Natural Products: A Promising Therapeutics for Targeting Tumor Angiogenesis

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Tumor-associated angiogenesis is a key target for anti-cancer therapy. The imbalance between pro-angiogenic and anti-angiogenic signals elicited by tumor cells or tumor microenvironment always results in activating “angiogenic switch”. Tumor angiogenesis functions in multi-aspects of tumor biology, including endothelial cell apoptosis, tumor metastasis, and cancer stem cell proliferation. Numerous studies have indicated the important roles of inexpensive and less toxic natural products in targeting tumor angiogenesis-associated cytokines and apoptotic signaling pathways. Our current knowledge of tumor angiogenesis is based mainly on experiments performed on cells and animals, so we summarized the well-established models for angiogenesis both in vitro and in vivo. In this review, we classified and summarized the anti-angiogenic natural agents (Polyphenols, Polysaccharides, Alkaloids, Terpenoids, Saponins) in targeting various tumor types according to their chemical structures at present, and discussed the mechanistic principles of these natural products on regulating angiogenesis-associated cytokines and apoptotic signaling pathways. This review is to help understanding the recent progress of natural product research for drug development on anti-tumor angiogenesis.

Keywords: tumor angiogenesis, natural products, angiogenic factors, endothelial cell apoptosis, anti-angiogenic mechanism, chemical structures

HIGHLIGHTS

1. The primary mechanism of tumor angiogenesis was depicted.
2. The current in vivo and in vitro models toward targeting angiogenesis were recapitulated.
3. Natural agents as therapeutics against tumor angiogenesis were summarized.
INTRODUCTION
Angiogenesis refers to the process of new blood vessel formation from pre-existing endothelial cells in established vessels. The main cellular element of newly formed capillaries is endothelial cells (ECs), that are primarily modulated by vascular endothelial growth factor (VEGF) (1). After stimulating by VEGF, ECs can migrate to the lead of growing capillaries, that are referred to as tip cells. Upon the transformation of ECs to tip cells, the following ECs (stalk cells) will proliferate and maintain the structural and functional integrity of nascent vessels (2). Unlike physiological condition, tumor cells exposed to hypoxic condition secrete high levels of pro-angiogenic factors, such as VEGF. VEGF is the key regulator of the proper development of tumor blood vessels. Members of the angiopoietins, platelet-derived growth factor (PDGF-B), transforming growth factor (TGF-β) families and basic fibroblast growth factor (bFGF) are also significant factors in the formation of an immature vascular network in tumors (3). Moreover, recent literature has demonstrated that a variety of pro-angiogenic factors (VEGF, angiopoietin-1, bFGF) have the ability of inhibiting EC apoptosis (4) in tumor angiogenesis.

Natural products isolated from plants have been used as medicine from ancient times. The discovery of natural products for treatment dated back to 2600 BC in Mesopotamia (5). Traditional Chinese medicine (TCM) and Indian Ayurveda system are well documented over thousands of years. Early experiments have verified their properties of anti-inflammatory, anti-allergic and anti-infectious diseases (6, 7). Natural phytochemicals have been applied to the therapy of various diseases, including tumors (8). These phytochemicals can effectively inhibit the initiation, development and progression of neoplasm by regulating cellular proliferation, apoptosis and metastasis (9). Recent studies have indicated the important roles of natural compounds in modulating tumor angiogenesis by promoting the apoptosis of endothelial cell and inhibiting the angiogenesis-associated cytokines (10). In this review, we recapitulate the process of tumor angiogenesis and present some natural products that have the effect of anti-tumor angiogenesis.

A systematic literature search was conducted in PubMed database from 2010 to 2020. The following search terms were used: “natural products (or) natural product (or) polyphenols (or) polysaccharides (or) alkaloids (or) terpenoids (or) saponins” and “tumor angiogenesis (or) anti-angiogenic (or) angiogenic factors (or) vascular endothelial cells”. There were no language restrictions, and the abstracts of the papers identified by the initial search were evaluated by the lead reviewer Peng Song for appropriateness to this review. The inclusion criteria of references was that the abstracts of the references introduced the molecular mechanism investigation of natural products against tumor angiogenesis through in vitro or in vivo experiments.

PHYSIOLOGICAL VASCULATURE
The function of an extensive vascular network is to supply nutrients and oxygen and remove metabolic waste. During early embryogenesis, vascular growth is the results of combination of vasculogenesis and angiogenesis (11). Vasculogenesis refers to that new blood vessels are formed from primitive ECs precursors, as opposed to angiogenesis, in which the blood vessels developed from pre-existing ECs in established vessels (12). In adulthood, new blood vessels are rarely formed except in several physiological or pathological processes such as female reproductive cycling and wound healing. The sprouting, migration and proliferation of ECs are regulated by various cytokines, among them VEGF is a pivotal one (13).

NEOPLASM ANGIOGENESIS
Angiogenic Switch
At the early stage of neoplasm events, tumors present a balance between cell apoptosis and cell proliferation (14). Tumor cells produce pro-angiogenic factors, such as VEGF, PDGF and anti-angiogenic factors, such as angiostatin and thrombospondin. The secretion of these factors is in balance and tumors maintain at the “dormancy state”. However, once the average volume of a tumor exceeds 1-2 mm³, insufficient supply of oxygen and nutrients to tumor tissues will occur. Under hypoxic and/or acidic conditions, this balance is disturbed, and the tumors switch from a non-vascular to a vascular state, which turns on “angiogenic switch”. At this state, hypoxia inducible factor 1 alpha (HIF1-α) is able to bind to hypoxia-regulators and induce the production of VEGF and other pro-angiogenic factors (15). Oncogene Ras and the mutated tumor suppressor gene TP53 also mediate this pro-angiogenic effect. The synthesis of anti-angiogenic factors are found decreased in these tumors (16). Even if only 1% of tumor cells turns on the “angiogenic switch”, tumor growth occurs. In turn, the growth of neoplasm tissues promotes the initiation of angiogenesis (17).

Activated Factors and ECs Apoptosis in Tumor Angiogenesis
The most well-known receptors for tumor angiogenesis on the membrane of endothelial cells are tyrosine kinase receptors with their co-receptor, neuropilin. These receptors bind to VEGF or bFGF. The transcription of several pro-angiogenic factors can be initiated by the second messenger cascade of these receptors. High levels of VEGF can be found in most tumor types (1, 18). VEGF exerts the key role in the formation of new blood vessels and the proliferation of ECs. There are three tyrosine kinase receptors of VEGF, VEGFR-1 to -3. VEGFR-2 is the most prominent receptor in angiogenesis, which binds to VEGFA with strong tyrosine kinase activity (19). Moreover, latent forms of VEGF ligands are separated in the extracellular matrix, that are regulated by the release and activation of extracellular matrix-degrading proteases (e.g., MMP-9) (20). The up-regulation of other pro-angiogenic signals, such as FGF family, is involved in sustaining tumor angiogenesis (3, 21). Besides the VEGF signaling pathway, other signaling pathways and associated factors are involved in tumor angiogenesis. Angiopoietin 1 (ANGPT1) and ANGPT2 are important ligands from the ANGPT family, that bind to the receptor tyrosine kinase TIE2 on the membrane of ECs. Since ANGPT1 acts as an agonist of TIE2, its function is to promote vessel maturation. The activation of TIE2 mediated by ANGPT2 can induce vascular disruption and increase
angiogenesis (22). Another important system that regulates tumor angiogenesis is the Notch-Notch-ligand system. Endothelial-specific ligand Delta-like 4 (DLL4) mediates the formation of the tip and stalk cells following VEGF stimulation (23).

Apparently, neovascularization is strongly governed by ECs apoptosis. Both proangiogenic growth factors and extracellular matrix (ECM) act as the key roles in EC survival and angiogenesis (4). Induction of angiogenic growth factors and associated pathways are capable of inhibiting ECs apoptosis. For instance, ECs sustainment has been shown to be linked with the modulation of cell apoptosis by VEGF (24). By increasing the expression of anti-apoptotic proteins, such as Bcl-2 and survivin, bFGF is able to decrease ECs apoptosis, which guarantees the cells survival (25). Of note, ANGPT1 involves in ECs apoptosis by modulating PI3K/Akt signaling and upregulating the anti-apoptotic protein surviving (26). Regarding the role of cell matrix and cell-cell interactions in angiogenesis, the anti-apoptotic effect of VEGF is dependent on the regulation of αvβ3-integrin and VE-cadherin protein (27, 28). Since the pivotal role of ECs in angiogenesis, many natural products are developed to target EC apoptosis. For example, resveratrol is able to increase Gly-LDL-induced vascular endothelial cell apoptosis (29). Similarly, Physalis alkekengi L. extract can reduce the apoptosis of ECs after exposure to hyperglycemia (30). Overall, angiogenic factors secreted by tumor cells (Figure 1) and EC apoptosis (Figure 2) are of significance in triggering and processing vessel formation in tumor microenvironment.

**ANALYSIS OF VASCULATURE IN IN VIVO AND IN VITRO MODELS**

Vasculation has been explored for many decades and the application of in vitro and in vivo assays to evaluate the induction and inhibition of vascularization has exerted a significant role for researchers to study and understand angiogenesis (31). The well-established in vitro models, such as the model of ECs, are easily analyzed and reproducible, yet the cells become senescent in the culture after a few passages (32). Unlike the in vitro models, in vivo models, for example, the model of chick chorioallantoic membrane (CAM), owns the advantages of short experimental period and low cost, which is available for drug screening (33). As an ideal anti-tumor angiogenesis model, zebrafish has been widely used in drug screening due to its small size, transparent embryos, easy large-scale rearing, strong reproductive capacity and short experimental period (34). The aortic ring test is a model of angiogenesis based on organ culture. In this model, the molecular mechanism in regulating angiogenesis can be clarified, but it cannot truly reflect the microvascular environment of tumor growth (35). Another widely used in vivo model is xenograft tumor in mice. Of note, tumor angiogenic environment in animals is different from human, so assays in animals could not replace that in human (31). We have summarized the advantages and disadvantages of the current common angiogenesis models both in vitro and in vivo, which will provide clues for human cancer study (Table 1).

**NATURAL ANTI-TUMOR ANGIOGENIC COMPOUNDS DERIVED FROM PLANTS**

**Polyphenols**

Polyphenols are members of a large family of chemical compounds with several phenolic groups, that can be found in foods and beverages of plant origin, including the spices, dried herbs, tea, red wine, coffee, cocoa products, seeds and nuts, vegetables, and fruits. Polyphenols are usually classified as phenolic acids, flavonoids, stilbenes, lignans, secoiridoids, among others. Polyphenols are of significance in the sustainment of human health. Recent studies have illustrated the pharmacologic functions of polyphenols that include antioxidation, vascular wall protection, improving enterogastric digestion, promoting immune response, and prevention of chronic disorders, such as tumor, atherosclerosis, hypertension, diabetes and...
so on. In addition to the summary of the chemical structures of polyphenols (Figure 3), the effect of several polyphenols (Ellagic acid, Chlorogenic acid, Quercetin, Catechin, Baicalin, Delphinidin, 6-methoxyequol, et al.) on tumor angiogenesis have also been studied in recent years (Table 2). Ellagic acid can inhibit angiogenesis by inhibiting the expression of VEGFR2 in ECV304 cell line. Moreover, researchers found that ellagic acid was able to regulate angiogenesis by inhibiting VEGF/VEGFR2, PI3K/Akt and MAPK signaling cascades in hamster cheek touch carcinogenesis model (39, 40). Chlorogenic acid is one of the hydroxygenic acid derivatives, which derives from *Eucommia ulmoides* Oliv. Chlorogenic acid suppressed tumor angiogenesis by blocking HIF-1α/Akt signaling pathway in lung cancer A549 cells (41). Quercetin, a flavanol-like compound, is derived from *Quercus iberica*. Quercetin reduces angiogenesis by inhibiting ERK phosphorylation and VEGFR-2 mRNA expression, and the calcineurin/NFAT signaling pathway (45, 46). Catechin is a flavanol-like compound and derived from black tea, which can affect angiogenesis by inhibiting VEGF (47). Baicalin, originated from *Scutellaria baicalensis* Georgi, can also inhibit tumor angiogenesis by regulating VEGFR (51). As for Delphinidin, it regulates angiogenesis by affecting the expression of HIF-1α and VEGF in A549 cells (56). 6-Methoxyequol is an isoflavone-like compound derived from soybean and can affect tumor angiogenesis through MAPK signaling pathway (59).

### Polysaccharides

Polysaccharides are polymeric carbohydrate macromolecules, that are composed of long-chain monosaccharide units connected by glycosidic bonds. As pivotal bioactive macromolecules, polysaccharides are mainly extracted from plants, animals and microorganisms. Polysaccharides are currently applied to various biomedical products and functional foods because of their significant biological functions, such as inhibiting tumor growth, triggering immunity, antioxidation, anti-virus and neuroprotection. Recent studies indicated that polysaccharides extracted from higher plants showed anti-tumor activity by enhancing immunity. In addition to anti-tumor effect through immunomodulation, polysaccharides can directly inhibit tumor angiogenesis. Various polysaccharides, such as dandelion polysaccharide, sulfated polysaccharide, Fucoidan, LEP-2a, and Galactomannan, exert important roles in tumor angiogenesis (Table 3). Dandelion polysaccharide has been proved to inhibit angiogenesis both in vivo and in vitro. The PI3K/Akt signaling pathway is involved in this process, which inhibits the expression of VEGF and HIF-1α (66). Sulfurized polysaccharide is derived from *Phellinus ribis*. In the Lewis lung carcinoma (LLC) mouse model, sulfurized polysaccharide can inhibit vessel formation by modulating VEGF/VEGFR signaling pathway (67). Fucoidan, extracted from *Laminaria japonica*, regulates tumor angiogenesis by modulating MAPK and PI3K/Akt signaling pathways (68). Fucoidan is proved to reduce the expression of VEGF and PDGF in two chicken embryo chorioallantoic membrane (CAM) models (69). Moreover, in mice xenografted with DU-145 human prostate cancer cells, fucoidan can decrease tumor growth and angiogenesis by inhibiting JAK/STAT3/VEGF signaling pathway (70). Another important polysaccharide, Lep-2a, can restrain the expression of VEGF, CD105, bFGF, MMP-2 and MMP-9 in hepatocellular carcinoma (72). PSP001 is a galactomannan derived from the
fruit rind of *Punica granatum* *L*. A recent study found that galactomannan was able to suppress the expression of VEGF, MMP-2 and MMP-9 and up-regulate the expression of TIMP-1 and TIMP-2 in cancer cells (74).

**Alkaloids**

Alkaloids are a group of natural compounds with nitrogen structure and physiological function. Many alkaloids have complex nitrogen heterocyclic structures, and several compounds are organic amines with non-nitrogen heterocycles. Alkaloids have the properties of alkali, that are important active ingredients in Chinese herbal medicine. Although certain vitamins, amino acids and peptides from natural sources are also nitrogenous compounds, they are not included in the category of alkaloids. Alkaloids are ubiquitous in nature, especially in the plant kingdom. Alkaloids have been reported in at least 140 species of plants,

| Table 1: Properties of common experimental models of angiogenesis in vivo and in vitro. |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Assay type**                          | **Description**                               | **Advantages**                               | **Disadvantages**                             |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Endothelial cells                            | The proliferation of EC initializes the formation of blood vessel. Angiogenic-associated factors trigger the activation of EC, thereby degrading local basement membrane, promoting EC migration and invading the proximal ECM, which leads to EC sprout and capillary network formation. Therefore, vitro models of ECs were established to simulate angiogenesis in human body.  
1. Evaluates EC proliferation by MTT and cell cycle.  
2. Evaluates EC migration and invasion on a porous membrane with matrigel.  
3. Evaluates EC capillary network formation on the matrigel. | Simple, reproducible, and quantitatively analyzed.  
1. Limited use for the senescent property of ECs after a few passages.  
2. Unrepresentative of the physiological reaction in vivo. | (32) |
| Tumor cells                                 | Tumor cells are able to secrete a variety of cytokines in tumor growth, which affect tumor angiogenesis. Therefore, we can indirectly evaluate the role of tumor angiogenesis by detecting the expression of related cytokines.  
1. Evaluates the expression of angiogenic factors secreted by tumor cells, such as VEGF, bFGF, etc.  
2. Evaluates the expression of matrix metalloproteinases secreted by tumor cells, such as MMP-2, MMP-9, etc. | Specifically use for anti-angiogenic drugs development and drug detection of anti-angiogenic effects. | Unequal to human experiments because of the different local environment between tumor cell models and human models. | (36–38) |
| **Chick chorioallantoic membrane (CAM)** | CAMs is one of the most commonly used models to study the anti-angiogenic effect of drugs in vivo, which has been approved by FDA. At 6-8 days after hatching, the development of embryo membrane and vascular network is stable, but the immune system has not been completely established. Therefore, the embryo has no rejection to various foreign materials during this period, which makes it convenient to observe the effects of various drugs on angiogenesis.  
Methods: The 8-day-old fertile eggs were opened from the end of the air chamber. After the opening, we can observe the growth of blood vessels on CAM and determine the best position of drug intervention, thereby avoiding the damage of chicken embryo caused by mechanical stimulation and eggshell detachment. | 1. Convenient to obtain materials and observe results.  
2. Short experimental period and low cost.  
3. Suitable for the screening of a large number of angiogenesis drugs. | The possibility of false positive results due to cellular damage, inflammatory reaction and fibrin degradation products. | (33) |
| Rat aortic rings                            | Aortic ring assay is a model of vascular regeneration based on organ culture. In this assay, the angiogenic vessels developed from a small segment of the aorta.  
Methods: the rat aorta was removed, cut into 1 mm vascular rings, embedded with fibrin glue or collagen glue, and then cultured in serum-free MCDB131 medium. During the cultural process, the number of new microvessels produced by aortic rings was calculated and analyzed quantitatively. | 1. A wide range of materials and simple observation method.  
2. Clear elucidation of angiogenic-associated molecular mechanism. | Hardly reflection of the true microvascular environment of tumor growth. | (35) |
| Zebrafish                                   | As an ideal anti-tumor angiogenesis model, zebrafish has been widely used in drug screening:  
1. Zebrafish tumor is highly similar to human cancer at the levels of histology, gene expression and genome. This model can be used for imaging and high-throughput genetic screening, which provides a unique opportunity for cancer genome research in vivo.  
2. Using the techniques of forward genetics, reverse genetics, gene knockout, cancer cell transplantation and chemical inducers, we can conduct the replication of various zebrafish tumor models, the study of pathogenesis and the screening of antitumor drugs. | 1. Small size, transparent embryos, easy large-scale rearing, strong reproductive capacity and short experimental period.  
2. Highly similar to the human genome sequence (87%). | | (34) |
| Xenograft mice with tumor cells             | The model of mice bearing with tumor cells is used to study the potential antitumor activity of drugs and their effects on tumor size (diameter, area or volume) and survival time of animals. This model can also be used to study the potential anti-angiogenic activity, uptake and distribution of drugs. If a drug has the anti-angiogenic effect, it will prevent or reduce the number of tumor neovascularization. | 1. Implantation of the local environment of spontaneous tumor growth.  
2. The differences about tumor growth environment between animal and human. | | (31) |
FIGURE 3 | The chemical structures of polyphenols involved in tumor angiogenesis.
especially in Papaveraceae, tetrandridae, Solanaceae, Leguminosae, Apocynaceae, Ranunculaceae, and tillering family, et al. The common alkaloids include pyrrole, pyridine, quinoline, isoquinoline, indole, imidazole, purine, anisodamine, terpenoids, steroids, organic amines, and so on and the chemical structures of these alkaloids are shown in Figure 4. Current studies proved the biological activities of alkaloids, including anti-tumor, antibacterial, anti-inflammatory, antiviral, antiarrhythmic, analgesic, and antispasmodic effects. Voacangine is an indole-like compound, which is rich in Ervatamia Stapf. Treatment with voacangine decreases the VEGFR2 kinase activity in athymic nude mice bearing glioblastoma tumors and HUVECs, suggesting that its anti-angiogenic role is closely associated with VEGFR2 (81). Evodiamine is an indoloquinazoline-like compound, which is derived from Euodia rutaecarpa (Juss.). Evodiamine is able to modulate angiogenesis by inhibiting the expression of VEGF through the c-Mer/Src/STAT3 signaling pathway (82). By inhibiting β-catenin, which reduces VEGF-A expression, Le Shi et al. found the anti-angiogenic role of evodiamine (83). As an isocarbostyril compound, narciclasine regulates HUVECs...
proliferation by a RhoA-independent activation of the Rho kinase Rock (84). Tetromethylpyrazine is an amide alkaloid, which is extracted from *Ligusticum chuanxiong hort*. Tetromethylpyrazine combined with paclitaxel inhibited angiogenesis both *in vivo* and *in vitro* through blocking ERK1/2 and AKT signaling pathways (85). Previous studies found that harmine, a β-carboline alkaloid, suppressed bladder cancer growth by its anti-angiogenic effect, which was linked to VEGFR2 signaling pathway (86). Oxysoxophorine is a quinolizidine alkaloid and it reduces the levels of HO-1, VEGF, MMP-9 and HIF-1α in OSCC cells (87). 3-acetyl-norerthrophlamide is a cassaditerpene alkaloid, which was linked to VEGFR2 signaling pathway (86). 3-Oxysophocarpine is a quinolizidine alkaloid and it reduces the expression of HO-1, VEGF, MMP-9 and HIF-1α in OSCC cells (87).

**Terpenoids**

Terpenoids are natural products that derive from mevalonic acid. Terpenoids are composed of multiple isoprene (C5) units with the general formula of (C5H8)n. More than 20,000 terpenoids exist in nature and are widely distributed in the plant kingdom, such as Compositae, Ranunculaceae, Araliaceae, Oleaceae, Magnoliaceae, Lauraceae, Aristolochiaceae, and more. Based on the different molecular structures (*Figure 5*), terpenoids are divided into five groups: monoterpenes, sesquiterpenes, diterpenoids, triterpenoids and terpenes compound. Most of the bioactive terpenoids have been isolated from medicinal plants. For example, monoterpenes and sesquiterpenes are extracted from essential oils of medicinal plants and triterpenes are primarily available in balsams and resins. Recent studies have found that terpenoids have a variety of biological functions, including the regulation of enzyme system, cell surface signaling transduction, immune function, cell differentiation, tumor proliferation and angiogenesis. Important terpenoids (Perillyl Alcohol, β-elemene, Alantolactone, Tanshinone IIA, Triptolide, Ursolic acid, Koetjapic acid, et al) and their molecular signaling pathways participate in modulating tumor angiogenesis (*Table 5*). Perillyl Alcohol, hugely available in the essential oils of several plants (Lavendin, Mints, Cherries, etc.), possesses the anti-angiogenic property, the mechanism of which is probably to decrease the release of VEGF in cancer cells and stimulate the expression of Ang2 in endothelial cells (98). β-elemene is a

| Category                  | Name                          | Source                   | Experimental model                                                                 | Anti-angiogenic mechanism                                                                 | Refs       |
|---------------------------|-------------------------------|--------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------|
| α-type polysaccharide     | Dandelion                     | the root of dandelion    | HUVECs, CAM, Mice xenografted with Hepa1-6 and H22 cancer cells                    | Inhibits PI3K/AKT/HIF-1α/VEGF pathway                                                    | (66)       |
| Sulfated polysaccharide   | Polysaccharide PRP-S16        | Phellinus ribis          | LLC (Lewis lung carcinoma) allografts tumor-bearing mice                           | Inhibits HIF-1α/VEGF/VEGFR-2/AKT pathway                                                  | (67)       |
| A fucose-rich polysaccharide | Fucoidan                    | Laminaria japonica, Fucus vesiculosus | TNBC, HUVECs, CAM, Mice xenografted with DU-145 human prostate cancer              | Suppresses MAPK and PI3K/AKT signaling pathway                                          | (68–70)   |
| Homogeneous polysaccharide | HH1-1                         | safflower                | CAM, BxPC-3 xenograft model and PDX model                                          | Inhibits GAG and PDGF expression, Inhibits JAK/STAT3/VEGF pathway Impedes the combination of EGFR and Galectin-3 | (71)       |
| Exopolysaccharide         | LEP-2a                        | Lachnum sp.              | H22 (hepatocellular carcinoma) allografts tumor-bearing mice                       | Suppresses VEGF, CD115, bFGF, MMP-2 and MMP-9 expression                                | (72)       |
| Water-soluble polysaccharide | PTP                          | the roots of Polygala tarutolifol/ the fruit rind of Punica granatum L. | SKOV3 xenograft, Tumor growth in BALB/c mice                                       | Decreases EGFR, VEGF, and CD34 expression expression                                    | (73)       |
| Galactomannan             | PSP001                        |                           | CAM, A375 and A549 cells, B16F10                                                  | Suppresses the expression of VEGF, MMP-2 and MMP-9                                      | (74)       |
| Water-soluble polysaccharide | ZTCP2                        | Sargassum thunbergii     | HUVECs, A549 cells                                                                | Upregulates the expression of TIMP-1 and TIMP-2                                        | (75)       |
| Apigalacturonan-Rich Polysaccharide | ZCMP                      | The sea grass Zostera caespitosa Miki | HUVECs                                                                           | –                                                                                         | (76)       |
| Pectic polysaccharide     | Corn pectic polysaccharide (CPP) | com (Zea mays L.) | Mice were given B16F10 and injected through the lateral tail vein                 | Suppresses the expression of VEGF, MMP-2 and MMP-9                                      | (77)       |
| Arabinogalactan           | Arabinogalactan               | flowers of Panax notoginseng | BxPC-3, Pancreatic cancer cell xenograft tumor in nude mice, HMEC-1                   | Suppresses BMP2/Smad/Id1 signaling pathway                                              | (78)       |
| Huaiher polysaccharide    | TP-1                          | Huaier fungus            | To establish an in vivo pulmonary metastasis model, SMMC-7721 cells were injected into BALB/c nude mice via the tail vein | Inhibits HIF-1α/VEGF pathway                                                           | (79)       |
| SP-1                      | Trametes robiniophila murr (Huair) |                           | Mice xenografted with SMMC-7721 human hepatocellular carcinoma cells              | Suppresses the expression of VEGF, MMP-2, HIF-1α, STAT3 and MMP-9                    | (80)       |
sesquiterpene compound isolated from *Curcuma Zedoaria*. It inhibits the proliferation and metastasis of melanoma by suppressing VEGF-mediated angiogenesis (102). Alantolactone is also a sesquiterpene compound extracted from *Inula Helenium*. Alantolactone inhibits angiogenesis by reducing the phosphorylation of VEGFR2 and its downstream protein kinases, including PLCγ1, FAK, Src, and Akt in breast cancer (106). Tanshinone IIA is the key compound of Diterpene, isolated from *Salvia Miltiorrhiza Bunge*. Tanshinone IIA has anti-angiogenic activity in human EPCs, which is associated with the regulation of VEGF, PLC, Akt and JNK signaling pathways (109). Triptolide is also a Diterpene compound, derived from *Tripterygium Wilfordii*. Triptolide exerts the anti-angiogenic role in breast cancer by inhibiting ERK1/2-HIF1-α-VEGFA signaling pathway both in vitro and in vivo (113). As an important Triterpene compound, ursolic acid is able to decrease the expression of VEGF and iNOS in ehrlich ascites carcinoma (114). Koetjapic acid is also a significant Triterpene compound. Koetjapic acid is found to reduce the expression of VEGF in various angiogenic models, such as rat aortic ring, CAM and HUVECs (116).

**Saponins**

Saponins are composed of sapogenins and sugars. The sapogenins are triterpenes or spirostanes and the make-up sugars are commonly glucose, galactose, rhamnose, arabinose, xylose, glucuronic acid and galacturonic acid. Lipophilic sapogenins and hydrophilic sugar chains make the saponin an excellent surfactant. Saponins are mainly distributed in terrestrial higher plants and marine organisms, such as starfish and sea cucumber. Many
Chinese herbal medicines, such as *Ginseng, Polygala Tenuifolia, Platycodon grandiflorum, licorice, Anemarrhena and Bupleurum*, contain saponins as the main active ingredients. According to the different structures of sapogenins, saponins have the biological functions of anti-tumor, hypoglycemic, cholesterol lowering, liver protection, immune regulation, anti-inflammatory and antimicrobial effects. The chemical structures (Figure 6) and anti-angiogenic property of several saponins (Timosaponin AIII,
Ginsenoside Rg3, β-Escin, sea cucumber saponins, et al) has been identified in recent years (Table 6). Timosaponin AIII is a steroidal saponin, derived from *Anemarrhena asphodeloides* Bge. It exerts anti-angiogenic effect through VEGF/PI3K/Akt/MAPK signaling pathway in the zebrafish embryos model (119). Ginsenoside Rg3 is a triterpene saponin, isolated from *Panax ginseng*. Ginsenoside Rg3 can decrease the expression of MMP-2, MMP-9 and VEGF in B16 cell tumor mouse model and *in vitro* B16 cell model (122). β-escin is also a kind of triterpene saponin, extracted from *Aesculus hippocastanum* seeds. β-escin can inhibit melanoma angiogenesis by increasing the expression of TIMP-1 and TIMP-2 (123). Sea cucumber saponins are crude saponins, that are prevalent in *Holothuria leucospilota*. The saponins extracted from sea cucumber can inhibit the expression of VEGF-D and TGF-β in MCF7 cells (126).

**CONCLUSIONS**

This review article shed a light on the role of natural compounds in cancer therapy by modulating angiogenic factors and ECs apoptosis. In addition, the chemical structures of natural compounds involved in tumor angiogenesis were summarized and shown in supplementary material with the format of CS.
ChemDraw Drawing, which could be conveniently used for the related researchers. Natural products have presented as new stars in the field of anti-tumor neovascularization research for their easy availability and cost-effectiveness (128). A large number of epidemiological studies proved the reduction of cancer incidence upon the high nutritional ingestion of vegetables and fruits (129). Moreover, natural products emerged as SIRT6 modulators can be successfully applied to treat cancer, inflammation, Alzheimer’s Disease, etc (130).

Currently, anti-angiogenic drugs are widely used and recognized in cancer treatments because they enriched the arsenal of chemotherapeutic drugs. The majority of modern targeted drugs fail to achieve the expected therapeutic effects. Consequently, the anti-cancer regimens have shifted to multi-targeted therapies using
FIGURE 6 | The chemical structures of saponins involved in tumor angiogenesis.

TABLE 6 | Natural anti-tumor angiogenesis saponins and their sources, experimental models and anti-angiogenic mechanisms.

| Category          | Name                  | Source                        | Experimental model                        | Anti-angiogenic mechanism                                         | Refs |
|-------------------|-----------------------|-------------------------------|-------------------------------------------|-------------------------------------------------------------------|------|
| Steroidal saponin | Timosaponin AllI      | Anemarrhena asphodeloides Bge | Zebrafish embryos, HUVECs                | Inhibits VEGF/Pi3K/Akt/MAPK signaling cascade                      | (119) |
|                   | DT-13                 | Dwarf lily turf tuber         | HUVECs, CAM                               | Inhibits the levels of p-VEGFR-2, p-ERK1/2 and p-Akt,             | (120) |
|                   | Paris saponin II      | Rhizoma paridis              | HUVECs, SKOV3 cells                       | Inhibits the expression of VEGF                                   | (121) |
| Triterpene saponin| Ginsenoside Rg3       | Panax ginseng                 | B16 melanoma cells, C57BL/6 mice with B16 cells | Inhibits the expression of MMP-2, MMP-9 and VEGF                  | (122) |
|                   | β-Escin               | Aesculus hippocastanum seeds | B16F10 and SK-MEL5 cells                  | Increases the expression of TIMP-1 and TIMP-2                     | (123) |
|                   | Astragaloside IV      | Astragal radix                | C57BL/6 mice with LLC cells               | Blocks the M2 polarization of macrophages partially through the AMPK signaling pathway | (124) |
|                   | Platycodin D (PD)     | the roots of Platycodon grandiflorum | C57BL/6 mice with H22 cells            | Inhibits the expression of VEGF                                   | (125) |
| Crude saponins    | Sea cucumber saponins (SCS) | Holothuria leucospilota (sea cucumber) | MCF7 cells                               | Inhibits the expression of VEGF-D and TGF-β                      | (126) |
|                   | Rh.Sp saponins        | Rumex hastatus D. Don.        | CAM                                       |                                                                   | (127) |
traditional and integrative natural products. There is a huge number of natural products for anti-angiogenic substances and the study on the complex mechanisms of these compounds is just started. Studies on the role of different structures of natural compounds in inhibiting tumor angiogenesis would assist in anti-cancer drug discovery and development. The anti-angiogenic therapy of human cancer patients is based on pre-clinical models that simulate the pathogenesis of human cancers, and most of them are elucidated in this review. It is certain that future patients will be benefited from the novel discoveries of natural products, thus a lot of research works are warranted.

**PERSPECTIVES AND LIMITATIONS**

As for clinical application of natural products in tumor, issues have emerged during the past few decades. The bioavailability of natural products is the major restriction, since these compounds have the properties of poor aqueous solubility and low absorption rate. Prior to the use of natural products in anti-tumor therapy, the concentration problem needs to be resolved. At present, several carriers (nanoparticles, micelles, lipids, etc) with natural products are being developed to apply to the delivery of these compounds to human body systems. Therefore, as hopeful therapeutic targets towards tumor angiogenesis, more efforts should be made to the development of natural compounds and their modifiers according to their molecular mechanisms and involved signaling pathways in tumors.

**AUTHOR CONTRIBUTIONS**

PS, Z-SC, and DD conceived and designed the review. RL and XS created the tables and figures, and wrote the draft manuscript. RL, XS, and YG revised the manuscript and performed the table design. PS, Z-SC, and DD reviewed and edited the manuscript. All authors read and approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.772915/full#supplementary-material
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