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THEMED ISSUE REVIEW

Natural products targeting tumour angiogenesis

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Abstract

Tumour angiogenesis is the formation of new blood vessels to support the growth of a tumour. This process is critical for tumour progression and metastasis, making it an attractive approach to cancer therapy. Natural products derived from plants, animals or microorganisms exert anti-angiogenic properties and can be used to inhibit tumour growth and progression. In this review, we comprehensively report on the current status of natural products against tumour angiogenesis from four perspectives until March 2023: (1) the role of pro-angiogenic factors and antiangiogenic factors in tumour angiogenesis; (2) the development of anti-tumour angiogenesis therapy (monoclonal antibodies, VEGFR-targeted small molecules and fusion proteins); (3) the summary of anti-angiogenic natural agents, including polyphenols, polysaccharides, alkaloids, terpenoids, saponins and their mechanisms of action, and (4) the future perspectives of anti-angiogenic natural products (bioavailability improvement, testing of dosage and side effects, combination use and discovery of unique natural-based compounds). Our review aims to better understand the potential of natural products for drug development in inhibiting tumour angiogenesis and further aid the effective transition of these outcomes into clinical trials.

KEYWORDS
natural products, phytochemicals, targeted chemotherapy, tumour angiogenesis, VEGFR-2 inhibitors

1 | INTRODUCTION

Cancer is characterized by the abnormal development of cells that proliferate through uncontrolled cell division. It remains a significant global public health concern and ranks as the second leading cause of death, following cardiovascular disease. In Europe, there were an estimated 3.91 million new cases of cancer (excluding non-melanoma skin cancer) and 1.93 million deaths from cancer in 2018 (Ferlay et al., 2018). Meanwhile, an estimated 4.3 million new cancer cases and 2.9 million new cancer deaths occurred in China in 2018 (Feng, Zong, et al., 2019). In 2022, 1,918,030 new cancer cases and 609,360 cancer deaths are projected to occur in the United States, including approximately 350 deaths per day from lung cancer (Siegel et al., 2022). The increasing number of cancer patients in the world highlights the need for more cancer prevention and therapy efforts.

Inducing angiogenesis represents a main hallmark of cancer, which is acquired during the multistep development of human tumours (Hanahan, 2022). Abnormal angiogenesis has been considered a prerequisite for tumour progression and metastasis (Fares et al., 2020). Many intracellular, extracellular and cell surface molecules can directly

Abbreviations: ECs, endothelial cells; HIF-1, hypoxia-inducible factor-1; HUVECs, human umbilical vein endothelial cells; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; ROS, reactive oxygen species; TKIs, tyrosine kinase inhibitors; TSP-1, thrombospondin 1.

or indirectly regulate angiogenesis. Particularly, **vascular endothelial growth factors (VEGFs)** and their membrane receptors (**VEGFRs**) are of great importance during tumour-induced angiogenesis (Olsson et al., 2006). VEGFRs represent a family of three receptor protein tyrosine kinases. The activation of VEGFRs is facilitated through ligand binding. Currently, VEGFR inhibitors, such as **apatinib**, **sunitinib**, **sorafenib**, **axitinib**, **cabozantinib**, **lenvatinib**, **nintedanib** and **pazopanib** have been widely used in the treatment of various tumours (Farghaly et al., 2021; Ivy et al., 2009). However, current VEGFR inhibitors are limited to a certain extent due to several issues such as weak response, resistance development and serious adverse effects, which hinder their clinical application (Qu et al., 2016; Teng et al., 2018; Zhu et al., 2017).

Natural products have been valuable sources of new therapeutic agents for the treatment of various diseases, especially cancer (Atanasov et al., 2021). The discovery of natural products for treatment dates back to ancient Mesopotamia about 2,600 BC (Christensen, 2021). Until the end of the 19th century, all available drugs were natural products or minerals (Christensen, 2021). Natural products are currently still the basis for half of all new drugs, either as the parental natural products or optimized derivatives. Nearly 80% of approved drugs during the last three decades of cancer treatment are derived from either natural compounds per se or their derivatives (Bishayee & Sethi, 2016). This may be related to their abundant pool of diverse chemotypes and diverse pharmacological activities. A plethora of papers have documented that natural products effectively inhibit the initiation, development and progression of neoplasm by regulating cellular functions and pathways, such as perturbation of redox homeostasis, various programmed cell death and cancer metastasis (Gaikwad & Srivastava, 2021). Recent studies have indicated the important roles of natural compounds in modulating tumour angiogenesis through VEGFs (Fakhri et al., 2021). Several reviews have summarized the natural agents as therapeutics against tumour angiogenesis (Ai et al., 2022; Khalid et al., 2016; Li, Song, et al., 2021; Wahl et al., 2011; Yang & Wu, 2015).

Our group has reported a series of antiangiogenic natural products and medical plant extracts (Anfosso et al., 2006; Dell'Eva et al., 2004; Krusche et al., 2013; Kuete et al., 2011; Lu, Elbadawi, et al., 2022; Mahmoud et al., 2022; Seo et al., 2013; Soomro et al., 2011). In the present review, we provide a comprehensive overview of the natural products targeting tumour angiogenesis. This review summarizes the scientific literature in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) until March 2023. The initial search items were used as follows: ((natural products [Title/Abstract]) OR (natural agents [Title/Abstract]) OR (phytochemicals [Title/Abstract])) AND ((angiogenesis [Title/Abstract]) OR (anti-angiogenic [Title/Abstract])) AND ((tumour [Title/Abstract]) OR (cancer [Title/Abstract])).

1.1 | Physiological angiogenesis

Angiogenesis, which was first termed and invented by the British surgeon Dr. John Hunter in 1787, describes a normal yet complex process of the formation of new blood vessels from pre-existing endothelial cells (ECs) by the remodelling of pre-existing blood vessels (Lenzi et al., 2016). Whenever there is a physiological process of wound healing or the female reproductive cycle, angiogenesis can be initiated from existing blood vessels (Ribatti & Pezzella, 2021; Wahl et al., 2011). Physiological blood vessel formation is thus a tightly regulated process that ceases when the need for new blood vessels has been met. The sprouting, migration and proliferation of ECs are regulated by various cytokines, among which VEGF is pivotal (Ferrara, 2005). VEGF signalling often represents a critical rate-limiting step in physiological angiogenesis.

1.2 | Initiation of tumour angiogenesis: An angiogenic switch

Rapidly growing tumours are heavily vascularized. Tumour vascularization is orchestrated by a range of secreted factors and signalling pathways through several cellular processes, including sprouting angiogenesis, intussusceptive angiogenesis, vasculogenesis, recruitment of endothelial progenitor cells, vascular mimicry and transdifferentiation of cancer stem cells (Lugano et al., 2020).

Tumour angiogenesis is typically initiated from the capillaries and is essential for cancer development, growth and metastasis. Tumour cells produce not only pro-angiogenic factors such as VEGF and platelet-derived growth factor (PDGF) but also anti-angiogenic factors, such as **angiostatin (plasminogen)** and thrombospondin. If these are in balance, the vasculature and ECs are non-proliferative. Thus, tumours maintain a 'dormancy state'. Once a tumour grows beyond 1–2 mm, an insufficient supply of nutrients and oxygen to the tumour tissues will occur. Under hypoxic and/or acidic conditions, hypoxia-inducible factor 1 alpha (HIF1-α) participates in vasculature formation through synergistic correlations with pro-angiogenic factors and induces the excessive production of VEGF and **placental growth factor (PlGF)** or angiopoietins, leading to an imbalance of pro-angiogenic and anti-angiogenic factors and further turning on the 'angiogenic switch', where new vasculature is formed in and around the tumour, allowing it to grow exponentially (Carmeliet, 2005; Li, Song, et al., 2021; Zimna & Kurpisz, 2015) (see Figure 1). Tumour angiogenesis is thus deregulated due to the persistence of pro-angiogenic factors in the tumour microenvironment (Lugano et al., 2020). Additionally, the angiogenic switch can be triggered by tumour-associated inflammation and the recruitment of immune cells (Ono, 2008). Non-ECs, such as progenitors or cancer stem cells, can also be involved in tumour angiogenesis (Yao et al., 2016).

1.3 | Pro-angiogenic factors and anti-angiogenic factors in tumour angiogenesis

Besides a wide range of pro-angiogenic growth factors and their cognate receptors, pro-inflammatory cytokines, chemokines (mainly CXC family), transcription factors, angiopoietins, **ephrins**, apelin (APLN),

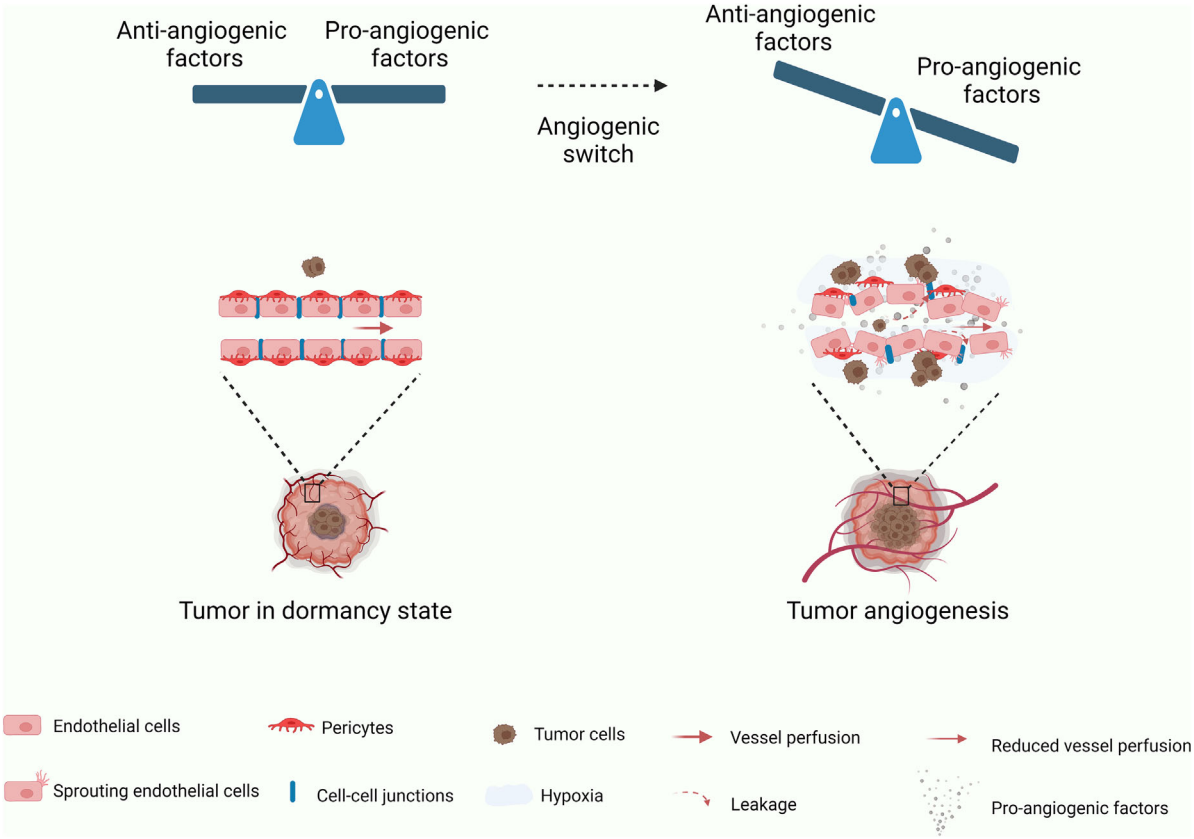

FIGURE 1 The angiogenic switch involves a complex interplay of pro- and anti-angiogenic factors that regulate the formation of new blood vessels. Under normal conditions, these factors are balanced, which maintains the integrity of the vascular system. However, this balance is disrupted in cancer, leading to the extensive activation of pro-angiogenic factors and the formation of new blood vessels, which supply the tumour with the necessary nutrients and oxygen to grow and metastasize. The figure is drawn with biorender; https://app.biorender.com/.

matrix metalloproteases (MMPs) and neurite outgrowth inhibitors have been reported to initiate or support vessel formation in tumours (Fields, 2019; Lugano et al., 2020; Ribatti, 2019; Turner & Grose, 2010; Xu et al., 2019; Yu et al., 2017; Zhou et al., 2021). Among them, the VEGF family plays a dominant role in tumour angiogenesis. This family consists of five secreted proteins in humans, including VEGF (also referred to as **VEGFA**), **VEGFB**, **VEGFC**, **VEGFD** and PlGF. VEGF, the most potent inducer of tumour angiogenesis, is produced and secreted by tumour cells and surrounding stroma. Though PlGF is a member of the VEGF family, its role in modulating tumour angiogenesis is controversial (Autiero et al., 2003; Schomber et al., 2007). VEGF receptors refer to **VEGFR-1 (Flt1)**, **VEGFR-2 (KDR)**, **VEGFR-3 (Flt4)** and the **neuropilins** (**NP-1** and -2) with different functions in various cell types (Ellis & Hicklin, 2008). VEGF orchestrates blood vessel formation mainly via activation of VEGFR-2, which is expressed on the cell surface of ECs. VEGFR-2 activation initiates several signalling pathways such as **PLC-ERK1/ERK2** and **PI3K-AKT–mTOR**, leading to specific endothelial responses such as cell survival, proliferation, migration, invasion, vascular permeability and vascular inflammation (Kowanetz & Ferrara, 2006; Lu, Blatt, et al., 2022; Simons et al., 2016).

Several natural angiogenesis inhibitors, which disrupt blood vessel formation or support the removal of existing vessels, have been identified. Examples of such molecules are thrombospondin 1 and 2 (TSP-1 and TSP-2), angiostatin, endostatin, tumstatin, arrestin, canstatin, pigment epithelium-derived factor, anti-angiogenic metargidin peptide and so forth (Carpino et al., 2021; Lawler, 2022; Li et al., 2018; Teleanu et al., 2019; Zhu et al., 2022).

Transforming growth factor-β (TGF-β, a multifunctional cytokine), **tumour necrosis factor α (TNF α**, a pro-inflammatory cytokine) and **interferon-γ (IFN-γ)**, **granulocyte-colony stimulating factor (G-CSF)**, **CXCL4 (platelet factor 4, PF4)**, **CXCL14** and **secreted phosphoprotein 1/osteopontin (SPP1)** play a crucial role in stimulating as well as inhibiting tumour angiogenesis depending on the stage of tumour progression and the cellular context (Lamagna et al., 2006; Lord et al., 2017; Montrucchio et al., 1994; Natori et al., 2002; Pandey et al., 1995; Pardali & Dijke, 2009; Shellenberger et al., 2004; Tu et al., 2022). Several interleukins (ILs), such as **IL-4**, **IL-10**, **IL-12**, **IL-18**, **IL-23**, **IL-25** and **IL-27**, also displayed controversial effects in angiogenesis (Cao et al., 1999; Corrigan et al., 2011; Huang et al., 1996; Kim et al., 2007; Meng et al., 2009; Ribatti, 2019; Shimizu et al., 2006; Short et al., 2022; Volpert et al., 1998).

The main natural pro-angiogenic and anti-angiogenic factors in tumour angiogenesis are summarized in Table 1.

2 | ANTI-TUMOUR ANGIOGENESIS THERAPY

Judah Folkman introduced the concept of targeting angiogenesis as a therapy to starve tumours 52 years ago (Folkman, 1971). Since then, several antiangiogenic therapies, mainly targeting VEGF/VEGFR-2 signalling pathway, have been developed and approved for the treatment of a variety of tumours. As of today, the FDA has approved a total of 19 anti-angiogenesis drugs. Among these, three are antibodies, 13 are VEGFR tyrosine kinase inhibitors (VEGFR-TKIs) and three are fusion proteins. (Table 2).

2.1 | Anti-angiogenic monoclonal antibodies and their applications

The dysfunctional VEGF-VEGFR signal axis is widely involved in tumours. Monoclonal antibodies targeting VEGF or VEGFR-2 have shown treatment efficacy for different types of solid tumours. Specifically, **bevacizumab** and **ranibizumab** as recombinant humanized monoclonal antibodies targeting VEGF and **ramucirumab** targeting VEGFR-2, exert beneficial clinical effects (Cobo et al., 2017; Hurwitz & Saini, 2006).

However, the main drawbacks of anti-VEGF/VEGFR-2 monoclonal antibodies are high immunogenicity, high cost and low stability (Liu, Li, et al., 2022). Despite promising results shown by preclinical studies, bevacizumab has only provided limited benefits in certain tumour types including advanced-stage renal cell carcinoma, hepatocellular carcinoma (HCC) and colorectal carcinoma (Vasudev & Reynolds, 2014). Furthermore, the clinical application of anti-VEGF/VEGFR monoclonal antibodies is severely limited by considerable side effects associated with the inhibition of physiological angiogenesis, which is one of the most common side effects of antiangiogenic therapies (Liu, Li, et al., 2022).

2.2 | VEGFR-targeted small molecules and their applications

Currently, VEGFR inhibitors are widely used in the treatment of various tumours. Sorafenib was approved as the first VEGFR inhibitor by the FDA for the treatment of advanced renal cell carcinoma in 2005. To date, a total of 13 VEGFR-TKIs have been approved (Table 2). Additionally, **motesanib**, **lucitanib** and **vatalanib** are promising VEGFR-TKIs under investigation. According to their binding mode, VEGFR-2 inhibitors are divided into three major classifications: (1) Type I inhibitors, such as sunitinib, nintedanib, pazopanib, **vandetanib**, axitinib, **ponatinib**, motesanib, competing with ATP to bind to the active 'DFG-in' conformation in the ATP-binding pocket; (2) Type II inhibitors, such as sorafenib, cabozantinib, lenvatinib, **regorafenib**, lucitanib and **tivozanib**, target the inactive (DFG-out) conformation of the kinase and occupy a hydrophobic pocket adjacent to the ATP-binding site and (3), Type III inhibitors, such as vatalanib, irreversibly bind to cysteines at specific sites on the kinases (Liu, Li, et al., 2022).

However, current VEGFR inhibitors are limited to a certain extent due to limited clinical efficacy and potential toxicity, which hinder their clinical application. Beyond gastrointestinal events (abdominal pain, diarrhoea, nausea and vomiting), haematological events (neutropenia and thrombocytopenia), fatigue and skin toxicities, VEGFR-TKIs have displayed varying degrees of hypertension and cardiotoxic risks. In a network meta-analysis, a total of 20,027 patients from 45 randomized controlled trials, associated with nine FDA-approved VEGFR-TKIs were enrolled, and it was shown, that lenvatinib had the most significant probability of provoking all grades of cardiovascular incidents and hypertension, followed by vandetanib, cabozantinib, axitinib, pazopanib, sorafenib, sunitinib, regorafenib and nintedanib (Hou et al., 2021). Thus, the development of new strategies to improve clinical outcomes and minimize the toxic effects of VEGFR inhibitors is required.

2.3 | Fusion proteins

More recently, a different class of drugs, fusion proteins, also known as VEGF-traps, have provided an alternative treatment strategy. Unlike the first two types of VEGF/VEGFR inhibitors, VEGF-traps are mainly applied in the antiangiogenic treatment of ocular diseases, including aflibercept, **ziv-aflibercept** and conbercept (Li et al., 2014; Patel & Sun, 2014; Tang & Moore, 2013). Aflibercept consists of the extracellular domains of VEGFR-1 and VEGFR-2 with the constant region (Fc) of human immunoglobin G1. It has approximately 100-fold greater binding affinity for VEGF-A than either bevacizumab or ranibizumab.

3 | NATURAL PRODUCTS TARGETING TUMOUR ANGIOGENESIS

3.1 | Polyphenols

Polyphenols are a class of natural products, which consist of at least two phenol rings and one or multiple hydroxyl substituents. Grapes, berries, green and black tea, coffee and cocoa are examples of food containing high levels of polyphenols. They have been proven to have anti-angiogenic, anti-oxidative and anti-inflammatory properties as well as contributing to the colour and flavour of certain foods. The advantage of polyphenols is that they occur as secondary metabolites in plants and are non-toxic at physiological doses and can be taken orally (Cao et al., 2002). Based on the number of phenol rings and elements that bind these together, polyphenols can be categorized into different groups. To date, a total of 34 polyphenols have been reported to have anti-angiogenesis effects (Table 3).

TABLE 1 Natural pro-angiogenic and anti-angiogenic factors.

Symbol	Name	Cellular function	Reference
Natural pro-angiogenic factors			
1. Growth factors			
VEGF	Vascular endothelial growth factor	• Stimulates angiogenesis by binding to VEGFRs and vascular permeability and vasodilation by nitric oxide and the cGMP pathway • Promotes survival of new ECs by inhibition of apoptosis • Promotes proliferation, migration, invasion of ECs, and chemotaxis of bone marrow-derived progenitor cells • Activates secondary angiogenic pathways, including bFGF, TGF-ß, PlGF	(Ferrara et al., 2003; Wahl et al., 2011)
FGF-2/bFGF	Fibroblast growth factor-2/basic fibroblast growth factor	• Promotes angiogenesis by binding to FGFR and inducing the secretion of MMPs • Promotes blood and lymphatic vascular development by modulating endothelial metabolism	(Turner & Grose, 2010; Yu et al., 2017)
PDGF	Platelet-derived growth factor	• Signals through two cell-surface tyrosine kinase receptors **PDGFR-α** and **PDGFR-β** to regulate angiogenesis by stimulating VEGF expression and recruiting pericytes	(Franco et al., 2011; Guo et al., 2003)
PlGF/PGF	Placental growth factor	• Primarily expressed by placental cells and stimulates angiogenesis by synergistic effect with VEGF • Displaces VEGF from the 'VEGFR-1 sink', thus increasing the fraction of VEGF available to activate VEGFR-2 • Amplifies VEGF-driven angiogenesis through intermolecular transphosphorylation of Flk1	(Autiero et al., 2003; Carmeliet et al., 2001)
IGF-1	Insulin-like growth factor 1	• Signals through the IGF-1 receptor to regulate VEGF and FGF-2 • Promotes angiogenesis indirectly by inducing the expression of extracellular matrix (ECM) proteins, such as fibronectin and laminin	(Reinmuth et al., 2002)
EGF	Epidermal growth factor	• Induces the expression of VEGF • Promotes the migration and proliferation of ECs • Promotes the recruitment of immune cells to the tumour microenvironment	(Danielsen & Rofstad, 1998)
PTN	Pleiotropin, heparin-binding growth factor 8, Neurite growth-promoting factor 1	• A proto-oncogene functions as an important 'driver' of tumour angiogenesis • Stimulates the proliferation, migration, and tube formation of ECs • Stimulates the production of pro-angiogenic factors, such as VEGF, and suppresses the production of anti-angiogenic factors, TSP-1	(Perez-Pinera et al., 2008)
ANGPT1, ANGPT2	Angiopoietins	• Regulate the development, maintenance and remodelling of the blood vessels	(Kiss & Saharinen, 2019)

(Continues)

TABLE 1 (Continued)

Symbol	Name	Cellular function	Reference
Natural pro-angiogenic factors			
		• Control tumour growth and angiogenesis by angiopoietin-Tie-2 signalling pathway	
2. Cytokines: Interferons (IFN-, tumour necrosis factors (TNF-), colony-stimulating factors (-CSF), interleukins (IL-)			
IL-1α, IL-1β	Interleukin-1α/1β	• A pro-inflammatory cytokine • Signal through the same IL-1 receptors • Induces the expression of pro-angiogenic factors (VEGF, bFGF), pro-inflammatory cytokines and chemokines • Promotes the activation and recruitment of immune cells such as macrophages	(Voronov et al., 2014)
IL-5	Interleukin-5	• Increases proliferation, migration and colony tube formation in human umbilical vein endothelial cells (HUVECs) associated with the phosphorylation of ERK and AKT/eNOS • Promotes microvessel sprouting by stimulating the expression of HSP70–1 via the eNOS signalling pathway	(Park et al., 2017)
IL-6	Interleukin-6/interferon-β2	• Promotes endothelial progenitor cell migration and proliferation and regulation of bFGF and VEGF • Exerts pro-angiogenic activity predominantly through STAT3 signalling	(Middleton et al., 2014)
IL-8/CXCL8	Interleukin-8	• Directly enhances EC proliferation, survival and MMP expression in CXCR1- and CXCR2-expressing ECs • Acts as a chemoattractant for neutrophils and other immune cells, further contributing to tumour angiogenesis by releasing VEGF and MMPs	(Heidemann et al., 2003; Li et al., 2003; Lugano et al., 2020)
IL-17	Interleukin-17	• A pro-inflammatory cytokine • Induces the expression of pro-angiogenic factors (VEGF, bFGF and IL-8) • Recruits and activates immune cells such as neutrophils • Promotes tumour angiogenesis through Stat3 pathway-mediated upregulation of VEGF in gastric cancer	(Wu et al., 2016)
3. Chemokines: CXC family, CC family, CX3C family, C family			
CXCL1/ GROα	Growth-regulated protein α	• Induces angiogenesis through the CXCR2 and the ERK1/2 and EGF pathways • Promotes the recruitment of myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages (TAMs) to the tumour microenvironment	(Miyake et al., 2013)

TABLE 1 (Continued)

Symbol	Name	Cellular function	Reference
Natural pro-angiogenic factors			
CXCL2/GROβ	Growth-regulated protein β	• Induces angiogenesis through the CXCR2 • AKIP1 is crucial in cervical cancer angiogenesis and growth by elevating the levels of the NF-κB-dependent chemokines CXCL1, CXCL2, CXCL8 • Promotes the recruitment of immune cells, such as neutrophils, to the tumour microenvironment	(Zhang et al., 2018)
CXCL3/GROγ	Growth-regulated protein γ	• Signals through CXCR2 to regulate inflammation and angiogenesis by activating the ERK1/2 pathway	(Rollins, 2006) (Payne & Cornelius, 2002)
CXCL5/ENA-78	Epithelial-derived neutrophil-activating peptide 78	• Induces tumour angiogenesis via enhancing the expression of FOXD1 mediated by the AKT/NF-κB pathway in colorectal cancer • Stimulates the proliferation and migration of ECs • Recruits pro-angiogenic immune cells, such as neutrophils and macrophages, to the tumour microenvironment	(Chen et al., 2019)
CXCL6/GCP-2	Granulocyte chemotactic protein 2	• Stimulates the proliferation and migration of ECs • Recruits pro-angiogenic immune cells, such as neutrophils and macrophages	(Ma et al., 2017)
CXCL7/NAP-2	Neutrophil-activating peptide-2	• Binds to CXCR2 to regulate angiogenesis and related to poor prognosis in colorectal cancer patients	(Li, Song, et al., 2021)
CXCL12/SDF-1	Stromal cell-derived factor-1	• Promotes VEGF-mediated tumour angiogenesis through AKT signalling pathway and CXCR4/CXCL12 axis	(Liang et al., 2007; Liekens et al., 2010)
4. Transcription factors			
HIF-1	Hypoxia-inducible factor-1	• Activates transcription of genes encoding angiogenic growth factors • Directly activates VEGF and VEGF receptor transcription by binding to hypoxia-response element (HRE)	(Manuelli et al., 2022)
NF-κB	Nuclear factor-κB	• Regulates the expression of pro-angiogenic factors, such as VEGF and IL-8	(Wu & Zhou, 2010)
STAT3	Signal transducer and activator of transcription 3	• Induces the expression of several pro-angiogenic factors (VEGF, FGF-2 and angiopoietin-2) • Inhibits the expression of anti-angiogenic factors (TSP-1 and endostatin) • Interact with other pro-angiogenic pathways, such as the HIF-1α and NF-κB pathways	(Yu et al., 2009)
FoxM1	Forkhead box protein M1	• Induction of pro-angiogenic factors and inhibition of anti-angiogenic factors • Recruits bone marrow-derived cells, such as endothelial progenitor cells	(Wang et al., 2007)

(Continues)

TABLE 1 (Continued)

Symbol	Name	Cellular function	Reference
Natural pro-angiogenic factors			
		and MDSCs, to the tumour microenvironment	
5. Others			
NO	Nitric oxide	• Enhances endothelial cell proliferation by increasing expression of VEGF or FGF • May suppress the production of anti-angiogenic factors angiostatin • Relaxes the smooth muscle cells in blood vessels and increases blood flow, thus leading to increased oxygen and nutrient supply to the tumour microenvironment	(Cooke & Losordo, 2002; Dong et al., 1997)
APLN	Apelin	• A peptide hormone • Regulates vascular patterning in the embryo • Stimulates tumour cell proliferation, migration and metastasis • Stimulates neoangiogenesis and microvascular proliferation within the tumour	(Berta et al., 2010; Sorli et al., 2007)
Eph/ephrin signalling	-	• Involved in embryogenesis including vascular development, tissue-border formation, cell migration and axon guidance • Promotes tumour angiogenesis by controlling VEGF signalling by inducing VEGFR-2 and VEGFR-3 internalization • Promotes tumour progression and metastasis	(Adams & Klein, 2000; Sawamiphak et al., 2010)
Natural anti-angiogenic factors			
TSP-1	Thrombospondin 1	• A naturally occurring glycoprotein • Displays both pro-angiogenic and anti-angiogenic effects • Inhibits angiogenesis through direct effects on endothelial cell migration, proliferation, survival and apoptosis via antagonizing the activity of VEGF • Induces endothelial cell apoptosis	(Lawler, 2022)
TSP-2	Thrombospondin 2	• Displays both pro-angiogenic and anti-angiogenic effects • Inhibits angiogenesis along with TSP-1 and PEDF	(Carpino et al., 2021)
ANG	Angiostatin (plasminogen)	• Inhibits endothelial cell proliferation and migration, tube formation • Induces endothelial cell apoptosis and TSP-1 production • Attenuates VEGF expression and suppresses integrin signalling in ECs	(Teleanu et al., 2019)
-	Endostatin	• Inhibits the migration of vascular ECs via blockage of MAPK signal blocking • Inhibits MMPs, especially MMP2, MMP9 and MMP13	(Poluzzi et al., 2016)
-	Tumstatin	• Displays anti-tumour activity by inducing apoptosis of proliferating ECs	(Hamano & Kalluri, 2005)

TABLE 1 (Continued)

Symbol	Name	Cellular function	Reference
Natural pro-angiogenic factors			
		• Functions as an endogenous inhibitor of pathological angiogenesis	
-	Vasostatin	• Inhibits the proliferation of ECs • Induces apoptosis, or programmed cell death in ECs	(Vazquez-Rodriguez et al., 2022)
-	Arrestin	• Inhibit angiogenic behaviours of HUVECs via inhibiting the PI3K/AKT signalling pathway	(Zhu et al., 2022)
-	Canstatin	• Inhibits proliferation, migration and tube formation of ECs • Induces apoptosis in ECs and disrupts ECM	(Zhu et al., 2022)
PEDF	Pigment epithelium-derived factor	• A glycoprotein • Inhibits the proliferation of ECs • Inhibits the activity of various angiogenic factors	(Huang, Chong, et al., 2019)
AMEP	Anti-angiogenic metargidin peptide	• Binds to $\alpha_5\beta_1$ and $\alpha_V\beta_3$ integrins via its Arg-Gly-asp (RGD) integrin binding sequence	(Li et al., 2018)
2-ME	2-Methoxyestradiol	• Inhibits the proliferation and migration of ECs and disrupts the cytoskeleton of ECs • Inhibits the expression and activity of various pro-angiogenic factors, including VEGF, bFGF and HIF-1α	(Sun et al., 2021)

Note: "-" means not applicable.

The focus here has been put on those polyphenols that have either been recently discovered to possess antiangiogenic effects or have seen notable advancements in research regarding their antiangiogenic properties. Currently, three main anti-angiogenic mechanisms of action of polyphenols are being discussed:- (1) The inhibition of the expression of VEGF, which is based on the anti-oxidative properties of polyphenols and detoxifying reactive oxygen species (ROS). **Curcumin** and green tea polyphenols are such natural products that inhibit the p38 MAPK pathway and HIF-1α, which in consequence downregulates the expression of VEGF (Lv et al., 2020; Oak et al., 2005; Sagar et al., 2006). (2) The second anti-angiogenic mechanism is to inhibit the expression of pro-angiogenic factor MMP2 and the transformation from pro- to active **MMP2**, such as polyphenolic compounds in red wine and green tea (Oak et al., 2005). **Epigallocatechin-3-gallate** has been found to directly inhibit endothelial cell proliferation by inhibiting MMP2 and **MMP9** and downregulating VEGF production. (3) Polyphenols prevent the migration and proliferation of ECs by impeding mitosis, increasing the expression of the tumour suppressor gene protein p53 and increasing the levels of the kinase inhibitor p21. Inhibiting the proliferation of vascular smooth muscle cells (VSMCs) can be achieved by polyphenols found in red wine by down-regulating cyclin and inhibiting the p38 MAPK and PI3K/AKT pathways (Oak et al., 2005). Since polyphenols have been found to have promising antiangiogenic characteristics, clinical trials have been conducted, exploring them as therapeutic agents alone as well as combined with chemotherapy (Cháirez-Ramírez et al., 2021).

3.2 | Polysaccharides

Polysaccharides are constituted of long-chain monosaccharide elements that are connected by glycosidic bonds. Polysaccharides are highly abundant bioactive macromolecules that can be found in plants, algae and microorganisms such as fungi and bacteria (Mohammed et al., 2021). They play a crucial role in physiological and biological processes such as anti-tumour activity (Guo, Chen, et al., 2022). To date, more than 25 polysaccharides have been reported to display anti-angiogenic properties (Table 4).

In the context of anti-angiogenic effects, several polysaccharides have been extensively researched and show promising potential. Among them are *pachyman*, dandelion polysaccharide (DP), asparagus polysaccharide and *Polygala tenuifolia* polysaccharide (PTP). Additionally, Table 4 summarizes other reported polysaccharides with potential anti-angiogenic effects. *Pachyman* is largely found in the mycelia of *Poria cocos* and has proven to display anti-angiogenic pathways, specifically in hepatocellular carcinoma treatment. The *in vitro* treatment of hepatocellular carcinoma samples with *pachyman* displayed a

TABLE 2 VEGF/VEGFR-2-mediated anti-angiogenic FDA-approved drugs.

Drug	Target molecules	Diseases	Side effects	References
1. Monoclonal antibodies				
Bevacizumab	VEGFA	Colorectal cancer, non-small cell lung cancer, cervical cancer, ovarian cancer, renal cell carcinoma, glioblastoma	Hypertension, proteinuria, bleeding, impaired surgical wound healing, arterial thrombotic events, gastrointestinal perforation	(Hurwitz & Saini, 2006)
Ranibizumab	VEGFA	Neovascular (wet) age-related macular degeneration, macular oedema following retinal vein occlusion, diabetic macular oedema, diabetic retinopathy, myopic choroidal neovascularization	Nasopharyngitis, intraocular pressure rise	(Menke et al., 2015)
Ramucirumab	VEGFR-2	Gastric or gastro-oesophageal junction cancers, colorectal cancer, hepatocellular carcinoma, non-small cell lung carcinoma	Fatigue, neutropenia, febrile neutropenia, leukopenia, hypertension, haemorrhage, gastrointestinal perforation, impaired wound healing	(Cobo et al., 2017)
2. Small molecule drugs				
Sorafenib	VEGFR-1, VEGFR-2, VEGFR-3, **RAF**, PDGFR family	hepatocellular carcinoma, renal cell carcinoma, thyroid cancer	Diarrhoea, hypertension, skin toxicities	(Abdel-Rahman & Lamarca, 2017)
Sunitinib	VEGFR-1, VEGFR-2, VEGFR-3, **Kit**, PDGFR family, FLT3, **CSF-1R**, **RET**	Renal cell carcinoma, gastrointestinal stromal tumours	Diarrhoea, hypertension, skin discoloration, mucositis, fatigue hypothyroidism	(Lugano et al., 2020)
Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, Kit, PDGFR family, **Itk**, **LcK**, **c-FMS**	Renal cell carcinoma, soft tissue sarcoma, epithelial ovarian cancer	High blood pressure, abnormal ventricular, repolarization	(Teleanu et al., 2019)
Vandetanib	VEGFR-2, FGFR family, RET, **BRT**, **TIE-2**, EPH, Src family	Late-stage metastatic medullary thyroid tumour	Skin reactions, diarrhoea, hypertension, nausea, vomiting, fatigue, headache, cardiac toxicity, elevated thyroid-stimulating hormone	(Tsang et al., 2016)
Regorafenib	VEGFR-1, VEGFR-2, VEGFR-3, RET, FGFR1, PDGFR-β, **BRAF**, Kit	Metastatic colorectal cancer, gastrointestinal stroma tumour, hepatocellular carcinoma	Hand-foot skin reactions, diarrhoea, hypertension, fatigue	(Krishnamoorthy et al., 2015)
Axitinib	VEGFR-1, VEGFR-2, VEGFR-3, Kit, PDGFR family	Advanced renal cell carcinoma	Hypertension, diarrhoea, fatigue, anorexia, nausea, hand-foot syndrome, rash	(Gunnarsson et al., 2015)
Cabozantinib	VEGFR-2, **c-met**, RET, AXL, FLT3	Hepatocellular carcinoma, medullary thyroid cancer, renal cell carcinoma	Diarrhoea, hypertension, fatigue, hand-foot syndrome	(Grüllich, 2018)
Ponatinib	VEGFR-2, FGFR1, BCR-ABL, Src, PDGFR-α	Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Rash, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and oedema, hepatic dysfunction, hypertension, pyrexia, nausea, haemorrhage, pancreatitis, diarrhoea, vomiting, myalgia	(Cortes et al., 2018)
Lenvatinib	VEGFR-1, VEGFR-2, VEGFR-3, Kit FGFRs, PDGFR-α, RET	Hepatocellular carcinoma, thyroid cancer, advanced renal cell carcinoma	Haematuria, fatigue, decreased appetite, thrombocytopenia, hypertension, hypertension, oedema, peripheral,	(Zhu et al., 2016)
Nintedanib	VEGFRs, FGFR, PDGFR	Idiopathic pulmonary fibrosis, chronic fibrosing interstitial lung diseases with a progressive phenotype	Nausea, diarrhoea, appetite loss, gastrointestinal adverse effects, liver dysfunction	(Kato et al., 2019)

TABLE 2 (Continued)

Drug	Target molecules	Diseases	Side effects	References
Vandetanib	RET, VEGFRs, EGFR	Advanced medullary thyroid cancer	Diarrhoea, rash, acne, nausea, hypertension, headache, fatigue, decreased appetite, abdominal pain	(Wells et al., 2010)
Tivozanib	VEGFR-1, VEGFR-2, VEGFR-3	Relapsed or refractory advanced renal cell carcinoma	Fatigue, hypertension, diarrhoea, decreased appetite, nausea, dysphonia, cough, hypothyroidism, stomatitis	(Rini et al., 2020)
Apatinib	VEGFR-2, c-kit, c-Src	Advanced gastric cancer (approved in China and South Korea)	Hypertension, hand-foot syndrome, gastrointestinal symptoms (nausea, vomiting, diarrhoea), loss of appetite	(Qin, Li, et al., 2021)
3. Fusion proteins				
Aflibercept	VEGFA, VEGFB, PlGF1, PlGF2	Diabetic retinopathy, wet age-related macular degeneration, diabetic macular oedema, macular oedema following retinal vein occlusion	Hypertension, proteinuria, fatigue, headache	(Tang & Moore, 2013)
Ziv-aflibercept	VEGFA, VEGFB, PlGF	Metastatic colorectal cancer	Diarrhoea, fatigue, proteinuria, hypertension, abdominal pain, decreased appetite, headache	(Patel & Sun, 2014)
Conbercept	VEGFA, VEGFB, PlGF	Neovascular age-related macular degeneration	Eye pain, transient intraocular pressure increase, conjunctival haemorrhage	(Li et al., 2014)

decrease in VEGF-A expression compared to the untreated hepatocellular carcinoma ones (Qin, Huang, et al., 2021). A further compound inhibiting angiogenesis in the strongly vascularized hepatocellular carcinoma *in vitro* and *in vivo* is dandelion polysaccharide (DP), which resulted in a substantial downregulation of VEGF as well as HIF-1α expression through modulation of the PI3K/AKT pathway in hepatocellular carcinoma cells after dandelion polysaccharide treatment (Ren et al., 2020). Asparagus polysaccharide is often used in traditional Chinese medicine and represses HIF-1α and VEGF expression in hypoxic conditions. In consequence, migration, invasion and angiogenesis can be prevented (Cheng et al., 2021). Extracted from the roots of *Polygala tenuifolia*, PTP is a polysaccharide with a backbone composed of 1,4,6-linked-β-Galp, 1,4-linked-β-Galp and 1,4-linked-β-Glcp which was examined in the treatment of BALB/c mice with SKOV3 xenograft tumour growth and demonstrated a downregulating effect of **EGFR**, VEGF and CD34, therefore effectively inhibiting tumour angiogenesis (Yao et al., 2018).

3.3 | Alkaloids

Alkaloids are a large cluster of molecules found in a wide variety of plants. They are all secondary metabolites and are categorized based on the amino acids that deliver their nitrogen atoms and part of their skeleton. Extensive studies show that alkaloids display significant antiproliferative, antibacterial and antioxidant effects, which contribute to a great therapeutic potential. To date, more than 25 alkaloids are of pharmaceutical relevance in anti-angiogenic activity (Table 5).

Some typical, recently well-researched, and potentially more promising alkaloids include **berberine**, (Z)-3β-ethylamino-pregn-17 (20)-en and capsaicinoids. Berberine has been used in traditional Chinese medicine for thousands of years and can be isolated from *Rhizoma coptidis*. Translational research has demonstrated significant anti-angiogenic activity of berberine by targeting and inhibiting the phosphorylation of VEGFR-2 and ERK and therefore diminishing tumour vascular density (Jin et al., 2018). (Z)-3β-ethylamino-pregn-17 (20)-en is a pregnane alkaloid derivative found in *Pachysandra terminalis*. *In vitro* and in vivo research on triple-negative breast cancer cells has shown that it can bind to heat shock protein 90 alpha family class member 1 (**HSP90α**) and therefore downregulate HIF-1α, which is a key factor for cancer cell migration, invasion and angiogenesis. Furthermore, it inhibits the VEGF/VEGFR-2 downstream signalling pathway by preventing the phosphorylation of AKT, mTOR and **FAK** (Liu, Wang, et al., 2022). Capsaicinoids, a group of bioactive compounds, can be found mainly in the placental tissue of peppers and account for the pungency as well as the level of hotness based on their concentration among other factors (Hamed et al., 2019). **Capsaicin** and capsiate are found in peppers and have demonstrated antiangiogenic effects. Capsaicin inhibited cyclin D1 expression which reduced the phosphorylation of Rb. In consequence, HUVECs were arrested in the G1 stage. Additionally, capsaicin significantly downregulated the expression of VEGF in myelomas and NSCLC (Friedman et al., 2019).

TABLE 3 Anti-angiogenic polyphenols and their sources, experimental models and mechanisms.

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Curcuminoids	Curcumin	*Curcuma longa*	HCT-116 and LoVo colorectal cancer cells, PC3 prostate cancer cells, A549 and PC9 lung cancer cells, MBCDF-T and EA.hy926 breast cancer cells, HUVECs, human microvascular endothelial cells (HMEC-1), chicken chorioallantoic membrane (CAM) assay, xenograft tumour mice model	- Downregulates MMP9 and VEGF expression and upregulates metalloproteinases - Inhibits the activity of other angiogenic factors, bFGF, PDGF - Regulates PI3K/AKT and MAPK pathways	(Basak et al., 2020; Buzzá et al., 2019; Calibasi-Kocal et al., 2019)
Flavan-3-ols/ Catechins	Epigallocatechin-3-gallate (EGCG)	Green tea	A549 and PC9 lung cancer cells, HUVECs, CAM assay, HepG2 and AsPC-1 xenograft tumour mice models	- Downregulates VEGF signalling and MMPs - Inhibits the PI3K/AKT/HIF-1α/VEGF and MAPK/ERK1/2 signalling pathways - Induces apoptosis in ECs	(Liao et al., 2020; Niedzwiecki et al., 2016; Zhu et al., 2007)
Flavan-3-ols/ catechins	Catechin	Black tea	HUVECs and HASMCs	- Inhibits VEGF expression	(Negrão et al., 2013)
Flavan-3-ols/ catechins	Theaflavine	Black tea	A2780/CP70 and OVCAR-3 ovarian carcinoma cells	- Decreases the levels of VEGF and HIF-1α protein - Downregulates the PI3K/AKT/mTOR pathway	(O'Neill et al., 2021)
Tannins	Ellagic acid	Berries, walnuts, pomegranates	Caco-2 intestinal cells, MDA-MB-231 breast cancer cells, LnCa cancer cells, CAM assay, Balb c nude mice	- Inhibits VEGFR-2 tyrosine kinase activity and the PI3K/AKT, notch and SHH pathways - Induces a significant decrease in **HO-1**, **HO-2** and **CYP2J2** expression and in VEGF and OPG levels	(Vanella et al., 2013; Wang, Wang, et al., 2012; Zhao, Tang, et al., 2013)
Stilbenes	Resveratrol	*Polygonum cuspidatum*, grapes, berries, peanuts	MDA-MB-231, MBCDF-T and EA. hy926 breast cancer cells, A549 lung cancer cells, HT29 colon cancer cells, HUVECs, BAE cells, MBCDF-T xenograft tumour nude mice model	- Inhibits proliferation of HUVECs - Decreases the lytic activity of MMP2 - Through the **GSK3β**/β-**catenin**/T-cell factor (TCF)-dependent pathway	(García-Quiroz et al., 2019; Igura et al., 2001; Sagar et al., 2006; Wang et al., 2010)
Flavonolignans	Silibinin	*Silybum marianum*	HT29 colorectal cancer cells, HT29 xenograft tumour nude mice model, transgenic adenocarcinoma of the mouse prostate model	- Downregulates VEGF and epidermal growth factor receptor (EGFR) - Downregulates NOS, COX, HIF-1α expression	(Sagar et al., 2006; Singh, Gu, & Agarwal, 2008; Singh, Raina, et al., 2008)

TABLE 3 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Flavonols	Quercetin	*Quercus iberica*, red wine, onions, green tea, apples, berries	MCF-7 breast cancer cells, Eca109 oesophageal cancer cells, HUVECs, BAE cells, CLR-1730 cells, BALB/c nude mice xenograft model	- Inhibits p-ERK and VEGFR-2 expression - Suppresses expression of VEGF-A, MMP2/9 - Downregulates MALAT1 and MIAT LncRNAs	(Esteghlal et al., 2021; Igura et al., 2001; Liu et al., 2021; Zhao et al., 2016)
Flavones	Luteolin	*Reseda odorata L.*, parsley, thyme, peppermint and celery	A375 and B16-F10 melanoma cells, HUVECs, NSCLC-VECs, Sprague–Dawley rats	- Blocks activation of VEGFR-2 - Decreases the expression of p-AKT, HIF-1α, VEGF-A, p-VEGFR-2, MMP2/9 - Via miR-133a-3p/PURB- mediated MAPK and PI3K/AKT pathways	(Li et al., 2019; Lin et al., 2008; Pan et al., 2022)
Flavones	Baicalein	*Scutellaria Baicalensis Georgi*	MG-63 osteosarcoma cells, HUVECs, CAM assay	- Decreases the expression of CDK2, cyclin D1, cyclin E1, **Bcl-2**, N-cadherin, vimentin, MMP2, MMP9, p-ERK/ERK - Increases G1 phase numbers, apoptosis and the expression level of p21, p27, cleaved caspase 3/9, Bax, E-cad, ZO-1	(Lin, Hao, et al., 2020; Liu et al., 2003)
Flavones	Baicalin	*Scutellaria Baicalensis Georgi*	SW1990 pancreatic cancer cells, OVCAR-3 and CP70 ovarian carcinoma cells, HUVECs, CAM assay	- Targets PI3K/AKT/mTOR, NF-κB, MAPK/ERK, Wnt/β-catenin signalling - Downregulates the HIF-1α, VEGF and Ras–Raf-MAPK pathway	(Liu et al., 2003; Singh et al., 2021)
Flavones	Apigenin	*Apium graveolens*	SK-MEL-24 melanoma cells, HUVECs, CAM assay, NCI–H1703 and NCI–H1299 xenograft tumour mice model	- Inhibits HIF-1α and VEGFA expression and its downstream VEGF-A/VEGFR-2 and PDGF-BB/PDGFβR signalling pathway - Suppresses the endothelial cellular motilities and pericyte recruitment to newly-formed endothelial cells tubes	(Fu et al., 2022; Ghiu et al., 2021)
Flavones	Eupatorin	*Orthosiphon stamineus*	MCF-7 and MDA-MB-231 cells, 4 T1 challenged BALB/c mice model	- Inhibits phospho-AKT pathway - Downregulates the expression of pro-inflammatory and metastatic-related genes (IL-1β, MMP9, TNF-α and NF-κB)	(Abd Razak et al., 2020; Razak et al., 2019)
Flavones	Xanthomicrol	*Dracocephalum kotschyii* Boiss	HeLa cervical cancer cells, HUVECs, rat aortic ring assay, B16F10 xenograft mice model	- Interferes with PI3K/AKT signalling pathway - Inhibits VEGF expression and has little or no effect on bFGF expression	(Abbaszadeh et al., 2014; Ghazizadeh et al., 2020)

(Continues)

TABLE 3 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Flavones	Calycopterin	*Dracocephalum kotschyii* Boiss	HUVECs, rat aortic ring assay	- Suppresses microvessel outgrowth, tube formation and cell proliferation - Inhibits VEGF expression and has little or no effect on bFGF expression	(Abbaszadeh et al., 2014)
Hydroxycinamic acid derivatives	Chlorogenic acid	*Eucommia ulmoides Oliv*	A549 lung cancer cells, EA.hy926 cells, HUVECs	- Decreases HIF-1α protein level - Inhibits HIF-1α/AKT signalling pathway	(Park et al., 2015)
Anthocyanins	Delphinidin	*Pharbitis nil (L.) Choisy*	Bovine aortic endothelial cells (BAECs), EA.hy926	- Inhibits endothelial cell proliferation through cyclin D1- and A-dependent pathways - Inhibits AKT signalling pathway	(Barkallah et al., 2021; Martin et al., 2003)
Anthocyanins	Cyanidin-3-glucoside	Raspberries and strawberries	MDA-MB-231 and Hs-578 T breast cancer cells	- Inhibits VEGF expression and secretion - Inhibits STAT3/VEGF pathway	(Ma & Ning, 2019)
Anthocyanins	Malvidin-3-galactoside	Blueberry	Huh-7 hepatocellular carcinoma cells	- Inhibits AKT/PTEN, MAPK and MMP pathways	(Lin, Tian, et al., 2020)
Isoflavone	6-Methoxyequol	Soybean	HUVECs, primary bovine brain capillary endothelial cells (BBCECs), A-431 xenograft mice model	- Inhibits VEGF-induced proliferation of ECs by targeting the phosphorylation of MEK1/2	(Bellou et al., 2012; Watanabe & Uehara, 2019)
Isoflavone	Barbigerone	*Suberect spatholobus*	A549 and SPC-A1 lung cancer cells, HUVECs, aortic ring assay, zebrafish model, A549 and SPC-A1 xenograft mice model	- Inhibits VEGFR-2 signalling pathways - Prolongs life span and has little adverse effects in tumour-bearing mice, CAM assay	(Li et al., 2012)
Isoflavone	Genistein	*Pterocarpus indicus*, *Ficus septica*	E6 cell line, RT4, J82, 5,637 and T24 bladder cancer cell lines, TSGH8301 xenograft mice model	- Inhibits expression/excretion of VEGF165, PDGF, tissue factor, **urokinase plasminogen activator**, MMP2/9 - Uupregulates plasminogen activator inhibitor-1, endostatin, angiostatin and TSP-1	(Su et al., 2005)
Dihydroxyflavanone	Pinocembrin	*Carya cathayensis* Sarg.	HUVECs, mouse aortic ring assay	- Suppresses VEGF-induced HUVEC proliferation and migration	(Tian et al., 2014)
Dihydroxyflavone	Chrysin	*Carya cathayensis* Sarg.	HUVECs, mouse aortic ring assay	- Suppresses VEGF-induced HUVEC proliferation and migration	(Tian et al., 2014)
Dihydroxyflavone	Wogonin	*Carya cathayensis* Sarg.	MCF-7 breast cancer cells, HUVECs, mouse aortic ring assay, CAM assay	- Suppresses PI3K/AKT/NF-κB signalling	(Song et al., 2013; Tian et al., 2014; Zhao et al., 2014)

TABLE 3 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
				- Inhibits secretion of VEGF by decreasing HIF-1α - Enhances prolyl hydroxylase domain (PDH) and von Hippel–Lindau (VHL) expression and inhibits HSP90α function	
Chalcone	Cardamonin	*Alpinia katsumadai*, *Carya cathayensis* Sarg. *G. biloba*, *Gynostemma pentaphyllum*	SKOV3 ovarian cancer cells, HUVECs, mouse aortic ring assay	- Inhibits the protein expression of HIF-1/2α and VEGF - Decreases the phosphorylation of ERK and AKT induced by VEGF	(Tian et al., 2014; Xue et al., 2016)
Chalcone	Pinostrobin	*Cajanus cajan*	HUVECs, mouse aortic ring assay	- Inhibits the vessel formation - Suppresses cell migration of HUVECs	(Ashidi et al., 2008)
Chalcone	Xanthohumol	*Humulus lupulus* L.	MCF-7 breast cancer cells, MCF-7 xenograft mice model	- Hinders tumour and inflammatory cells and angiogenesis	(Monteiro et al., 2008)
Biflavonoid	Amentoflavone	*Selaginella tamariscina*	MCF-7 breast cancer cells, SKOV3 and OVCAR-3 ovarian cancer cells, hypertrophic scar fibroblasts (HSFBs)	- Reduces NF-κB activation and secretion of angiogenesis- and metastasis-related proteins - Represses the expression of Skp2 through ROS/AMPK/mTOR signalling	(Chen, Chen, & Liu, 2015)
Biflavonoid	Hinokiflavone	*Selaginella tamariscina*, *Juniperus phoenicea*, *Rhus succedanea*	KYSE150 and TE14 oesophageal squamous cancer cells	- Blocks PI3K/AKT/mTOR signalling pathway	(Guo, Zhang, et al., 2022)
Biflavonoid	Ginkgetin	*Ginkgo biloba* leaves	Retinal pigment epithelial cells, HUVECs, zebrafish embryos, HT29 xenograft mice model	- Reduces HIF-1α and VEGF expression - Binds with VEGF	(Hu et al., 2019)
Biflavonoid	Isoginkgetin	*Metasequoia glyptostroboides*	HT1080 fibrosarcoma cells, MDA-MB-231 cells	- Decreases MMP9 expression and invasion through inhibition of PI3K/AKT pathway	(Yoon et al., 2006)
Biflavonoid	Morelloflavone	*Garcinia dulcis*	PC-3 prostate cancer cells, PC-3 xenograft mice model	- Targets the activation of rho-GTPases and ERK signalling pathways	(Pang, Yi, Zhang, et al., 2009)
Biflavonoid	Delicaflavone	*Selaginella doederleinii* Hieron	HT29 and HCT116 prostate cancer cells	- Inhibits PI3K/AKT/mTOR and Ras/MEK/ERK signalling pathways	(Yao et al., 2020)

Abbreviations: BAECs, bovine aortic endothelial cells, BBCECs, bovine brain capillary endothelial cells; bFGF basic fibroblast growth factor; CAM, chicken chorioallantoic membrane; HASMCs, human aortic smooth muscle cells; MMPs, matrix metalloproteases; NSCLC, non-small-cell lung cancer; SHH, sonic hedgehog.

TABLE 4 Anti-angiogenic polysaccharides and their sources, experimental models and mechanisms.

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
-	Pachyman	*Poria cocos*	HepG2 liver cancer cells, HUVECs, CAM assay	- Albumin (ALB) and VEGF-A in hepatocellular carcinoma might be potent targets - Represses HIF-1α and VEGF expression	(Qin, Huang, et al., 2021)
α-Type polysaccharides	Dandelion polysaccharide	Roots of dandelion	HepG2 liver cancer cells, HUVECs, CAM assay	- Downregulates VEGF and HIF-1α expression through modulation of the PI3K/AKT pathway	(Ren et al., 2020)
-	Asparagus polysaccharide	Asparagus plant	SK-Hep1, Hep-3B, L0–2, A549 hepatocellular carcinoma cells, HUVECs	- Regulates HIF-1α/VEGF expression via MAPK and PI3K signalling pathways	(Cheng et al., 2021)
Water-soluble Polysaccharide	Polygala tenuifolia polysaccharide (PTP)	Roots of *Polygala tenuifolia*	SKOV3 xenograft mice model	- Suppresses EGFR, VEGF, CD34 levels	(Yao et al., 2018)
Huaier polysaccharide	TP-1	Huaier fungus	SMMC-7721 hepatocellular carcinoma cancer cells, SMMC-7721 xenograft mice model	- Downregulation of HIF-1α/VEGF and AUF-1/AEG-1	(Li et al., 2015)
Huaier polysaccharide	SP1	Mushroom Huaier	SMMC-7721 hepatocellular carcinoma cancer cells	- Decreases serum MMP2 and VEGF levels - Downregulates HIF-1, VEGF, MMP2, bcl-2, N-cadherin, STAT3 - Upregulates bax and NE-cadherin	(Zou et al., 2015)
-	Galactomannan, PSP001	Fruit rind of *Punica granatum*	HUVECs, CAM assay	- Inhibits expression of VEGF, MMP2/9	(Varghese et al., 2017)
Exopolysaccharide	LEP-2a	*Lachnum* sp.	H22 hepatocellular carcinoma cells, H22 xenograft mice model	- Inhibits expression of bFGF, MMP2/9	(Zong et al., 2018)
-	Protein-bound polysaccharide	*Phellinus linteus* mushroom	SW480 colon cancer cells, HUVECs, SW480 xenograft mice model	- Inhibits tumour growth and metastasis through the immunopotentiation - Inhibits HUVEC proliferation and capillary tube formation	(Li et al., 2004; Song et al., 2011)
-	*Grateloupia longifolia* polysaccharide (GLP)	*Grateloupia longifolia*	MKN-28 gastric cancer cells, HCT-116 colon cancer cells, MDA-MB-435 breast carcinoma cells, SK-OV-3 ovary cancer cells, S-180 sarcoma cells, NIH-3 T3 fibroblast cells, HMEC-1, HUVECs, CAM assay, S-180 xenograft mice model	- Decreases mRNA and protein levels of tissue factor - Decreases tumour weight	(Zhang et al., 2006)
Pectic polysaccharide	Corn pectic polysaccharide (COPP)	*Zea mays* L.	B16F10 melanoma cells, B16F10 xenograft mice model	- Inhibits galectin-3 mediated hemagglutination - Modulates cancer-specific markers such as galectin-3, VEGF, MMP2/9, NF-κB	(Jayaram et al., 2015)
Fucose-containing sulfated polysaccharide	Fucoidan	*Laminaria japonica*, *Fucus vesiculosus*	T24 urinary bladder cancer cells, HUVECs	- Downregulates PI3K/AKT and mTOR signalling pathways	(Chen, Hsu, et al., 2015)

TABLE 4 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
				- Inhibits HIF-1α and VEGF expression	
Fucoidan-like polysaccharide (water-soluble)	STPC2	*Sargassum thunbergii*	A549 lung cancer cells, HUVECs, CAM assay, mice	- Reduces MMP2 expression at the transcriptional level and enzymatic activity - Decreases VEGF and HIF-1α expression	(Hu et al., 2017; Ou et al., 2017)
Sulfated polysaccharide	PRP-S16	*Phellinus ribis*	EA.hy926 ECs, CAM assay	- Blocks the formation of new vessels in CAM assay - Inhibits VEGF-induced signalling pathway	(Liu, Xu, et al., 2018)
Sulfated polysaccharide	SIP-SII	*Sepiella maindroni* ink	B16F10 melanoma cells, SKOV3 ovarian carcinoma cells, EA.hy926 ECs, CAM assay, 16F10 xenograft mice model	- Suppresses melanoma metastasis via the inhibition of the tumour adhesion mediated by **ICAM-1** and the angiogenesis mediated by bFGF	(Zong et al., 2013)
Homogeneous polysaccharide	HH1–1	*Safflower*	BxPC-3, AsPC-1, CFPAC-1, Capan-1, SW1990, Miapaca-2, PANC-1, HPAC, MDA-MB-231, U87, K652, SW116, BEL-7402, HeLa, A375, A549, L02, HPDE6-C7 cells, BxPC-3 xenograft mice model	- Blocks the interaction between Galectin-3 and EGFR - Affects the Galectin-3/EGFR/AKT/FOXO3 signalling pathway	(Yao et al., 2019)
Apigalacturonan-rich polysaccharide	ZCMP	*Zostera caespitosa* Miki.	RAW264.7 mouse macrophage cells, HUVECs	- Inhibits HUVEC proliferation and migration	(Lv et al., 2015)
Galacturonic acid-containing polysaccharide	EUP3	*Eucommia ulmoides*	Mesenchymal stem cells (MSCs), HUVECs	- Exhibits an affinity for FGF-2 and PDGF-BB	(Li et al., 2016)
Low molecular weight polysaccharide	LMPAB	*Agaricus blazei*	S180 sarcoma cells, CAM assay, S180 xenograft mice model	- Downregulates RNA and protein levels of VEGF	(Niu et al., 2009)
-	HBE-I, -II, -III, -IV	*Citrus* hallabong fruit	MDA-MB-231 cells, HUVECs	- Inhibits tube formation and MMP9-mediated migration	(Park et al., 2016)
-	CCPSn	*Cipangopaludina chinensis*	RAW264.7 mouse macrophage cells, HUVECs	- Decreases the pro−/anti-inflammatory cytokine secretion ratios, NO, **prostaglandin E2 (PGE_2)**, **cyclooxygenase (COX-2)**, **inducible nitric oxide synthase (iNOS)** - Inhibits proliferation, migration, tube formation, VEGF of HUVECs	(Xiong et al., 2017)
Neutral polysaccharide	JHB0S2	Flowers of *Chrysanthemum morifolium*	B16F10 melanoma cells, HMEC-1	- Inhibits the tube formation of HMEC-1 cells	(Zheng et al., 2015)

(Continues)

TABLE 4 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Pectic polysaccharide		*Diospyros kaki* leaves	HUVECs	- Reduces mRNA/protein expression of angiogenesis-related factors (VEGF/MMP9) - Suppresses the phosphorylation of PI3K/AKT and p38, JNK, NF-κB p65	(Park & Shin, 2021)
-	SargA	*Sargassum stenophyllum*	CAM assay, mice	- Inhibits migration and viability of B16F10 cells - Modulates the activity of heparin-binding angiogenic growth factors	(Dias et al., 2005)
-	SFPS	*Sargassum fusiforme*	SPC-A-1 lung adenocarcinoma cells, HUVECs, SPC-A-1 xenograft mice model	- Decreases CD31, VEGFA expression and the tumour microvessel density - Induction of cell cycle arrest and apoptosis	(Chen et al., 2017)

Abbreviations: bFGF basic fibroblast growth factor, CAMchicken chorioallantoic membrane; HMEC-1, cells, human microvascular; MMPs, matrix metalloproteases.

3.4 | Terpenoids

Terpenoids, also known as phytosterol, make up the largest and a highly diverse group of natural products. Terpenoids consist of varying numbers of isoprene units (C_5) and all share the general formula: $(C_5H_8)_n$. The number of carbon atoms for a terpenoid possesses leads to the following categorization: hemiterpenoids (C_5), monoterpenoids (C_{10}), homoterpenoids ($C_{11,16}$), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), sesterpenoids (C_{25}), triterpenoids (C_{30}), tetraterpenoids (C_{40}) and polyterpenoids ($C_{>40}$) (Boncan et al., 2020). Terpenoids are bioactive compounds and display anti-tumour effects, including anti-proliferative, apoptotic, anti-angiogenic and anti-metastatic effects, resulting in terpenoids being of major medicinal interest. Some important terpenoids in modulating the angiogenic pathway in tumours include **lupeol**, **artemisinin**, **oleanolic acid**, perillyl alcohol, β-elemene, alantolactone, tanshinone IIA, triptolide, ursolic acid and koetjapic acid (Li, Song, et al., 2021). To date, more than 45 terpenoids are of pharmaceutical relevance in anti-angiogenic activity (Table 6).

Some examples of terpenoids which have displayed recent research advancements in regard to their antiangiogenic effect include lupeol and artemisinin-type compounds. A phytochemical extraction containing the terpenoids lupeol, isomeldenin, nimocinol and gedunin was isolated from the leaves of *Azadirachta indica*, of which the triterpenoid lupeol displayed the highest anticancer effect. The anti-tumour efficacy of this extraction was studied on male Wistar rats and showed that angiogenesis of hepatocellular carcinoma could be repressed by the terpenoids, mainly lupeol, which docked to the AKT binding pocket and therefore downregulated the expression of proangiogenic mRNAs, VEGFR, HIF-1 and **MMP2** (Akinloye et al., 2021). A recent study regarding the anti-angiogenic effects of artemisinin on breast tumour xenografts in nude mice showed that artemisinin could modulate the Notch1 signalling pathway by downregulating the mRNA expression of Notch1, Dll4 and Jagged1, leading to a reduced content of VEGF and HIF-1α, therefore, inhibiting angiogenesis (Dong et al., 2020).

3.5 | Saponins

Saponins are high molecular weight secondary metabolites that can be found in many different plants such as *Quillaja saponaria*, *Yucca schidiggera* and *Medicago sativa*. Saponins are amphiphilic compounds, which consist of a lipid-soluble sterol or triterpenoid as well as a water-soluble sugar residue and display detergent characteristics. These bioactive compounds display hepatoprotective, anti-ulcer, anti-tumour, antimicrobial, adjuvant and anti-inflammatory activities (Moghimipour & Handali, 2015). To date, more than 23 saponins are of pharmaceutical relevance in anti-angiogenic activity, including saikosaponin A, *Pulsatilla* saponins, Paris saponin I and theasaponin E1 (Table 7).

Saponins that have been extensively studied in recent years and show promising results include saikosaponin A (SSA), *Pulsatilla* saponins, as well as *Paris* saponin. SSA, a natural triterpenoid saponin, can

TABLE 5 Anti-angiogenic alkaloids and their sources, experimental models and mechanisms.

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Isoquinoline alkaloid	Berberine	*Rhizoma coptidis*	U87 and U251 glioblastoma cells, HUVECs, U87 xenograft mice model	- Inhibits phosphorylation of VEGFR-2 and ERK	(Jin et al., 2018)
Isoquinoline alkaloid	Sinomenine	*Sinomenium acutum*	HUVECs, mice	- Inhibits angiogenesis via HIF-1α–VEGF–ANG-1 axis	(Feng, Yang, et al., 2019)
Pregnane alkaloid	(Z)-3β-ethylamino-pregn-17(20)-en	*Pachysandra terminalis*	MDA-MB-231 cells, HUVECs	- Downregulates HIF-1α/VEGF/VEGFR-2 pathway - Binds to HSP90α	(Liu, Wang, et al., 2022)
Amide alkaloid	Capsaicin	*Capsicum frutescens*, *Capsucum annum* L.	HUVECs, HDMECs, CAM assay	- Downregulates the expression of VEGF - Suppresses tumour-induced angiogenesis - Causes G1 arrest in ECs and decreases cyclin D1	(Friedman et al., 2019)
Indolizidine alkaloid	Lycorine	Amaryllidaceae family	HUVECs	- Docks to PDGFR-α and inhibits its phosphorylation	(Lv et al., 2022)
Indole alkaloid	Brucine	*Strychnos nux-vomica* L.	Ehrlich ascites carcinoma (EAC) cells, HUVECs, rat aortic ring assay, EAC xenograft mice model	- Downregulates VEGF, NO, IL-6, IL-8, TNF-α, IFN-γ - Suppresses VEGF-induced p-VEGFR-2 kinase activity - Inhibits the downstream of VEGFR-2, including Src, FAK, ERK, AKT, mTOR	(Saraswati & Agrawal, 2013)
Indole alkaloid	Reserpine	*Rauwolfia serpentina*	CCRF-CEM and CEM/ADR5000 leukaemia cells, MDA-MB-231 BCRP clone 23 cells, HCT116 (p53+/+) colon cancer cells, U87MG.ΔEGFR cells	- Lack of cross-resistance to most resistance mechanisms - Inhibits TGF-β dependent **Smad2/3/4** phosphorylation	(Abdelfatah & Efferth, 2015)
Indole alkaloid	6″-Debromohamacanthin A (DBHA)	*Spongosorites* sp.	HUVECs	- Targets VEGFR-2-mediated PI3K/AKT/mTOR signalling pathway	(Kim et al., 2013)
Alkylpyrazine	Tetramethylpyrazine	*Ligusticum chuanxiong*	A549 lung adenocarcinoma cells, SKOV3 and A2780 ovarian cancer cells, HUVECs, A2780 xenograft mice model	- Inhibits both ERK1/2 and AKT pathways	(Zou et al., 2019)
Benzylisoquinoline alkaloid	Noscapine	*Papaver somniferum L.*	MDA-MB-231 and MDA-MB-468 cells, mice	- Inactivates NF-KB and anti-angiogenic pathways while stimulating apoptosis	(Chougule et al., 2011)

(Continues)

TABLE 5 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Indole alkaloid	Voacangine	*Voacanga africana* and *Tabernaemontana catharinensis*	HepG2 liver carcinoma cells, HUVECs, CAM assay	- Decreases the expression levels of HIF-1α and VEGF	(Kim et al., 2012)
Cassaine diterpene alkaloid	3β-acetyl-nor-erythrophlamide	*Erythrophleum fordii*	A549 lung adenocarcinoma cells, HUVECs, A549 xenograft mice model	- Inhibits VEGF-mediated eNOS activation and NO production	(Tae et al., 2017)
Benzophenanthridine alkaloid	Sanguinarine	*Sanguinaria canadensi*	A549 lung adenocarcinoma cells, MCF-7 breast cancer cells, HMVECs, melanoma mice model	- Inhibits the phosphorylation of AKT, p38 and VE-cadherin - Blocks the VEGF-induced blood vessel growth	(Gaziano et al., 2016)
Bisbenzylisoquinoline alkaloid	Tetrandrine	*Stephania tetrandra* S Moore	DU145 and PC-3 prostate cancer cells, RT-2 glioma cells, CT26 colorectal adenocarcinoma cells, U87 glioma cells, ECV304 ECs, RT-2, 4 T1 and CT26 xenograft mice model	- Inhibits expression of VEGF - Targets HIF-1α, integrin 5, endothelial cell-specific molecule-1, intercellular adhesion molecule-1	(Liu et al., 2016)
Indoloquinazoline Alkaloid	Evodiamine	*Euodia rutaecarpa* (Juss.) Benth. (Rutaceae)	HepG2, SMMC-7721 and H22 hepatocellular carcinoma cells, HUVECs, CAM assay, SMMC-7721 xenograft mice model	- Decreases protein expression of VEGF and activation of p44/42 mitogen-activated protein kinase - Inhibits β-catenin-mediated angiogenesis	(Shi et al., 2016)
Isocarbostyril alkaloid	Narciclasine	*Amaryllidaceae family*	HUVECs	- Activates rho kinase and downregulates VEGFR-2 - Shifts the cells into the G0/G1 phase of the cell cycle	(Bräutigam et al., 2019)
β-Carboline alkaloid	Harmine	*Peganum harmala*	4 T1 and MCF7 breast cancer cells, 4 T1 xenograft mice model	- Downregulates VEGF, MMP2, IL-4, Ki-67 - Increases E-cadherin	(Rashidi et al., 2022)
Quinolizidine alkaloid	Oxysophocarpine	*Siphocampylus verticillatus*	Hep3B and HepG2 hepatocellular carcinoma cells, AN3-CA endometrial adenocarcinoma cells	- Downregulates FGFR1 expression along with downstream AKT/mTOR and ERK signalling	(Zhao et al., 2021)
Quinolizidine alkaloid	Punarnavine	*Boerhaavia diffusa*	HUVECs, Ehrlich ascites model, sponge implant assay	- Inhibits endothelial cell migration and invasion and capillary structure formation - Inhibits MMP2/9 expression	(Saraswati et al., 2013)
Quinolizidine alkaloid	Halofuginone	*Dichroa febrifuga*	HSC3 and HN6 oral squamous carcinoma cells, HUVECs	- Blocks MMP2/9 activity and TGF-β signalling - Reduces VEGF secretion and phosphorylation of Smad2	(Mi et al., 2022)

TABLE 5 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Isosteroidal alkaloid	Chuanbeinone	Bulbus of *Fritillaria pallidiflora*	Lewis lung carcinoma cells	- Reduces the expression of the antiapoptotic Bcl-2 and increases proapoptotic protein Bax and caspase-3	(Wang, Li, et al., 2016)
Phenanthroindolizidine alkaloid	Antofine	Asclepiadaceae family	D3 embryonic stem cells, HUVECs, aortic ring assay	- Suppresses angiogenesis via regulation of AKT/mTOR and AMPK pathway	(Oh et al., 2017)
-	30-hydroxyzoanthenamine, 11-dehydroxy-18-epi-kuroshine A, 30-hydroxyzoanthamine	*Zoanthus vietnamensis*	Endothelial progenitor cells (EPCs)	- Blocks cell growth and tube formation of EPCs	(Chen et al., 2021)

Abbreviations: ANG, angiostatin (plasminogen); CAM, chicken chorioallantoic membrane; EAC, Ehrlich ascites carcinoma; MMPs, matrix metalloproteases.

be extracted from *Radix Bupleurum* and is known to have various pharmacological activities such as antidepressant, immunoregulatory and anti-inflammatory characteristics. A recent study has shown that SSA effectively inhibits angiogenesis of 4 T1 breast cancer cells as well as HCT-15 colorectal adenocarcinoma cells in mice by inhibiting the phosphorylation of VEGFR-2 and blocking the downstream PLCγ1, FAK, Src and AKT pathways (Zhang et al., 2021). *Pulsatilla chinensis* is a plant rich in triterpenoid saponins which plays an important role in traditional Chinese medicine. *Pulsatilla* saponins have shown dose-dependent anti-angiogenic activity in HUVECs by inhibiting HIF-1α and VEGF expression (Zhong et al., 2022). *Paris polyphylla* contains four main saponins, including Paris saponin I, II, VI and VII, among which Paris saponin I was the most potent inhibitor of HUVEC proliferation and *in vitro* angiogenesis by modulating VEGFR-2, PI3K/AKT/mTOR, **Src**/**eNOS**, **PLCγ1**/ERK/MERK and **JAK2**-**STAT3** pathways (Wang et al., 2020).

4 | FUTURE PERSPECTIVES

4.1 | Improvement of bioavailability of natural products

Natural products hold great potential as sources of therapeutic and health-promoting compounds. However, their practical application may be limited by certain shortcomings, including poor bioavailability, aqueous solubility, chemical complexity, susceptibility to degradation and low absorption rates. Notably, poor bioavailability was identified as a major restriction.

To overcome these limitations and improve the therapeutic potential of natural products, various formulation strategies have been explored. Nanoparticles, liposomes, micelles and solid dispersions have been investigated to enhance the solubility and stability of natural products, thus leading to improved bioavailability (Mahran et al., 2017). For instance, in the context of curcumin delivery, a diverse range of nanoparticle platforms, such as micelles, polymeric, lipid-based and metallic nanoparticles have been explored. Additionally, attachment of poly (ethylene glycol) chains and active targeting moieties have been utilized to enhance targeted delivery. Studies focusing on curcumin nanoparticles have demonstrated their safety in different *in vivo* models of breast cancer. Furthermore, these curcumin nanoparticles have shown promising outcomes, surpassing treatments with free curcumin, in terms of efficacy and overall results (Ombredane et al., 2021).

4.2 | Drug discovery strategies to overcome drug resistance

Drug resistance is a complex, multifactorial process, and it can vary from person to person as well as from tumour to tumour. Like many other cancer therapies, natural products that have anti-angiogenesis effects can also encounter drug resistance. Tumours can adapt to

TABLE 6 Anti-angiogenic terpenoids and their sources, experimental models and mechanisms.

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Monoterpenoid	Perillyl alcohol	Essential oils of lavendin, mints, cherries	K562 lymphoblastoma cells, B16 skin melanoma cells, MDA-MB-231 cells, HUVECs, bovine lung microvascular endothelial cells (BLMVECs), CAM assay	- Modulates the release of VEGF and **Ang2** - Suppresses neovascularization and induces vessel regression	(Loutrari et al., 2004)
Monoterpenoid	Linalool	Essential oils of, rose, lavender, orange	HDMECs, aortic ring assay	- Downregulates intracellular ATP levels and activates **TRPM8**	(Becker et al., 2021)
Monoterpenoid	Geraniol	*Monarda fistulosa*, ninde oil, rose oil, palmarosa oil, citronella oil	Murine endothelial-like eEND2 cells, aortic ring assay, CT26 xenograft mice model	- Blocks VEGF/VEGFR-2 signal transduction - Decreases Ki67-positive cells and CD31-positive microvessels	(Wittig et al., 2015)
Sesquiterpene	Aspfalcolide	*Asparagus falcatus* L.	HUVECs	- Inhibits VEGF-induced HUVECs proliferation, migration and tube formation	(Ghalib et al., 2012)
Sesquiterpene	Costunolide	*Saussurea lappa*	HUVECs, mouse corneal neovascularization assay	- Inhibits the autophosphorylation of KDR/Flk-1 (VEGFR-2) without affecting that of Flt-1	(Jeong et al., 2002)
Sesquiterpene	Dehydrocostuslactone	*Saussurea costus* (Falc.)	HUVECs, matrigel-plug nude mice mode	- Inhibits AKT/GSK-3β and mTOR signalling pathways	(Wang, Tsai, et al., 2012)
Sesquiterpene	5α-hydroxycostic acid and hydroxyisocostic acid	*Laggera alata*	MCF-7 breast cancer cells, HUVECs	- Downregulates VEGF-stimulated HUVEC migration, stress fibres, tube formation - Inhibits Ang2-induced phosphorylation of the receptor Tie2	(Liang, Li, & Chung, 2017)
Sesquiterpene	β-Elemene	*Rhizoma zedoariae, curcuma Wenyujin*	HUVECs, HemECs, mice, Hep2 xenograft mice model, hemangioma tissues and the matched adjacent normal tissues from patients	- Reduces expression of **ACE2**, HIF-1α, VEGF	(Wang et al., 2021)
Sesquiterpene	Alantolactone	*Inula helenium*	HUVECs, CAM assay, MDA-MB-231 xenograft mice model	- Suppresses p-VEGFR-2 and its downstream protein kinases, including PLCγ1, FAK, Src, AKT	(Liu, Cai, et al., 2018)
Sesquiterpene	Artemisinin	*Artemisia annua*	MDA-MB-231 cells, NIH-3 T3 and endometrium cells, HUVECs, MDA-MB-231 xenograft mice model	- Decreases the serum VEGF and HIF-1α - Downregulates the expression of notch signalling-related factors **notch1**, **Dll4** and Jagged1	(Dong et al., 2020)
Sesquiterpene	Bigelovin	*Inula helianthus-aquatica*	THP-1 acute monocytic leukaemia cells, HMEC-1, transgenic zebrafish line Tg (fli1a:EGFP)y1	- Inhibits the human monocyte adhesion to human ECs and the gene expressions of inflammation-related CAMs	(Yue et al., 2013)
Sesquiterpene	Codonolactone	*Atractylodes lancea*			(Wang et al., 2015)

TABLE 6 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
			HUVECs, EA.hy 926 cells, MDA-MB-231 and MDA-MB-468 cells	- Downregulates **BMP** signalling and Runx2 activation - Downregulates MMPs and VEGF-VEGFR-2	
Sesquiterpene	Cyperenoic acid	*Croton crassifolius* Geisel	MDA-MB-231 cells, HUVECs, MDA-MB-231 xenograft mice model	- Suppresses VEGF-induced angiogenesis - Suppresses tumour growth but no obvious toxic pathologic changes	(Huang et al., 2020)
Sesquiterpene	Calamusins J-K	*Sarcophyton glaucum*	Caco-2 cells, MCF-7 breast cancer cells, immortalized normal epithelium (hTERT-RPE1) cells	- Inactivation of VEGFR-2 enzyme	(Shaaban et al., 2021)
Sesquiterpene	Umbelliprenin	Coriander, celery, lemon, Angelica and ferula specie	MDA-MB-231 cells, 4 T1 xenograft mice model	- Downregulates CoCl2/EGF-mediated PI3K/AKT/ERK signalling	(Mahmoodi Khatonabadi et al., 2022)
Sesquiterpene	Cedrol	*Juniperus chinensis*	HT29 cells, HT29 xenograft mice model	- Downregulates minichromosome maintenance proteins	(Jin et al., 2022)
Sesquiterpene	Torilin	*Torilis japonica*	HT1080 fibrosarcoma cells, HepG2 hepatoblastoma cells, NIH3T3 fibroblast cells, HUVECs, BAECs, CAM assay, mouse matrigel plug assay	- Downregulates expression of hypoxia-inducible VEGF and IGF-II	(Kim et al., 2000)
Sesquiterpene	Widdrol	*J. chinensis*	HUVECs, HT29 xenograft mice model	- Inhibits the cell migration and tube formation of HUVECs - Suppresses phosphorylation of VEGFR-2 and its downstream proteins, such as AKT, FAK and eNOS	(Jin et al., 2015)
Sesquiterpene	Zerumbone	*Zingiber zerumbet* Smith	HUVECs, matrigel plug assay, rat aorta explants	- Inhibits phosphorylation of VEGFR-2 and FGFR1	(Ju-Hyung et al., 2015)
Sesquiterpene	α-Zingiberene	Essential oil from leaves of *Casearia sylvestris*	Subcutaneous sponge implants in an animal model	- Reduction in macrophage activation, mean blood vessels and the activity of MMP2/9	(Ferreira et al., 2022)
Diterpenoid	Andrographolide	*Andrographis paniculata*	HUVECs, matrigel plug assay, Hep3B xenograft mice model	- Inhibits VEGF-A-induced angiogenesis - Blocks VEGF-A-induced phosphorylated activation of VEGFR-2 and its downstream MAPKs	(Shen et al., 2014)

(Continues)

TABLE 6 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
				- Interferes with binding of VEGFA to VEGFR-2	
Diterpenoid	Crassifolin A, B, F, H, I	*C. crassifolius*	Tg (fli1a:EGFP)y1-type zebrafish embryos	- Displays strong inhibition in the vessel formation	(Wang, Chung, et al. 2016)
Diterpenoid	Casearlucin A	*Casearia graveolens*	HepG2, Hela, A549 cells, adult AB strain zebrafish, transgenic zebrafish Tg (fli1: EGFP), HepG2 xenograft zebrafish model	- Inhibits HepG2 cell migration via regulating a few of metastasis-related proteins - Inhibits tumour angiogenesis in zebrafish	(Li, Ma, et al., 2016)
Diterpenoid	CHKA	*Wedelia chinensis*	HUVECs, embryos of the Tg (fli1a: EGFP) y1-type zebrafish, aortic ring assay, matrigel plug assay	- Inhibits a series of VEGF-induced angiogenesis processes - Inhibits VEGFR-2 tyrosine kinase activity and its downstream signalling pathways	(Huang et al., 2016)
Diterpenoid	Penduliflaworosin	*C. crassifolius*	HEp-2, HepG2, MCF7, CNE cells, HUVECs, matrigel plug assay, aortic ring assay, Tg (fli1a:EGFP)y1-type zebrafish embryos, Sprague–Dawley rats	- Inhibits VEGFR-2 signalling pathway - Inhibits VEGF-induced sprout formation of aortic rings and blocks VEGF-induced vessel formation	(Liang, Zhang, et al., 2017)
Diterpenoid	Cafestol	Unfiltered coffee beverages	HUVECs	- Inhibits tube formation and migration of VEGF-stimulated HUVEC - Inhibits phosphorylation of FAK and AKT - Decreases NO production	(Wang, Yoon, et al., 2012)
Diterpenoid	Eriocalyxin B	*Isodon eriocalyx var. laxiflora*	HUVECs, transgenic zebrafish line Tg (fli1:EGFP)y1, matrigel plug model, 4 T1 xenograft mice model	- Suppression of VEGFR-2 downstream signal transduction cascades	(Zhou et al., 2016)
Diterpenoid	16-hydroxy-pentandralactone	*Vitex cofassus*	HUVECs	- Inhibits VEGF-stimulated HUVEC proliferation	(Rasyid et al., 2017)
Diterpenoid	Triptolide	*Tripterygium wilfordii* Hook. f.	A549 lung cancer cells, B16 and HaCaT cells, human immortalized skin HaCaT keratinocytes, HUVECs, mouse matrigel plug assay, B16 melanoma cells	- Downregulates **Tie2** and VEGFR-2 expression	(He et al., 2010)
Diterpenoid	Tanshinone IIA	Dried root and rootstock of *Salvia miltiorrhiza* Bunge	A2780 and ID-8 ovarian cancer cells, A2780 xenograft mice model	- Downregulates Bcl-2, VEGF and COX-2 - Upregulates Bax - Inhibits focal adhesion kinase phosphorylation,	(Zhou, Jiang, et al., 2020)
Diterpenoid	Phytol	*Hypericum* sp., *Tortula muralis*		- Inhibits CAM vascular growth	(Sakthivel et al., 2018)

TABLE 6 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
			A549 lung adenocarcinoma cells, L-132 normal human lung cells, CAM assay		
Triterpenoid	Lupeol	*Azadirachta indica*	RMCCA-1 and KKU-M213 cholangiocarcinoma cells, HUVECs, RMCCA-1 and KKU-M213 xenograft mice model, Wistar rats	- Docks to AKT binding pocket - Downregulates expression of proangiogenic mRNAs	(Akinloye et al., 2021)
Triterpenoid	Oleanolic acid	*Olea europaea*	MCF-7 and MCF-7/ADR breast cancer cells, HepG2 and Hep3B hepatocellular carcinoma cells, HUVECs, CAM assay	- Binds to VEGFR-2 and inhibits VEGFR-2 phosphorylation - Inhibits STAT3 and SHH signalling pathways - Reduces the expression of VEGF-A and bFGF	(Tang et al., 2022)
Triterpenoid	Boswellic acid	*Boswellia serrata*, *Boswellia carterii* Birdw	Murine sponge model	- Decreases vascularization, TNF-α, TGF-β1 - Decreases expression of VEGF, CD31 and microvessel density	(Saraswati et al., 2011)
Triterpenoid	Betulinic acid	*Betula* ssp.	BAECs, HUVECs	- Inhibits bFGF-induced invasion and tube formation - Modulation of mitochondrial function rather than aminopeptidase N activity	(Kwon et al., 2002)
Triterpenoid	Acetyl-11-keto-β-boswellic acid	*B. serrata*	HUVECs, rat aortic ring assay, matrigel plug assay in mice	- Suppresses VEGF-induced p-VEGFR-2 - Inhibits angiogenesis via VEGFR-2 signalling pathways	(Pang, Yi, Yi, et al., 2009)
Triterpenoid	Ursolic acid	*Hedyotic diffusa, Spica prunellae, Patrinia scabiosaefolia, Scutellaria barbata*	HT-29 colon carcinoma cells, HUVECs, CAM assay, HT-29 xenograft mice model	- Inhibits tumour volume and does not affect body weight changes - Inhibits the expression of critical angiogenic factors, such as VEGFA and bFGF - Suppresses the activation of SHH, STAT3, AKT and **p70S6K** pathways	(Lin et al., 2013)
Triterpenoid	Koetjapic acid	*Sandoricum koetjape*	HUVECs, rat aortic ring assay, Sprague Dawley male rats	- Inhibits new blood vessels growth and VEGF expression - Suppresses migration and differentiation of ECs	(Nassar et al., 2011)
Triterpenoid	Nimbolide	*A. indica*	WiDr colon adenocarcinoma cells, HCT-116, colon adenocarcinoma cells, HUVECs	- Inhibits ERK1/2 and activation of p38 and JNK1/2 - Inhibits MMP2/9 expression	(Babykutty et al., 2012)

(Continues)

TABLE 6 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
				- Suppresses nuclear translocation of p65/p50 and DNA binding of NF-κB	
Triterpenoid	Ganoderic acid F	*Ganoderma lucidum*	A549 non-small cell lung adenocarcinoma, MCF-7 breast adenocarcinoma, PC-3 prostatic small cell carcinoma, HUVECs	- Inhibits the formation of capillary-like structures	(Nguyen et al., 2015)
Triterpenoid	Pristimerin	*Celastrus* and *Maytenus* spp.	HUVECs, rat aortic ring assay, CAM assay, MDA-MB-231 xenograft mice model	- Suppresses VEGF-induced phosphorylation of VEGFR-2 and the activity of AKT, ERK1/2, mTOR, ribosomal protein S6 kinase	(Mu et al., 2012)

Abbreviations: ANG, angiostatin (plasminogen); CAM, chicken chorioallantoic membrane; EAC, Ehrlich ascites carcinoma; MMPs, matrix metalloproteases.

natural products over time and continue to grow despite treatment. The development of drug resistance related to natural products can be divided into two main mechanisms: One possible mechanism is the upregulation of alternative angiogenesis pathways or promoting tumour cell survival, such as the recruitment of bone marrow-derived cells to promote tumour growth (Bergers & Hanahan, 2008). Another mechanism is the development of genetic mutations or changes in the tumour microenvironment, which allow the tumour to become less dependent on angiogenesis (Jain et al., 2009). Some examples of natural products which trigger this type of resistance are curcumin, **resveratrol** and **epigallocatechin-3-gallate (EGCG**; Aggarwal et al., 2013).

Ongoing research is focused on developing new strategies to improve the effectiveness of anti-angiogenic therapies and overcome drug resistance. As mentioned earlier, nanoparticle-based delivery systems are capable of improving the bioavailability. This technology can also target specificity of natural products. For example, resveratrol-loaded nanoparticles enhanced the anti-angiogenic effects of resveratrol in breast cancer cells (Zu et al., 2016). One mechanism of drug resistance to anti-angiogenic therapy is the upregulation of alternative angiogenesis pathways. Therefore, targeting these alternative pathways may be a promising approach to overcoming drug resistance.

Identifying and developing new VEGFR-2 inhibitors would also be an effective method. A variety of techniques have encountered numerous breakthroughs. Structural biology techniques such as X-ray crystallography and NMR spectroscopy have been used to determine the three-dimensional structures of VEGFRs and their ligands (Shimada et al., 2019). This information has been used to identify the specific binding sites on VEGFRs. Based on the knowledge of the binding sites and the interactions between VEGFRs and their ligands, structure- and ligand-based drug designs have been widely applied in the development of natural-based lead compounds containing novel scaffolds and the molecular optimization of VEGFR-2 inhibitors. Furthermore, computer-aided drug design in combination with artificial intelligence and machine learning approaches provides an opportunity to develop novel natural-based compounds (Díaz et al., 2019). These strategies provide a comprehensive overview of the molecular mechanisms of ligand-protein interactions and promote the identification of potential natural-based VEGFR inhibitors via predicting structural similarity or reliable analyses of relevant signalling pathways (Figure 2).

4.3 | Combinations of natural products and VEGF/VEGFR-2 inhibitors

There is a growing interest in the potential of natural products to enhance the efficacy of VEGF/VEGFR-2 inhibitors and improve outcomes in cancer and other diseases. Natural products, including curcumin, resveratrol, green tea polyphenols, **quercetin** and **genistein**, can act synergistically with VEGF/VEGFR-2 inhibitors to enhance their anti-angiogenic effects (Table 8).

TABLE 7 Anti-angiogenic terpenoids and their sources, experimental models and mechanisms.

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Steroidal saponin	DT-13	Dwarf lilyturf tuber	HUVECs	- Suppresses the increased level of HIF-1α, p-extracellular signal-regulated kinase 1/2 and p-AKT - Suppresses VEGF excretion and p-VEGFR-2	(Zhao, Sun, et al., 2013)
Steroidal saponin	Dioscin	*Dioscorea opposita* Thunb.	B16F10 and A375 melanoma cells, HUVEC cells, CAM assay, B16F10 xenograft mice model	- Inhibits Src/STAT3 signalling-mediated angiogenesis	(Liu, Xu, et al., 2022)
Steroidal saponin	Paris saponin I, II, VI and VII	Rhizoma Paris	HUVECs	- Modulates VEGF2, PI3K/AKT/mTOR, Src/eNOS, PLCγ/ERK/MERK, JAK2-STAT3 pathways	(Wang et al., 2020)
Steroidal saponin	Polyphyllin D	*Paris polyphylla*	HMEC-1 cells, transgenic zebrafish line TG (flil: EGFP)	- Inhibits angiogenesis by suppressing cell proliferation, migration and tube formation - Impairs the formation of intersegmental vessels in zebrafish embryos	(Chan et al., 2011)
Steroidal saponin	Timosaponin AIII	*Anemarrhena asphodeloides* Bge	HUVECs, transgenic zebrafish line Tg (fli-1a: EGFP)y1	- Mediates through VEGF/PI3K/AKT/MAPK signalling cascade	(Zhou, Zhao, et al., 2020)
Sulfated triterpenoid saponin	Philinopside E (PE)	*Pentacta quadrangularis* (sea cucumber)	MKN-28 gastric adenocarcinoma cells, HCT-116 colon adenocarcinoma cells, MDA-MB-468 and MCF-7 breast adenocarcinoma cells, BEL-7402 hepatocellular carcinoma cells, SPC-A4 lung adenocarcinoma cells, HO-8910 ovarian epitheloid carcinoma cells, HUVECs, HMECs, CAM assay, sarcoma 180 or hepatoma 22 xenograft mice models	- Inactivates VEGFR-2 phosphorylation and downstream signalling	(Tian et al., 2005)
Triterpenoid saponin	AG36	*Ardisia gigantifolia* Stapf	HUVECs, MDA-MB-157 xenograft mice model	- Inhibits expressions of p-VEGFR-2 and p-AKT	(Mu et al., 2020)
Triterpenoid saponin	Capilliposide B	*Lysimachia capillipes* Hemsl	HRECs	- Inhibits VEGF-induced activation of VEGFR-2 and its downstream enzymes AKT and ERK	(Han et al., 2021)
Triterpenoid saponin	Gleditsioside B	*Gleditsia sinensis* Lam.	HUVECs	- Prevents the activation of MMP2 and FAK via inhibiting ERK and PI3K/AKT pathways	(Tong et al., 2013)
Triterpenoid saponin	Saikosaponin A (SSA), Saikosaponin D	*Radix Bupleurum*	4 T1 breast cancer cells, HUVECs, matrigel plug model, HCT-15 xenograft mice model	- Inhibits phosphorylation of VEGFR-2 - Downregulates PLCγ1, FAK, Src, AKT downstream pathways	(Zhang et al., 2021)

(Continues)

TABLE 7 (Continued)

Category	Name	Source	Experimental model	Anti-angiogenic mechanism	Reference
Triterpenoid saponin	Theasaponin E_1 (TSE1)	*Camellia sinensis*	OVCAR-3 and A2780/CP70 platinum-resistant ovarian cancer cells, IOSE-364 normal ovarian surface epithelial cells	- Represses HIF-1α expression - Inhibits AKT, mTOR, p70S6K and 4E-BP1 phosphorylation	(Li, Jiang, et al., 2021)
Triterpenoid saponin	Ginsenoside Rg3	*Panax ginseng*	B16 melanoma cells, B16 xenograft mice model	- Downregulates MMP2/9 and VEGF - Suppresses ERK and AKT signalling	(Meng et al., 2019)
Triterpenoid saponin	Ginsenoside Rh2	*P. ginseng* C.A	LNCaP, PC3 and DU145 prostate cancer cells	- Suppresses expression of CD31, VEGF, PDGF and CNNM1 genes	(Huang, Huang, et al., 2019)
Triterpenoid saponin	Platycodin D	*Platycodon grandiflorum*	HCT-15 colorectal adenocarcinoma cells, HUVECs, CAM assay, HCT-15 xenograft mice model	- Blocks VEGFR-2-mediated signalling pathway	(Luan et al., 2014)
Triterpenoid saponin	Escin	*Aesculus hippocastanum*	BxPC-3, AsPC-1 and SW1990 pancreatic adenocarcinoma cells, EA.hy 926	- Suppresses mRNA expression levels of TNF- α-induced IL-8 and VEGF - Reduces the secretion of IL-8 and VEGF by blocking NF-κB activity	(Omi et al., 2021)
Triterpenoid saponin	Oldhamianoside II	*Gypsophila oldhamiana*	SGC7901 and S180 cells, HUVECs, S180 xenograft mice model	- Reduces the expression of VEGF, bFGF and COX-2	(Wang et al., 2013)
Triterpenoid saponin	*Pulsatilla* saponin D (PSD)	*Pulsatilla koreana*	HT-29 and LoVo colon cancer cells, HUVECs, matrigel plug model, HT-29 xenograft mice model	- Decreases HIF-1α and VEGF - Suppresses the tube formation and migration of HUVEC	(Hong et al., 2012; Son et al., 2013)
Triterpenoid saponin	Raddeanin A (RA)	*Anemone raddeana* regel.	HUVECs, HCT-15 colorectal tumour cells, CAM assay, fli1a: EGFP transgenic zebrafishes, HCT-15 xenograft mice model	- Suppresses VEGF-induced phosphorylation of VEGFR-2 and its downstream protein kinases including PLCγ1, JAK2, FAK, Src, AKT	(Guan et al., 2015)
Triterpenoid saponin	Chiisanoside	Leaves of *Acanthopanax sessiliflorus*	Hepatoma 22 (H_{22}) cells, H_{22} xenograft mice model, male Wistar rats	- Promotes apoptosis and inhibits angiogenesis - Displays trait of fast absorption and rapid elimination in rats	(Bian et al., 2017)

Abbreviations: bFGF basic fibroblast growth factor, CAM chicken chorioallantoic membrane HMEC; cells, human microvascular endothelial cells; MMPs, matrix metalloproteases, NF-κB, nuclear factor-κB.

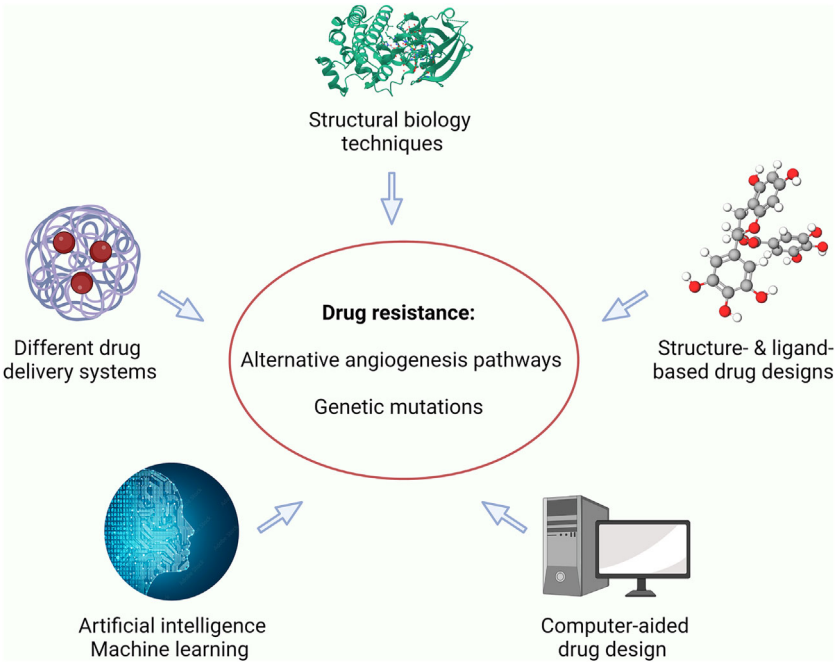

FIGURE 2 Drug discovery strategies to overcome drug resistance. The figure is drawn with biorender; https://app.biorender.com/.

Curcumin can act synergistically with bevacizumab, sorafenib and sunitinib. The combination of curcumin and the VEGF blocker bevacizumab is capable of inhibiting hepatocellular carcinoma progression by regulating the VEGF/VEGFR/K-Ras pathway (Gao et al., 2015). Additionally, curcumin enhanced the antitumor effects of sorafenib by regulating the metabolism and tumour microenvironment (Man et al., 2020). Curcumin potentiates the ability of sunitinib to eliminate von Hippel–Lindau (VHL)-lacking renal cancer cells (Ranjan Debata et al., 2013). Encouragingly, curcumin reverses the sunitinib resistance in clear cell renal cell carcinoma (ccRCC) through induction of ferroptosis via the ***ADAMTS18*** gene (Xu et al., 2021). Likewise, resveratrol can act synergistically with bevacizumab, and sorafenib. Resveratrol reverses the adverse effects of bevacizumab on the human retinal pigment epithelial cell line (Subramani et al., 2017). Moreover, Resveratrol potentiates Sorafenib in human breast cancer MDA-MB-231 cells (lo bennett, 2020).

The most abundant and well-studied polyphenols in green tea are epigallocatechin-3-gallate, **epicatechin gallate**, **epigallocatechin** and **epicatechin**. Epigallocatechin-3-gallate in particular has been shown to inhibit angiogenesis and enhance the anti-tumour effects of VEGF/VEGFR-2 inhibitors in preclinical studies. The combination of low-dose sorafenib and epigallocatechin-3-gallate displays an anti-angiogenic effect in hepatocellular carcinoma-induced Wistar rats (Irawan et al., 2022). Quercetin and sorafenib are a novel and effective couple in programmed cell death induction in human gliomas (Jakubowicz-Gil et al., 2014). In the phase I/II pilot study, genistein is combined with FOLFOX or FOLFOX-bevacizumab for the treatment of metastatic colorectal cancer (Pintova et al., 2019).

The mechanism through which natural products enhance the anti-angiogenic effects of VEGF/VEGFR-2 inhibitors is not fully understood but may involve multiple pathways. For example, targeting other angiogenic signalling pathways or modulating the tumour microenvironment to enhance the effects of VEGF/VEGFR-2 inhibitors. More research is still needed to understand the optimal combinations and dosing strategies for these natural products and VEGF/VEGFR-2 inhibitors.

4.4 | Testing of dosage and side effects of natural products *in vivo*

Natural products have undergone extensive *in vivo* testing to assess their safety and potential side effects, which widely vary depending on the specific product, experimental model employed, its concentration/dosage, and the duration of treatment. It is evident that there is a scarcity of clinical trials in comparison with *in vivo* studies. Given the significance of in vivo dosages as crucial references for potential clinical applications, it is imperative to thoroughly evaluate the safety of dosage *in vivo*.

Some natural products are well-tolerated and safe in vivo, while others may exhibit potential side effects or interactions with certain medications. For instance, a study investigating the effects of curcumin treatment on U-87 human glioblastoma cells, employed initial dosing with daily i.p. injections of 30, 60 and 120 $mg{\cdot}kg^{-1}$ starting from day 5 after inoculation. Interestingly, no obvious side effects of curcumin treatment were observed throughout the entire investigation (Perry et al., 2010). Similarly, if administering a dose of 70 $mg{\cdot}kg^{-1}$ of epigallocatechin-3-gallate or 400 $mg{\cdot}kg^{-1}$ of dandelion polysaccharide, no associated side effects were reported (Ren et al., 2019). Notably, in human volunteers, significantly higher doses of epigallocatechin-3-gallate, up to 10-fold greater, were administered with minimal to no adverse effects, suggesting a well-tolerated nature and potential therapeutic application (Fassina et al., 2004). On the other hand, toxicity and adverse effects were reported following

TABLE 8 Combinations of natural products and VEGF/VEGFR-2 inhibitors.

Natural products	VEGF/VEGFR-2 inhibitors	Experimental model	Mechanisms	Reference
Curcumin	Bevacizumab	Sprague Dawley rat hepatoma model	- Displays a synergistic effect on the inhibition of VEGF/VEGFR/K-Ras pathway	(Gao et al., 2015)
Curcumin	Sorafenib	H22-bearing mice	- Inhibits epithelial-to-mesenchymal transition (EMT) via the regulation of IL-6/JAK/STAT3 and IL-1β/NF-κB pathways - Activates immune function by increasing the number of immune cells, like NK cells	(Man et al., 2020)
Curcumin	Sorafenib	FTC133 thyroid cancer cells	- Inhibits PI3K/AKT and ERK pathways	(Zhang et al., 2016)
Curcumin	Sunitinib	786-O renal cancer cells	- Inhibits hyperphosphorylation of the tumour suppressor protein Rb	(Ranjan Debata et al., 2013)
Curcumin	Sunitinib	Sunitinib-resistant ccRCC cell model	- Inhibits ferroptosis-related protein expression	(Xu et al., 2021)
Curcumin	Regorafenib	HCT 116 colorectal cancer cells, HT-29 cells	- Curcumin enhances regorafenib-induced growth inhibition, apoptosis and autophagy	(Wu et al., 2019)
Curcumin	Lenvatinib	Resistant Huh-7 and PLC-PRF-5 hepatocellular carcinoma cell lines	- Anti-EFGR potential of curcumin might help overcome lenvatinib resistance in hepatocellular carcinoma	(Miyazaki et al., 2023)
Curcumin	Apatinib	MCF7 cells	- Combination therapy exerts more profound anti-proliferation effects on breast cancer cell	(Farhoudi Sefidan Jadid et al., 2023)
Resveratrol	Sorafenib	MDA-MB-231 cells	- Decreases cancer cell proliferation and progression - Potentiates sorafenib as an anticancer drug in breast cancer	(lo bennett, 2020)
Resveratrol	Sorafenib	MCF7 cells	- Resveratrol enhances the efficacy of sorafenib-mediated apoptosis through ROS, cell cycle inhibition, caspase 3 and **PARP** cleavage	(Mondal & Bennett, 2016)
Resveratrol	Sorafenib	HepG2 and Huh7 hepatocellular carcinoma cell lines, BALB/c nude mice	- Inhibits PKA/AMPK/eEF2K pathway	(Gao et al., 2021)
Resveratrol	Bevacizumab	ARPE-19 retinal pigment epithelial cell line	- Inhibits epithelial-to-mesenchymal transition - Reverses the adverse effects that precipitate fibrotic changes, drusen formation, tractional retinal detachment	(Subramani et al., 2017)
EGCG	Sorafenib	hepatocellular carcinoma-induced Wistar rats	- Decreases the level of VEGF - Reduces the expression of microvascular density and could prevent resistance and lower toxicity effects	(Irawan et al., 2022)
Quercetin	Sorafenib	Human anaplastic astrocytoma (MOGGCCM) and glioblastoma multiforme (T98G) cell lines	- Potentiates the proapoptotic properties of sorafenib - Increases the number of autophagic cells	(Jakubowicz-Gil et al., 2014)
Genistein	FOLFOX or FOLFOX-bevacizumab	Phase I/II pilot study, metastatic colorectal cancer patients	- Safe and tolerable, notable efficacy	(Pintova et al., 2019)

Abbreviations: EGC, epigallocatechin; EGCG, epigallocatechin-3-gallate, NF-κB, nuclear factor-κB.

the consumption of resveratrol. An acceptable daily intake of resveratrol was defined as 450 mg·kg^{-1}, while very high doses of resveratrol were found to be associated with some adverse effects, including diarrhoea, nausea, anaemia and abdominal discomfort (Shaito et al., 2020). Therefore, it is crucial to recognize that the safety and potential side effects of natural products are highly product-specific, and further research is needed to better understand their optimal dosing, long-term effects as well as the *in vivo* adverse effects for potential therapeutic use.

4.5 | Clinical trials of natural products as an anti-angiogenic therapy

There have been several clinical trials investigating the use of natural products to inhibit angiogenesis in cancer and other diseases, such as curcumin, resveratrol, green tea polyphenols, quercetin, lutein, zeaxanthin and soy isoflavones.

Curcumin has been studied for its anti-angiogenic effects in cancer patients. A phase II clinical trial showed that curcumin can inhibit angiogenesis and improve the response to chemotherapy in patients with advanced colorectal cancer (He et al., 2011). Another clinical trial showed that combination treatment with curcumin and quercetin can reduce the size and number of polyps in patients with familial adenomatous polyposis, a condition that predisposes them to colorectal cancer. In this study, Curcumin was suggested to have anti-inflammatory and anti-angiogenic properties which could contribute to this effect (Cruz-Correa et al., 2006). In the phase II clinical trial, the anti-angiogenic activity of curcumin was evaluated in patients with advanced pancreatic cancer. Curcumin was well-tolerated, and it appeared to have anti-angiogenic effects, as evidenced by a decrease in serum VEGF levels (Kanai et al., 2011).

Resveratrol can reduce the number of circulating ECs, which are involved in angiogenesis, in patients with colorectal cancer (Patel et al., 2010). Another clinical trial showed that Resveratrol can inhibit angiogenesis and improve the response to chemotherapy in patients with metastatic colorectal cancer (Howells et al., 2011).

Green tea catechins, such as epigallocatechin-3-gallate, have been studied for their anti-angiogenic effects in cancer patients. A clinical trial showed that epigallocatechin-3-gallate can reduce the levels of VEGF in patients with advanced solid tumours (Khan & Mukhtar, 2007). These findings suggest that epigallocatechin-3-gallate may have anti-angiogenic and anti-tumour effects in patients with advanced solid tumours. In the phase II clinical trial, the anti-angiogenic effects of green tea polyphenols were evaluated in patients with prostate cancer. The green tea polyphenols were well-tolerated and had some anti-angiogenic activity, as evidenced by a decrease in serum VEGF levels (McLarty et al., 2009).

While these clinical trials suggest that natural products may have anti-angiogenic effects, further research is needed to fully evaluate their efficacy and safety as anti-angiogenic agents. It is essential to conduct well-designed clinical trials with appropriate patient selection, dosing and outcome measures to establish the therapeutic potential of natural products as anti-angiogenic agents.

5 | CLOSING REMARKS

It is evident from the research reviewed here that natural products exert great potential in developing anti-angiogenesis and anti-cancer therapies, especially if their diverse structures and multiple mechanisms of action are taken into account. Additionally, natural products have less toxic side effects and better tolerance, which are important advantages for the development of new drugs. However, there are still some challenges associated with the difficulty of extraction and processing and poor bioavailability caused by the complexity of active ingredients in natural products, and the unclear mechanism of action, which makes their use for clinical treatment difficult. Further attempts need to be performed to discover unique and active natural products targeting angiogenesis and elucidate the in-depth mechanism of action by using high-throughput screening, genomics analysis, and other methods. Furthermore, rational computer-aided design technology or new drug delivery technology enable natural products as potential lead structures to be modified with enhanced anti-angiogenesis activities and high selectivity. It is important to mention, that combination treatment is thought of as a promising therapeutic choice, while considering safety and tolerance. Additional efforts need to be made to improve well-designed clinical trials and clinical combination use of natural products.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander et al., 2021a,b).

AUTHOR CONTRIBUTIONS

Xiaohua Lu: Conceptualization (lead); data curation (lead) and writing—original draft (lead). **Lara Johanna Friedrich:** Writing–review and editing (equal). **Thomas Efferth**: Funding acquisition (lead); supervision (lead) and writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

N/A-Review.

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