblastine in the in vivo embryonic chick CAM assay. Subsequently, numerous reports have demonstrated marked tumor regression in various mouse models following low doses of vinblastine in combination with VEGF-A-targeting drugs [184–186]. The concept of the antiangiogenic scheduling of chemotherapeutics undoubtedly holds great promise, and numerous studies are presently underway using the metronomic concept [187].
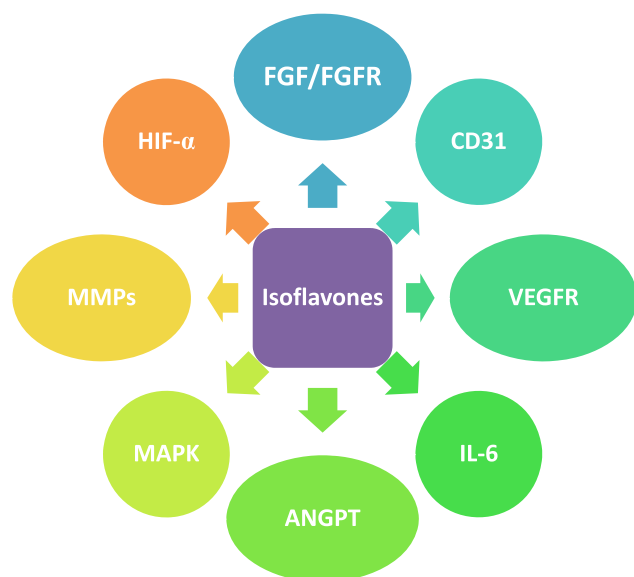


**Fig. 6** Multiple targets triggered and inhibited by isoflavones in cancer angiogenesis

*Vincristine's* inhibition of microtubule formation is especially powerful. The reason besides this is that the tubulin protein is dynamic. Its long chain of building blocks is always growing in some places and breaking in others. The less contiguous parts of a tubulin molecule have pieces only two building blocks long, called dimers. Vincristine has a high affinity for tubulin dimers, and the reaction between vincristine and the dimers is rapidly reversible [188]. That means a vincristine molecule will attach to a dimer at one site, break off, and then reattach at another site. This keeps two sites per dimer "poisoned" and unable to reassemble into the protein. So, vincristine's ability to destabilize tubulin is especially good [189, 190]. Angiogenesis is critical for cancer growth and progression. In the study by Pasquieret et al. [191], the investigators found that treatment with vincristine or in combination with $\beta$-blockers significantly inhibited vascular structures by established EC lines (BMH29L cells). However, one major point on vincristine and $\beta$-blockers' mechanism of action is their specificity to cancer-derived ECs. It is well established that cancer-derived ECs show increased proliferation, motility, pro-angiogenesis properties, and resistance to drug treatment compared with "normal" ECs (e.g., HUVECs). For example, human breast cancer-derived ECs and human hepatocellular carcinoma tumor-derived ECs presented increased resistance to vincristine and angiogenesis inhibitors [192, 193].

*Cyanogenic glycoside's* induction is a form of protection of plants against herbivores. Furthermore, many compounds such as amygdalin, prunasin, or linamarin show antineoplastic activities [194]. The aim of the study was to evaluate the anticancer properties by inhibiting angiogenesis of amygdalin (medicine under the name "laetrile" or vitamin $B_{17}$), which occurs, e.g., in the seeds of peaches, apricots, and almonds. Pro-apoptotic effect of amygdalin has been found in prostate cell lines DU145 and LNCaP [195]. Although these compounds are not very effective, they are still used mainly as an alternative or adjunct to the antiangiogenic therapy. Furthermore, the metabolism of cyanogenic glycosides proceeds with a production of poisonous cyanide (HCN), of which accumulation in the body may lead to severe poisoning; therefore, dosages of these compounds should be determined individually for each patient [178, 196].

*Glucosinolates* are found in plants of the cabbage family, such as cabbage, broccoli, and cauliflower (*Brassicaceae* Burnett., *Cruciferae* Juss.). The best-studied glucosinolates occurring in cruciferous plants are synigryna, gluconapin, glucoiberin, and glucoraphanin [180]. Glucosinolate molecule consists of three parts: the glucose in the form of the β-D-tioglucan, sulfuric acid oxime group, and side chain made up of amino acid residues [197]. Glucosinolates and their metabolic products, isothiocyanates (sulforaphane), and indoles (indole-3-carbinol) have antiangiogenic properties [198]. In the anticancer therapy, their function is to activate the enzymes in xenobiotic detox, which are mentioned as potential carcinogens. It has been observed that they activate glutathione transferase in colon cancer cells (HT-29) and liver cancer cells (HepG2) [199, 200]. By reducing the activity of cell cycle proteins, such as cyclin B1 or kinase Cdc25C, they lead to stopping of the cell cycle in G2/M [197].

*Polyamines* are a group of compounds with a simple chemical structure that includes structure amine groups. Due to the fact that they present typical properties of the hormones, they are included in the group of plant phytohormones. Among these compounds, there is putrescine (1,4-diaminobutane), which is a precursor to other polyamines such as spermine and spermidine [201, 202]. The immediate precursor of polyamines is the amino acid, arginine. Among the polyamines, putrescine arouses the greatest attention. In normal growing cells, it contributes to the regulation of cell cycle proliferation by controlling the transitions between different phases of the cycle and in the correct course of programmed cell death and angiogenesis. Utrescine also affects the limitation of the migration and the spreading of tumor cells. The factor inverting this situation is the compound difluoro-methyl ornithine/eflornithine ($\alpha$-DFMO) which lowers the level of putrescine and stops the cell cycle of tumor cells in the G1 phase [202, 203]. Moreover, by limiting the availability of nutrients, $\alpha$-DFMO inhibits angiogenesis in human gastric cancer cells and melanoma cells, leading to the death of these cells [204].

*Cytokinins* (CKs) are plant hormones that control the process of apoptosis of cancer [205]. In this regard, the strongest activity shows cytokinin ribosides and benzyl aminopurine (BAP). BAP has the ability to inhibit certain human protein kinases including CDK, which may limit cell proliferation, angiogenesis, and activation of apoptosis, which is one of the main goals of tumor therapy. Other cytokines have similar properties but must be used at higher concentrations [126]. Kinetin and isopentenyl adenine (IPA) and benzyl adenine (BA) effectively inhibit cell growth and induce the reduction of MTT and morphological changes in the mature granulocytes of myeloid leukemia [206], whereas cytokinin ribosides effectively inhibit growth and induce apoptosis, limiting the content of cellular ATP [207]. CKs play a crucial role in many physiological processes in plants. One of the interesting functions of CKs is the control of programmed cell death (PCD). It seems that all CK-dependent phenomena including PCD are accompanied by a special multistep phosphorelay signaling pathway. This pathway consists of three elements: histidine kinase receptors, histidine phosphotransfer proteins, and response regulators. A recent review by Kunikowska et al. (2013) shows the highlights of the latest knowledge about CK signaling pathways in many physiological processes in plants, with special attention paid to PCD process [208]. Other natural products that possess antiangiogenic activities recently described in the literature are summarized in Table 3. Besides, a general diagram binding therapeutic targets in angiogenesis and natural products is presented in Fig.7.

**Table 3**  Non-exhaustive list of bioactive compounds that inhibit angiogenesis

| Bioactive compound | Effect on angiogenesis | Source | References |
|---|---|---|---|
| Retinoic acid | Exerce and inhibition of reactivity of ECs to angiogenic growth factors | Most brightly colored fruits and vegetables | [209, 210] |
| Genistein | Downregulates MMP-9 and upregulates TIMP-1 and inhibits VEGF and COX-2 expression and suppresses VEGF-induced tyrosine phosphorylation | *Lupinus*, *Psoralea*, and coffee | [211, 212] |
| Apigenin | Inhibits HIF-1 and VEGF expression in human ovarian cancer cells and inhibits in vitro angiogenesis | Parsley, celery, celeriac, and chamomile tea | [213, 214] |
| Silibinin | Inhibits growth and survival of ECs in HUVEC and inhibits VEGF secretion from human cancer cells | *Silybum marianum* | [215, 216] |
| Grap seed procyanidins | Prevents growth, survival, migration, and invasion of HUVEC and decreases VEGF expression and microvessel density in tumor xenograft model | Grape | [109, 217] |
| Indole-3-carbinol | Decreases VEGF and Flk-1 expression in ECs and inhibits in vitro angiogenesis in Matrigel | Broccoli, cabbage, cauliflower, brussels sprouts, collard greens, and kale | [218, 219] |
| Withaferin | Withaferin inhibits human umbilical vein endothelial cell (HUVEC) sprouting in 3D collagen-I matrix | *Withania somnifera* | [220] |
| n-Butylidenephthalide | Inhibition of FGF-2-induced proliferation and migration in a wounding assay, chemotaxis, and tube formation with small vessel and large vessel ECs  In vivo inhibition of angiogenic model using the chick chorioallantoic membrane | Radix *Angelica sinensis* | [69] |
| Sesterterpenes | Antiangiogenic effects by blocking human umbilical vein EC proliferation, migration, and capillary-like tube formation on Matrigel | Marine sponges and other natural sources | [221] |



**Fig. 7** Major signaling pathways of angiogenesis targeted by natural products
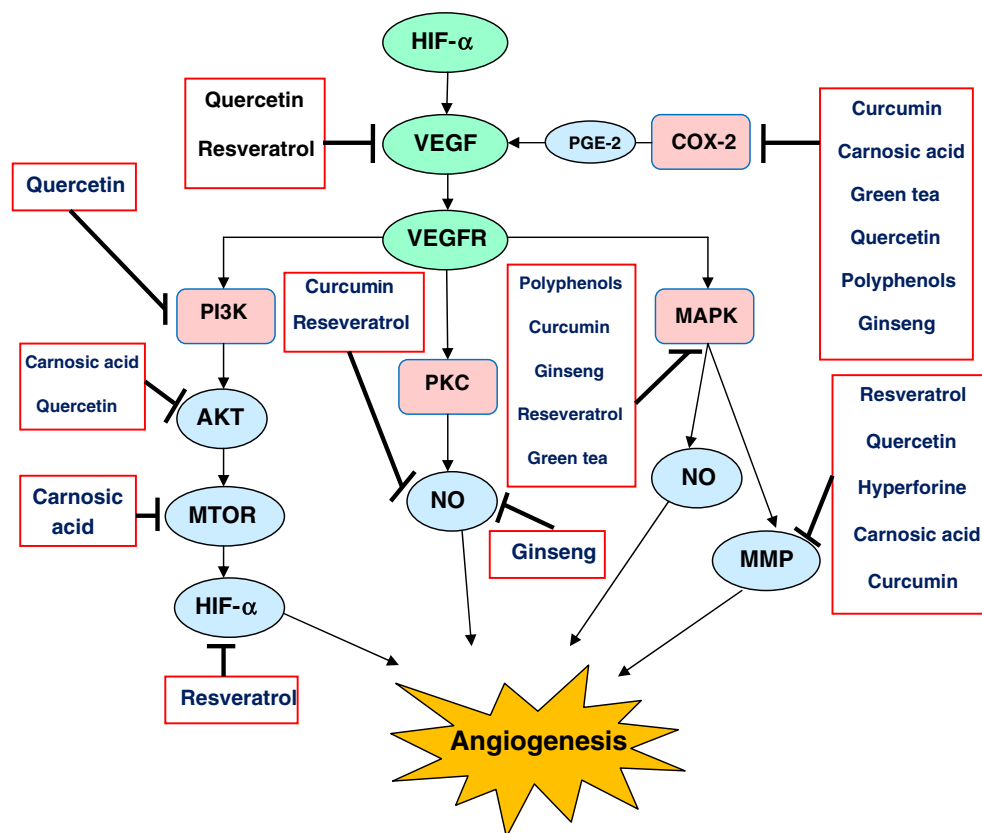
**Table 4** Combretastatin clinical trials (according to www.clinicaltrials.gov [227])

| Study | Type | Identifier | Results | Sponsor | Status |
|---|---|---|---|---|---|
| Safety and effectiveness of C A-4 phosphate combined with chemotherapy in advanced solid tumors | Interventional randomized phase II clinical trial | NCT00113438 | No results published for this study | OXiGENE | Completed |
| Combretastatin A4 phosphate in patients with neovascular age-related macular degeneration (AMD) | Prospective, interventional, dose-escalation clinical trial | NCT01570790 | Potential efficacy of CA4P in neovascular AMD | Johns Hopkins University | Completed |
| Safety and efficacy study of combretastatin A4 phosphate to treat patients with choroidal neovascularization secondary to pathologic myopia | Interventional non-randomized phase II safety/efficacy clinical trial | NCT01423149 | No results published for this study | OXiGENE | Completed |
| Combretastatin A4 phosphate in treating patients with advanced anaplastic thyroid cancer (ATC) | Interventional phase II Safety/ efficacy clinical trial | NCT00060242 | Combretastatin A4 has an acceptable safety profile in patients with advanced ATC, and one third survived more than 6 months | Case Comprehensive Cancer left | Completed |
| Study of combretastatin and paclitaxel/carboplatin in the treatment of anaplastic thyroid cancer | Interventional randomized phase II/III study | NCT00507429 | Approximately a quarter of patients treated with single-agent CA4P with more than 3 months of survival | OXiGENE | Terminated Has results |
| Induction chemotherapy using doxorubicin and cisplatin followed by combretastatin A4 phosphate and radiation therapy in treating patients with newly diagnosed regionally advanced anaplastic thyroid cancer | Interventional phase II safety/ efficacy clinical trial | NCT00077103 | No results published for this study | Case Comprehensive Cancer left | Terminated |
| Safety study of increasing doses of combretastatin in combination with bevacizumab (avastin) in patients with advanced solid tumors | Interventional randomized safety phase I study | NCT00395434 | No results published for this study | OXiGENE | Completed |
| Safety study of increasing doses of combretasatin A1 diphosphate (OXi4503) as monotherapy in subjects with hepatic tumor burden | Interventional non-randomized safety/efficacy phase 1b/2 study | NCT00960557 | No results published for this study | OXiGENE | Completed |
| A safety and efficacy study of carboplatin, paclitaxel, bevacizumab, and CA4P in non-small cell lung cancer | Interventional randomized safety/ efficacy phase II study | NCT00653939 | Progression-free survival in the intent-to-treat population | OXiGENE | Completed Has results |
| Study evaluating the safety and response of fosbretabulin in Asian patients with polypoidal choroidal vasculopathy (PCV) | Interventional randomized safety/ efficacy double-blind phase II trial | NCT01023295 | No results published for this study | OXiGENE | Completed |
| Combretastatin A4 phosphate in treating patients with advanced solid tumors | Interventional phase I Pharmacokinetic study | NCT00003768 | No results published for this study | Case Comprehensive Cancer left | Completed |
| A phase I clinical trial of OXi4503 for pelapsed and refractory AML and MDS | Interventional safety phase I clinical trial | NCT01085656 | No results published for this study | University of Florida | Terminated |
| Chemotherapy in treating patients with solid tumors | Interventional phase I trial | NCT00003698 | CA4P was well tolerated | University of Glasgow | Completed |
| Fosbretabulin or placebo in combination with carboplatin/ paclitaxel in anaplastic thyroid cancer | A phase 3, randomized, double-blind, placebo-controlled study | NCT01701349 | This study has been withdrawn prior to enrollment | OXiGENE | Withdrawn |
| PCC + bevacizumab + CA4P versus PCC + bevacizumab + placebo for subjects with platinum-resistant ovarian cancer | Interventional randomized double-blind, phase 2/3 study | NCT02641639 | This study is not yet open for participant recruitment | OXiGENE | Not yet recruiting |
| A phase 2 study of fosbretabulin in subjects with pancreatic or gastrointestinal neuroendocrine tumors with elevated biomarkers | Interventional safety/efficacy phase II study | NCT02132468 | This study is ongoing but not recruiting participants | OXiGENE | Active, not recruiting |
| Rollover protocol for subjects who have responded on study 4218s—a phase 2 study | Interventional safety/efficacy phase II trial | NCT02279602 | This study is enrolling participants by invitation only | OXiGENE | Enrolling by invitation |

**Table 4** (continued)

| Study | Type | Identifier | Results | Sponsor | Status |
|---|---|---|---|---|---|
| A study of AVE8062 in advanced-stage soft tissue sarcoma after failure of anthracycline and ifosfamide chemotherapies | A multinational, randomized, double-blind placebo-controlled phase III trial | NCT00699517 | No results published for this study | Sanofi | Completed |
| A phase I/II trial of crolibulin (EPC2407) plus cisplatin in adults with solid tumors with a focus on anaplastic thyroid cancer (ATC) | Interventional randomized phase I/II trial | NCT01240590 | This study is ongoing but not recruiting participants | National Cancer Institute | Active, not recruiting |

## Plants as a source of antiangiogenic drugs: clinical trials

Several clinical trials were conducted to evaluate the effect of natural products against tumor angiogenesis. Most of these studies were directed by the pharmaceutical companies OXiGEN and Novartis on combretastatin and vadimezan (ASA 404), respectively.

**Combretastastin (CA4-P)** CA4-P acts as antiangiogenic by destabilizing microtubules. Encouraging results in vivo models lead to preliminary clinical trials on CA4-P and its derivatives. CA4-P has been tested alone or in combination with targeted therapy or chemotherapy in patients with advanced cancer in a phase I trial. Many clinical trials studied the combination of CA4-P with other antiangiogenic drugs such as bevacizumab and endostar. It has been reported that when bevacizumab was administered 4 h after CA4-P, agio-permeability and tumor perfusion were statistically and significantly reduced, but these parameters were reversed after administration of CA4-P alone. These results demonstrated that bevacizumab sustained significant vascular modifications induced by CA4-P [222].

Recently, OXiGEN announced the results of the clinical trial Gynecologic Oncology Group protocol 186I (GOG 186I). A randomized phase II study investigated the combination of Avastin® (bevacizumab) with ZYBRESTAT® (CA4P) in recurrent ovarian cancer. GOG 186I showed a statistically significant increase in progression-free survival compared to bevacizumab alone [223]. Higher response rates were observed in relapsed patients with platinum-resistant ovarian cancer treated with standard chemotherapy (carboplatin and paclitaxel) and CA4-P as compared to patients treated with chemotherapy alone [224]. Interestingly, CA-4P revealed therapeutic potential in patients with metastatic anaplastic thyroid cancer [225]. Clinical trials of CA-4P in patients with neovascular age-related macular degeneration showed potential interest and efficacy. However, future clinical use is unlikely due to related adverse side effects observed during this investigation [226]. Other CA4-P clinical trials are listed in Table 4 and Fig. 8 [227]. Recruitment of patients for combretastatin-based clinical trials has evolved from patients in advanced stages of chemotherapy-resistant carcinomas, to phase III clinical trials, thus exhibiting clinical trust in combretastatin-based protocols.

**Vadimezan (ASA 404, DMXAA)** ASA 400 is a flavonoid derivative discovered at the Auckland Cancer Society Research Centre at the University of Auckland in New Zealand targeting stimulator of interferon genes (STING) pathway. In 2007, Novartis obtained the worldwide rights for it [228]. ASA 404 had been evaluated in combination with chemotherapy in two phase II trials for advanced non-small cell lung cancer (NSCLC) and showed survival extensions of

**Fig. 8** Global distribution of clinical trials on combretastatin
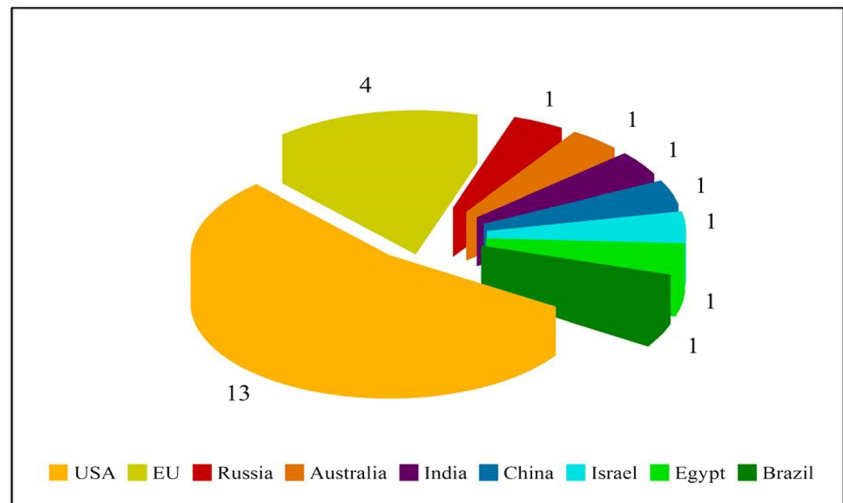


**Table 5** Vadimezan (ASA 404, DMXAA) clinical trials (according to www.clinicaltrials.gov [233])

| Conditions | Starting year | Type | Combined drugs | Mean results | Sponsor |
|---|---|---|---|---|---|
| Solid tumors | 2011 | Phase I | Phase 1: ASA404+ fluvoxamine Phase 2: ASA404 + paclitaxel, docetaxel or docetaxel + carboplatin | No study results posted | Novartis |
| Solid tumor malignancies | 2011 | Phase I | Taxanes | No study results posted | Novartis |
| Advanced urothelial carcinoma | 2010 | Phase II | Docetaxel | Withdrawn in 2015 before enrollment because of lack of efficacy of experimental treatment | Hoosier Cancer Research Network in collaboration with Novartis |
| Stage IIIb/IV non-small cell lung cancer | 2008 | Phase III | Docetaxel Placebo | No study results posted | Novartis |
| Advanced solid tumors | 2011 | Phase I | Single infusion of ASA404 | No study results posted | Novartis |
| Advanced or recurrent solid tumors | 2011 | Phase I | Docetaxel | No study results posted | Novartis |
| Metastatic cancer | 2011 | Phase I | Single infusion of ASA404 | No study results posted | Novartis |
| Histologically proven and radiologically confirmed solid tumors | 2011 | Phase I | Phase 1: ASA404 alone Phase 2: ASA404 + taxane | No study results posted | Novartis |
| Non-small cell lung cancer | 2008 | Phase I | Paclitaxel and carboplatin | No study results posted | Novartis |
| Metastatic cancer with impaired renal function Metastatic cancer with normal renal function | 2010 | Phase I | Paclitaxel + carboplatin or docetaxel alone | No study results posted | Novartis |
| Solid tumors | 2009 | Phase I | Single infusion of ASA404 | No study results posted | Cancer Research UK in collaboration Cancer Society Auckland |
| IIIb/IV non-small cell lung cancer | 2008 | Phase III | Carboplatin + paclitaxel | No study results posted | Novartis |
| Refractory solid tumors | 2009 | Phase I | Cetuximab + carboplatin + paclitaxel | This study has been withdrawn prior to enrollment because the investigator has left the institution (UCSF) prior to study start-up) | University of California, San Francisco in collaboration with Novartis |
| Lung cancer | 2010 | Phase II | Carboplatin + paclitaxel | No study results posted | Swiss Group for Clinical Cancer Research |
| Non-small cell lung cancer | 2009 | Phase I–II | Carboplatin + paclitaxel | No study results posted | Antisoma Research |
| Refractory tumors | 2009 | Phase I | Single infusion of ASA404 | No study results posted | Antisoma Research |
| Hormone refractory metastatic prostate cancer | 2005 | Phase II | Docetaxel | No study results posted | Antisoma Research |

around 5 months when compared to chemotherapy alone [229]. A phase III trial started in 2008 and showed in March 2010 poor results as a first-line therapy for NSCLC [230]. Temporary poor results in another randomized phase III placebo-controlled trial of carboplatin and paclitaxel with or without ASA 404 as the second-line therapy for NSCLC were obtained in 2011 [231]. Two parallel phase I clinical trials were conducted in the UK and New Zealand by Cancer Research UK, finding that ASA404 has anticancer effect at well-tolerated doses. A third phase I trial was designed for patients with recurrent tumors establishing the optimal dose for a phase II trial [232].

The largest two randomized double-blind placebo-controlled phase III trials, ATTRACT-1 and ATTRACT-2, were conducted by Novartis in advanced NSCLC using antiangiogenics. ATTRACT-2 assessed ASA404 in association with docetaxel and carboplatin as first-line therapy in patients with stage IIIB/IV NSCLC, whereas ATTRACT-1 evaluated the same drug associations as the second-line treatment for patients with advanced NSCLC. Both trials were unsuccessful to show survival advantages or significant amelioration [233]. Other clinical trials on ASA 404 are listed in Table 5.

Despite the interesting results at the preclinical stage, ASA 404 failed in human clinical trials. Recent studies have investigated the reason for the inefficacy. ASA 404 was shown to target the STING pathway. However, this activity is mouse specific; it has no effect on human STING target [234].

**Other drugs** The toxicity and the anticancer effect of MPC-6827 (verubulin, Azixa®) as a single drug were investigated in patients with advanced cancer. It has also recently been assessed in phase II bevacizumab recurrent glioblastomas [235]. The clinical trial with BCN105P has recently been published [236]. The main objective of this trial was to evaluate the safety, toxicity, pharmacokinetic, and pharmacodynamic effects of this drug. The results from this clinical trial show a favorable toxicity profile of this drug at the advisable dose level and has guided to more evaluation in phase II trials. Importantly, when using dynamic MRI at a higher concentration, significant modifications in vascular ultrastructure were observed in some patients.

CYT997 is the latest inhibitor of the microtubule assembly and antiangiogenic drug [237]. A phase I accelerated dose-escalation study examined the safety, tolerability, pharmacokinetics, and vascular-disrupting effects of orally administered CYT997. Preliminary evidence of significant efficacy was established [238]. Finally, it is required to start other clinical trials on natural products targeting angiogenesis alone (or in combination with chemoradiotherapy) and to carefully investigate the toxicity and the mechanisms of action of these combinations.

## Conclusion

Currently in clinical trials, there are many substances that inhibit angiogenesis, acting at the different stages of the process. Mechanisms of these actions are not yet fully known. However, antiangiogenic therapy carries some risks. It can cause systemic, generalized angio-suppression leading to dysfunction of female reproduction, wound healing, and merging fractures, and the therapy targeted on receptors for VEGF may lead to the development of diabetes. Therefore, we must remember the so-called therapeutic angiogenesis, which involves not only the inhibition of the formation of new blood vessels but also stimulating the formation of vessels in diseases characterized by their deficiency (pro-angiogenic therapy). However, nowadays, antiangiogenic therapy is more often used in the treatment.

Thus, results from plant-derived antiangiogenesis agents suggest that, unlike conventional chemotherapeutic agents generally employed at high doses for relatively short time periods, these angiogenic inhibitors may be best employed using less cytotoxic doses over months to years as a potential means to prevent dormant micrometastases from entering a rapid growth phase. The additional clinical testing of newly identified angiogenic inhibitors using a variety of delivery strategies is eagerly awaited. For millennia, the natural products have been used by man as a remedy in traditional medicine. Recent research has shown that such natural substances are able to prevent the development of many cancers. The discovery and characterization of new molecules will expand the drug library of therapeutic molecules, which must grow due to the emergence of new diseases and the emergence of resistance against conventional treatments.

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