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REVIEW ARTICLE

Natural products-based antiangiogenic agents: New frontiers in cancer therapy

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Abstract

Angiogenesis, vital for tumor growth and metastasis, is a promising target in cancer therapy. Natural compounds offer potential as antiangiogenic agents with reduced toxicity. This review provides a comprehensive overview of natural product-based antiangiogenic therapies, focusing on molecular mechanisms and therapeutic potential. A systematic search identified relevant articles from 2019 to 2023. Various natural compounds, including polyphenols, terpenes, alkaloids, cannabinoids, omega-3 fatty acids, polysaccharides, proteins, and carotenoids, were investigated for their antian-

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giogenic properties. Challenges such as dose standardization, routes of administration, and potential side effects remain. Further studies, including in-depth animal models and human epidemiological studies, must elucidate clinical efficacy and safety. Synergistic effects with current antiangiogenic therapies, such as bevacizumab and tyrosine kinase inhibitors, should be explored. Additionally, the potential hormone-dependent effects of compounds like genistein highlight the need for safety evaluation. In conclusion, natural products hold promise as adjunctive therapies to conventional antineoplastic drugs in modulating angiogenesis in cancer. However, robust clinical trials are needed to validate preclinical findings and ensure safety and efficacy.

KEYWORDS
angiogenesis, antiangiogenic therapy, cancer treatment, molecular mechanisms, natural compounds

1 | INTRODUCTION

Angiogenesis, the process by which pre-existing blood and lymphatic vessels divide to generate new ones, is fundamental for the growth and metastasis of tumors (Liu et al., 2023). The intricate process of angiogenesis, meticulously regulated in healthy tissues, can become dysregulated in cancer, leading to an aberrant formation of new blood vessels. Tumor cells secrete an abundance of proangiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), tipping the scales in favor of excessive blood vessel growth (Marech et al., 2016). This neovascularization provides the tumor with a vital lifeline, ensuring a steady supply of nutrients and oxygen to support its growth and metastasis (Nishida et al., 2006; Wendong et al., 2024). In this context, angiogenesis plays a vital role in cancer progression, making it a promising therapeutic target; by inhibiting tumor angiogenesis, researchers aim to starve tumors, prevent metastasis, and boost the efficacy of conventional cancer treatments, thereby improving patient outcomes (Rajabi & Mousa, 2017). The potential of natural compounds as anticancer agents is becoming more widely recognized (Kitic et al., 2024; Shaheen et al., 2024; Sharma et al., 2019). These substances originate from microbes, plants, and animals and include various chemical compounds (Herrera-Bravo et al., 2024; Khatua et al., 2024). While antiangiogenic therapies have shown promise in cancer treatment, their limitations, such as tumor resistance and side effects, highlight the need for safe alternative approaches (Ribatti et al., 2019). Natural products offer a promising avenue for developing novel antiangiogenic agents with enhanced efficacy and reduced toxicity (R. Li et al., 2021). Although considerable research has been carried out in recent years, further studies on the mechanisms of action and clinical efficacy of natural products are required to fully explore their potential as effective therapeutic strategies for cancer. In this context, this review article aims to provide a comprehensive overview of the current status, latest updates, and future perspectives of natural product-based antiangiogenic therapies. First, we address the molecular basis of angiogenesis and cancer. Then, we discuss several classes of natural compounds from plants and animals with antiangiogenic activities concerning their molecular mechanisms and therapeutic potential. Moreover, we describe preclinical and clinical studies and molecular targets of natural products in angiogenesis, and we mention the advantages and challenges of using these compounds as antiangiogenic agents. Finally, we discuss the challenges and future directions of these emergent antiangiogenesis food-derived substances. In conclusion, although diverse pharmaceutical agents targeting angiogenesis have received approval for specific cancer types, growing evidence suggests that common food constituents may also possess antiangiogenic effects. Therefore, this review represents a comprehensive outlook emphasizing that investigating dietary compounds' potential antiangiogenic properties represents an attractive and emergent scientific research field.

2 | REVIEW METHODOLOGY

This review systematically synthesizes the current literature on the antiangiogenic effects of natural compounds in cancer treatment. A detailed database search was followed by a qualitative synthesis of the extracted data to elucidate the molecular mechanisms through which these compounds act and their potential therapeutic implications. Three major electronic databases were searched: PubMed, Scopus, and Web of Science, covering publications from January 2019 to November 2023. The search strategy incorporated Medical Subject Headings (MeSH) and keywords related to "angiogenesis," "cancer," and "natural compounds." Specific names of natural compounds such as polyphenols, terpenes, alkaloids, cannabinoids, omega-3 fatty acids, polysaccharides, proteins, and carotenoids were also included. Boolean

operators "AND" and "OR" were utilized to combine search terms effectively. Inclusion criteria included studies discussing natural compounds' antiangiogenic effects on cancer models, articles written in English, and publications providing detailed mechanistic insights or clinical relevance. Review reviews, meta-analyses, randomized controlled trials, cohort studies, and laboratory-based experimental studies were considered for inclusion. Exclusions were applied to duplicate studies, non-English articles, and publications lacking primary data or clear methodologies.

3 | ANGIOGENESIS AND CANCER: A BRIEF OVERVIEW

As tumoral masses develop beyond the reach of O_2 diffusion, typically 1–2 mm in diameter, they require additional internal blood supply to deliver nutrients, sustain growth, and avoid hypoxic cell death (De Palma et al., 2017; Iqbal et al., 2024; Mortezaee, 2021; Sung et al., 2019). Tumors have long been found to develop their blood supply during their early phases when they reach only millimeters in diameter (Batlle et al., 2019; Kerbel & Folkman, 2002). This ability to induce or access vasculature to support tumor growth is recognized as a cancer hallmark (Hanahan, 2022). Compared with vessels in healthy tissues, vessels developed by tumors are often immature, tortuous, and hyperpermeable, resulting in increased flow resistance and fluid leakage into perivascular tissues (Bordeleau et al., 2017). Vessel hyperpermeability is related to structural changes in endothelial cells, notably wider pores and reduced intercellular tight junctions (Sengupta et al., 2005; Wautier & Wautier, 2022). In contrast, the convoluted shapes of tumor vessels have been associated with increased extracellular matrix stiffness (Bordeleau et al., 2017). The blood stasis and hypoxia-induced by tortuous tumor vessels promote tumor cell invasion. At the same time, a high density of highly permeable capillaries deprived of basement membranes facilitates tumor cell intravasation and metastasis (Yang et al., 2020). Normalizing the tumor vasculature to increase perfusion and reduce permeability has been found to exert significant antitumor effects (Tian et al., 2017).

Tumor vascularization develops through three different means, namely, via the co-option of pre-existing vessels to create cuff-like tumor nests, vasculogenesis of *de novo* blood vessels from bone marrow-derived progenitor cells, or angiogenesis, defined as the sprouting of new blood vessels from pre-existing ones (Santi et al., 2018). Vascularization via angiogenesis is most observed, especially in response to tumor hypoxia, and may exhibit classical sprouting structures glomeruloid and intussusceptive growth patterns (Carmeliet & Jain, 2011; Donnem et al., 2018). The metabolic adaptation and proangiogenic tumor responses to hypoxia are critically mediated by hypoxia-inducible factor (HIF). This transcription factor acts as the leading promoter of angiogenesis, as previously reviewed (de Heer et al., 2020). Critically, HIF controls the transcription of VEGF, which is considered the most prominent angiogenic growth factor. VEGF is a soluble or extracellular matrix-bound cytokine produced by various cell types, including fibroblasts, inflammatory cells, and many tumor cells (Lohela et al., 2009; Zhang & Brekken, 2022). VEGF promotes the development of blood and lymphatic vessels (Choueiri & Kaelin, 2020) through receptor tyrosine kinase VEGF receptors (VEGFRs). Several VEGF isoforms (VEGF-A, VEGF-B, VEGF-C, and VEGF-D) interact with different VEGFRs (VEGFR-1, VEGFR-2, and VEGFR-3). In general, VEGF-A promotes the growth of blood vessels, while VEGF-C and VEGF-D act over lymphatics, and VEGF-B mainly supports the cardiac vasculature. VEGF-A is the principal promoter of angiogenesis in solid tumors by binding to VEGFRs VEGFR-1 and VEGFR-2 (Carmeliet & Jain, 2011). In contrast, VEGF-C and VEGF-D mainly bind to VEGFR3 to drive lymphangiogenesis (Chung et al., 2010; Kuonqui et al., 2023), with specific contributions for establishing blood vessel networks (Tammela et al., 2011), as described below. VEGF participates actively in the angiogenic response by inducing endothelial cells' proliferation, migration, and survival, increasing microvascular permeability and the secretion of matrix metalloproteinases (MMPs) (Goggins et al., 2023; Lohela et al., 2009). The binding of VEGF to VEGFR leads to autophosphorylation of specific tyrosine residues in the VEGFR-2 cytoplasmic domain, initiating downstream signaling pathways critical to angiogenesis and producing a strong mitogenic and survival signal in endothelial cells (Koch et al., 2011). The VEGF-A stimulates the activation of several signaling proteins in endothelial cells, including extracellular-signal-regulated kinases (ERKs), focal adhesion kinase, mammalian target of rapamycin (mTOR), noncatalytic region of tyrosine kinase adaptor protein, protein kinase B, protein kinase C, phospholipase C-γ, p38 mitogen-activated protein kinases, Ras-related C3 botulinum toxin substrate, and Shc-related adaptor protein (Soumya et al., 2016). During blood vessel sprouting, tip cells migrate toward a VEGF-A gradient, and the sprout elongates via the proliferation of stalk cells. The tips from adjacent neovessels then meet and anastomose to form perfused networks lined by quiescent phalanx endothelial cells (Welti et al., 2013). Tip cell migration depends on VEGFR-2 stimulation by high VEGF-A levels, enhanced by its coreceptor neuropilin-1 (Fantin et al., 2013), resulting in VEGFR-2 internalization and upregulated signaling via ERK1/2 (Nakayama et al., 2013). Tip cells express Delta-like 4, a Notch ligand, which acts paracrinally over adjacent endothelial cells, downregulating VEGFR-2 and neuropilin-1 expression and upregulating VEGFR-1 which traps VEGF-A and committing those cells to the sprout's stalk (Geudens & Gerhardt, 2011; Jakobsson et al., 2010; Krueger et al., 2011) (Figure 1).

Finally, the tips of adjacent sprouting vessels fuse under the regulation of VEGF-C produced by perivascular macrophages, which activate VEGFR3 to promote the conversion of tip cells into stalk cells (Tammela et al., 2011). The neovessel's stalk is maintained and elongated by regulating Notch activity and sustaining proliferative stimuli via the Wnt signaling pathway (Phng et al., 2009). Angiopoietin-1 (Ang-1) is produced by perivascular cells and acts paracrinally over Tie2 receptors in endothelial cells, promoting survival and cell–cell adhesion and contributing to vessel normalization (Koh, 2013). Conversely, Ang-2 produced by endothelial cells destabilizes vessels, promoting cell migration and angiogenesis (Gerald et al., 2013). Tumor vessels tend to upregulate Ang-2 and show a high Ang-2/Ang-1 ratio, making this system an attractive therapeutic target (Daly et al., 2013). The expanding knowledge of the VEGF-VEGFR axis and other signaling pathways involved in angiogenesis prompted the development

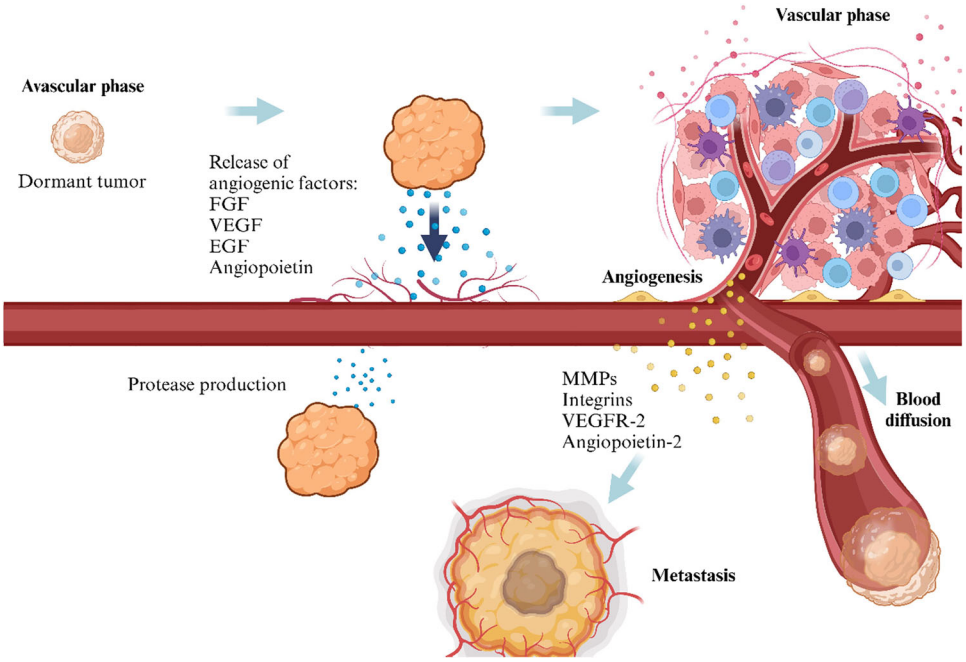

FIGURE 1 Progression from avascular to vascular phase in tumor development. This figure illustrates the transition of a tumor from the avascular phase to the vascular phase, highlighting the critical role of angiogenesis in tumor progression. Initially, the dormant tumor releases various angiogenic factors like FGF, VEGF, EGF, and angiopoietin, which stimulate nearby blood vessels to sprout new branches toward the tumor, marking the onset of the vascular phase. Protease production further assists in this transition by remodeling the extracellular matrix, allowing tumor expansion and increased vascularization. As the tumor becomes vascularized, factors such as MMPs, integrins, VEGFR-2, and angiopoietin-2 facilitate the formation of a robust blood supply network, enhancing the tumor's growth potential and metastatic capability through increased blood diffusion. Abbreviations: EGF, epidermal growth factor; FGF, fibroblast growth factor; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor 2.

of targeted antiangiogenic therapies with varying success (Majidpoor & Mortezaee, 2021). Multiple antibodies and small-molecule drugs have been developed against molecular targets involved in angiogenesis, among which bevacizumab is the most extensively studied (Garcia et al., 2020). Bevacizumab, an anti-VEGF monoclonal antibody, has been approved for treating colorectal, breast, ovarian, cervical, and non-small-cell lung cancer, renal cell carcinoma, and glioblastoma (Garcia et al., 2020). However, resistance to bevacizumab therapy may occur, for example, in metastatic breast cancer, where improvements in progression-free survival were modest and did not result in improved overall survival (de Heer et al., 2020). Multiple tyrosine kinase inhibitors are also able to target VEGFR in several types of cancer, like axitinib (Motzer et al., 2019) and panopazib (Sheng et al., 2020), which are used for treating renal cell carcinoma, tivozanib for glioblastoma (Kalpathy-Cramer et al., 2017) and sorafenib for hepatocellular carcinoma (HCC) (Yau et al., 2022). Other VEGF-independent strategies have been tested, like targeting Ang-Tie2 signaling with trebananib, a peptibody that inhibits Ang-1 and Ang-2 binding of Tie2, with limited clinical efficacy (Diéras et al., 2015; Vergote et al., 2019). Resistance to antiangiogenic therapies has been associated with alternative modes of vascularization like the co-option of existing vessels, recruitment of bone marrow endothelial precursors, and vascular mimicry, as well as with a boost in proangiogenic molecules driven by hypoxia following the therapeutic destruction of tumor blood vessels (Majidpoor & Mortezaee, 2021). These observations led to efforts aimed at normalizing the tumor vasculature rather than simply destroying it to allow effective delivery of combinatorial chemotherapies and avoid hyperpermeability and hypoxia (Augustin & Koh, 2022; Meng et al., 2021). Combining antiangiogenic therapies with immunotherapies is another relevant line of research, stemming from the observation that proangiogenic factors like VEGF exert immune suppressive functions in the tumor microenvironment (Gavalas et al., 2012; Khan & Kerbel, 2018; Ziogas et al., 2012). Such approaches have produced positive results, for example, in patients with melanoma (Hodi et al., 2014), breast cancer (Li et al., 2020), and HCC (Lee et al., 2020).

4 | PRECLINICAL STUDIES AND MOLECULAR TARGETS OF NATURAL PRODUCTS IN ANGIOGENESIS

Several studies using cancer cell lines or animal models have been conducted to address the effects of different bioactive compounds in angiogenesis in different types of cancers, with promising results. Experimental models commonly used to study angiogenesis include in vitro models such as cancer cell lines, rat aortic ring, and human umbilical vein endothelial cells (HUVECs) and *ex/in vivo* models such as chick chorioallantoic membrane (CAM) and xenograft models (mice, rat, and zebrafish). These natural products mainly target VEGFs (Cheng

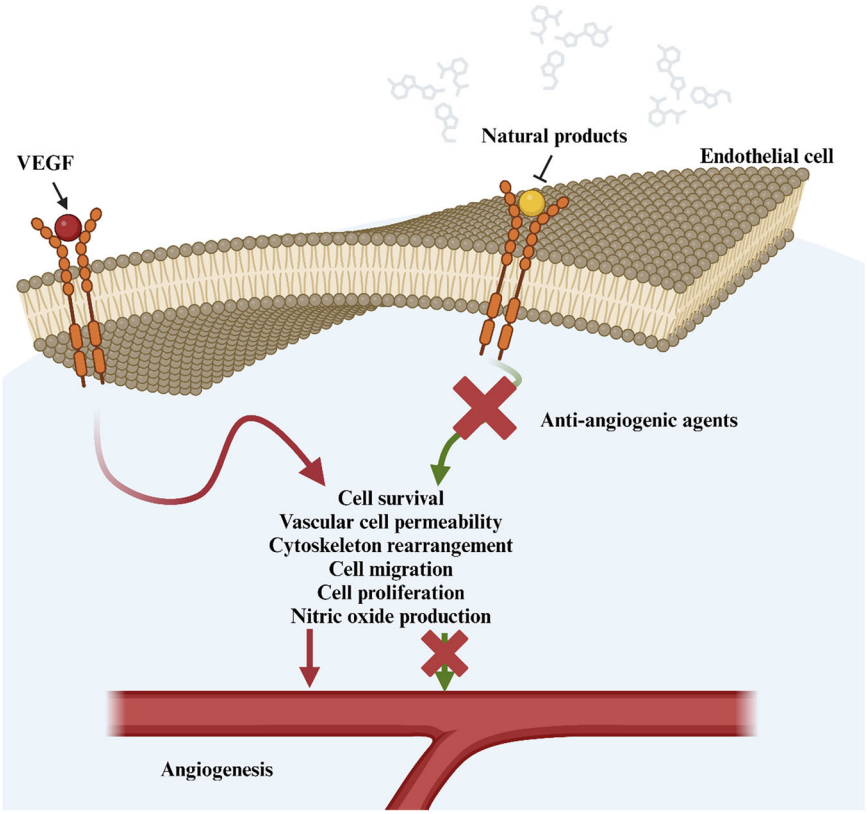

FIGURE 2 Summarized diagram of inhibition of angiogenesis by natural antiangiogenic agents. The figure depicts the molecular interaction between vascular endothelial growth factor (VEGF) and its receptor on endothelial cells, highlighting natural antiangiogenic agents' inhibition of angiogenic processes. The binding of VEGF to its receptor promotes a series of downstream effects that facilitate angiogenesis, including enhanced cell survival, vascular permeability, cytoskeletal rearrangement, cell migration, cell proliferation, and nitric oxide production. As shown by the red "X" marks, natural products can interfere with these processes, effectively inhibiting the angiogenesis pathway and potentially restricting tumor growth and metastasis.

et al., 2021) or VEGFRs (Yuan & Hu, 2023). However, some natural compounds are also able to target other molecules involved in tumor angiogenesis, like Aurora kinases (Tran et al., 2022), CD31 (Pal et al., 2019), EGFR (Metibemu et al., 2021), H1F-1α (Cheng et al., 2021), FLK-1 (Ayuningtyas et al., 2023), FLT-1 (Bae et al., 2020), IKBKE (Messeha et al., 2022), MMPs (Hsu et al., 2020), Sema3A (Yu et al., 2023), TGF-α (Ramadan et al., 2023), TGF-β (Ramadan et al., 2023), and vimentin (Pal et al., 2022), decreasing tube formation and angiogenic factors expression (Figure 2). Tube formation is the most popular angiogenesis assay using HUVECs with Matrigel, while the *ex vivo* CAM model assesses vessel number and density. In *in vivo* models, particularly in rodents, vascular density is the most frequently evaluated parameter. Natural extracts impair angiogenesis by tumor starvation.

This section comprehensively composes recent in vitro and in vivo studies on cancer models involving natural compounds. The featured compounds include macromolecules (polysaccharides, proteins, and peptides), omega-3 fatty acids, and secondary metabolites (polyphenols, terpenes/terpenoids, alkaloids, carotenoids, and cannabinoids) with antiangiogenic properties. Relevant studies from the last 5 years are summarized in Tables 1–8.

4.1 | Macromolecules

4.1.1 | Polysaccharides

Polysaccharides, macromolecules formed by long chains of monosaccharide units linked through α- or β-glycosidic linkages, display structures that can be linear or include branched side chains (Mohammed et al., 2021). Polysaccharides are essential in cell wall structures and energy reserves and are abundant in all organisms. These polysaccharides also exhibit diverse pharmacological effects, including anticancer properties by inducing cell cycle arrest, apoptosis, and inhibiting angiogenesis (Guo et al., 2022; Y. Li et al., 2021; Ying & Hao, 2023). Molecular weight, constituent monosaccharide subunits, and glycosidic bonds influence their anticancer activities. Table 1 summarizes several polysaccharides with antiangiogenic effects. Current polysaccharide antitumor research predominantly employs cell models, while animal experiments aim to elucidate the mechanisms, with limited focus on in vivo absorption, transport, and metabolism (Ju et al., 2023). Marine algae polysaccharides, such as laminarin, fucoidan, alginate, ulvan, and cellulose, display distinct compositions and structures compared to plant-derived polysaccharides (de Jesus Raposo et al., 2015). Extensively researched for their antiangiogenic properties (Ouyang et al., 2021; Sajadimajd et al., 2019), these polysaccharides also find application in formulations for delivering other compounds. Fucoidan, a fucose-rich polysaccharide from brown algae, particularly *Fucus vesiculosus*, has potential in anticancer applications by downregulating antiangiogenesis mediators, namely, VEGF-A, IGF-I, bFGF, MMP-2, and MMP-9 expression, inhibiting tube formation and impeding vascular development in various cancer cell lines and models (Hsu et al., 2020; Oliveira et al., 2019; Xue et al., 2013). Research has explored its sole use (Bae et al., 2020; Chen et al., 2021; Hsu et al., 2020; Oliveira et al., 2019; Pan et al., 2019), in combination with other drugs (Abdollah et al., 2023), or novel formulations enhancing cancer imaging and photodynamic therapy (Cho et al., 2020). Studies regarding

TABLE 1 Naturally occurring polysaccharides in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Bioactive compounds	Origin	Cellular/animal model	Treatment	Molecular target	Effects	Ref(s)
Asparagus polysaccharide	Standard	Hep3B and SK-Hep1 cells	2.5–10 mg/mL (24 h)	VEGF, HIF-1α	↓ VEGF and HIF-1α expression and CD34 expression	Cheng et al. (2021)
		Nude mice (Xen: Sk-Hep1 cells)	25–100 mg/kg/day (i.g., 12 days)			
Chondroitin sulfate	Isolated from *Litopenaeus vannamei*	RAEC	100 μg/mL (24 and 48 h)	VEGF	↓ Capillary formation, VEGFA expression	Palhares et al. (2020)
Dandelion polysaccharide	Standard	HUVECs	100–400 mg/L (24 and 48 h)	ND	↓ Tube formation	Ren et al. (2020)
		CAM, BALB/c mice (Xen: Hepa1-6 and H22 cancer cells)	BALB/c mice: 200 mg/kg, (i.p., 14 days); CAM: 100–400 mg/L	VEGF, HIF-1α	Inhibits PI3K/AKT/HIF-1a/VEGF pathway	
Fucoidan	Isolated from *Laminaria japonica*	HCC1806 and MDA-MB-231 cells, HUVECs	0.125–2 mg/mL (24 h)	VEGF, IGF-I	↓, *bFGF*, *IGF-I*, *MMP-2*, *MMP-9*, *VEGF-A* expression, tube formation	Hsu et al. (2020)
		Zebrafish [Tg(fli1:EGFP)]	0.1–2 mg/mL (24 h)	Impaired vascular development		
	Isolated from *Fucus vesiculosus*	CAM (MDA-MB-231 cells)	0.5 mg/mL (4 days)	ND	↓ No. of blood vessels and area	Oliveira et al. (2019)
	ND	A549 and H1650 cells	10 and 16 mg/mL (7 days)	VEGF	↓ VEGF expression	Chen et al. (2021)
		Mice (Xen: A549 cells)	25 mg/kg, gavage (14 days)	VEGF		
	Standard	Zebrafish [Tg(fli1:EGFP)]	300 μg/mL (48 h)	VEGF-A	↓ Vascular formation, VEGF-A, FLT-1, FLT-4, KDR, and KDRI	Bae et al. (2020)
HH1-1	ND	Nude mice (Xen: BxPC-3 cells)	0.5–50 mg/kg	EGFR	Prevents the binding of EGFR and Galectin-3, inhibits Galectin-3/GFR/KT/OXO3 signaling pathway	Yao et al. (2019)
		CAM	0.88 and 1.76 μM (12 and 72 h)	ND	↓ No. of vessel branches	

(Continues)

TABLE 1 (Continued)

Bioactive compounds	Origin	Cellular/animal model	Treatment	Molecular target	Effects	Ref(s)
IJP70-1	Isolated from *Inula japonica*	Zebrafish [Tg(fli1:EGFP)]	100–400 μg/mL (48 h)	ND	↓ No. and length of intact vessels	X. Wang et al. (2023)
Propylene glycol alginate sodium sulfate	Standard	Rat aortic ring	50–150 μg/mL (7 days)	ND	↓ Microvessel growth	Ma et al. (2019)
		CAM	100–200 μg/egg (48 h)	ND	↓ No. of total vessels	
PRP-S16	Isolated from *Phellinus ribis*	C57BL/6 J mice (Allo: LLC cells)	10–40 mg/kg (i.p., 14 days)	VEGF, VEGFR-2	Inhibits HIF-1a/VEGF/VEGFR-2/AKT pathway	Ding et al. (2020)
PSM001	Isolated from *Mangifera indica*	CAM	500–1000 μg/mL (3 days)	TIMP-1 and 2	↓ No. of vessels ↑ TIMP-1 and 2 expressions	Varghese et al. (2019)
		BALB/c mice (Allo: EAC cells)	200 mg/kg (6 days)			
PST001	Isolated from *Tamarindus indica*	CAM	100–200 μg/mL (3 days)	TIMP-1 and 2	↓ No. of vessels ↑ TIMP-1 and 2 expressions	Varghese et al. (2019)
		BALB/c mice (Allo: EAC cells)	200 mg/kg (6 days)			
SPS-1	Isolated from *Sambucus adnata*	C57BL/6 mice (Xen: LLC cells)	25–100 mg/kg (i.v., every 2 days, 18 days)	VEGF and VEGFR-2	↓ VEGF and VEGFR-2 protein expression	Yuan and Hu (2023)
Yulangsan polysaccharide	Isolated from *Millettia pulchra* (Benth.) Kurz var.	BALB/c mice (Allo: 4T1 cells)	150–300 mg/kg (14 days)	VEGF	↓ VEGF, number of vessels	Qin et al. (2019)
LHEPS-3	Isolated from *Lactobacillus helveticus*	CAM	2.5–10 mg/mL (3 days)	ND	↓ Number of vessel branches	Xiaomeng et al. (2023)

Abbreviations: Allo, allograft; bFGF, basic fibroblast growth factor; CAM, in vivo chick chorioallantoic membrane; CD34, cluster of differentiation 34; EGFR, epidermal growth factor receptor; FLT, fetal liver kinase; HIF-1α, hypoxia-inducible factor 1-α; i.p., intraperitoneal; i.v., intravenous; IGF-1, insulin-like growth factor 1; KDR, kinase insert domain receptor; KDRL, kinase insert domain receptor like; MVD, microdensity vessel; No., number; PI3K, phosphoinositide 3-kinases; RAEC, rat aortic endothelial cell; TIMP2, tissue inhibitor of metalloproteinases 2; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2; Xen, xenograft. **Symbols**: ↑ increase, ↓ decrease.

other marine algae-derived polysaccharides, like alginate and cellulose, primarily focus on their application in formulations to enhance absorption or target therapies (G. Chen et al., 2020; Gopinath et al., 2018; W. W. Hu et al., 2019; Marulanda et al., 2021; Schaly et al., 2022; Wang et al., 2018; Yang et al., 2022) to downregulate cancer-related angiogenesis. Propylene glycol alginate sodium sulfate, a heparinoid polysaccharide drug used in the clinic for over 30 years in China (Xue et al., 2023), inhibited FGF2-mediated angiogenesis in a rat aortic ring model and decreased MMP-2 and MMP-9 activity in murine melanoma (B16-F10) cells (Ma et al., 2019). Plants, a significant source of polysaccharides in our daily diet, also demonstrate potential in regulating cancer-associated angiogenesis (Ahmad et al., 2022; Urzì et al., 2023). *Sambucus adnata* polysaccharide (SPS-1) and a polysaccharide from *Inula japonica* (IJP70-1) exhibited antiangiogenic activities in various models, including C57BL/6 mice with xenografted Lewis tumor cells and zebrafish with altered vessel lengths, respectively (X. Wang et al., 2023; Yuan & Hu, 2023). A polysaccharide isolated from the root of dandelion (*Taraxacum mongolicum*) hinders angiogenesis by inhibiting the PI3K/AKT/HIF-1α/VEGF pathway in HUVECs, CAM, and BALB/c mice with xenografted murine HCC (Hepa1-6 and H22) cancer cell lines (Ren et al., 2020). HH1-1, a homogeneous polysaccharide from safflower (*Carthamus tinctorius*), exhibited antitumor effects in nude mice xenografted with human pancreatic cancer (BxPC-3) cells by preventing the binding of EGFR and Galectin-3, inhibiting the Galectin-3/GFR/KT/OXO3 signaling pathway (Yao et al., 2019). Additionally, PRP-S16 (a chemically sulfated polysaccharide from *Phellinus ribis*) (Ding et al., 2020), PSM001 (a homo-polysaccharide from *Mangifera indica* seed kernel) (Varghese et al., 2019), PST001 (a galactoxyloglucan from *Tamarindus indica* seeds) (Varghese et al., 2019), and Yulangsan polysaccharide (from *Millettia pulchra* root) (Qin et al., 2019) also show antiangiogenic effects, targeting diverse molecular pathways involved in angiogenesis. Asparagus polysaccharide inhibited VEGF, HIF-1α, and CD34 expression in human HCC (SK-Hep1 and Hep3B) cells and nude mice xenografted with SK-Hep1 cells (Cheng et al., 2021). Current research has also focused on modifying these natural compounds to improve their efficacy; namely, *Platycodon grandiflorum* derived acetylated glucomannan (PGP40-1) and its selenium-modified form, Se-PGP40-1, which showed significant antitumor activity by inhibiting proliferation, migration, inducing apoptosis and blocking angiogenesis in vitro and zebrafish models (Zhang et al., 2022). Also, EJP90-1-Se, a selenized polysaccharide from *Eriobotrya japonica*, demonstrated antiangiogenic effects in a zebrafish model (Zhang et al., 2021). Polysaccharides derived from animal sources, exemplified by chitosan and chondroitin sulfate, have also been investigated for their potential role in modulating angiogenesis. Chondroitin sulfate, isolated from *Litopenaeus vannamei*, when applied to rat aortic endothelial cells, exhibited antiangiogenic properties, as evidenced by the inhibition of capillary formation and a concurrent decrease in VEGFA expression (Palhares et al., 2020). In a study involving nude mice xenografted with human HCC (BEL-7402) cells, chitosan nanoparticles loaded with troxerutin revealed a reduction in microvessel formation coupled with downregulation of VEGFR2 mRNA expression (Subbaraj et al., 2023). Although there has not been much study done on polysaccharides originating from microorganisms, LHEPS-3, an exopolysaccharide from *Lactobacillus helveticus* MB2-1, has been shown to have antiangiogenic properties by lowering the number of vessel branches in CAM (Xiaomeng et al., 2023). Figure 3 illustrates the molecular interactions and pathways affected by polysaccharides, highlighting their roles in downregulating key angiogenic factors like VEGF, FGF2, and their receptors.

4.1.2 | Omega-3 fatty acids

Polyunsaturated fatty acids are a large group of fatty acids that contain long-chain carbon molecules, including omega-3 fatty acids (Lozac'h, 1986). Omega-3 fatty acids, characterized by a double bond between the third and fourth carbon atoms from the methyl end, are naturally present in fatty fish, certain seafood, nuts, and seeds (Cholewski et al., 2018).

α-Linoleic acid (ALA), an essential omega-3 fatty acid found mainly in green leafy vegetables, oil, seeds, and nuts, has been shown to decrease the expression of VEGF, MMP-2, and MMP-9 proteins in two human cervical cancer (SiHa and HeLa) cell lines (Deshpande et al., 2016). Docosahexaenoic acid (DHA), exclusively found in cold-water fish, demonstrated a reduction in microvessel count and Ki-67 expression in mice xenografted with human triple-negative breast cancer (MDA-MB-231) cells (Rose & Connolly, 1999). In another study, DHA reduced VEGF expression and tube formation miR-34a, miR-125b, miR-221, and miR-222, while increasing miR-9, miR-17-5p, miR-19a, miR-126, miR-130a, miR-132, miR-296, and miR-378 in human breast cancer (MDA-MB-231) cells (Ghaffari-Makhmalbaf et al., 2021). Another omega-3 fatty acid that is found in fish, eicosapentaenoic acid (EPA), was investigated in a fibrosarcoma model in mice and showed a significant decrease in tumor volume, as well as in the expression of VEGF-α (Tevar et al., 2002). Although omega-3 fatty acids have been studied in the past, studies are scarce, so the antiangiogenic properties of various omega-3 fatty acids, namely, DHA, 17-Oxo-DHA, ALA, EPA, and DHA-PC, have continued to be investigated in recent years (Table 2). For instance, 17-Oxo-DHA reduced the vessels and hemoglobin accumulation in SKH1-Hrhr mice subjected to UVB-induced skin carcinogenesis (Kim et al., 2023). DHA has exhibited further antiangiogenic properties in human breast cancer (MDA-MB-231 and BT-474) cells, leading to decreased expression of proangiogenic genes and microRNAs, including HIF-1α, TGF-β, SOX2, Snail1, VEGFR, miR-101, miR-199, and miR-342, while increasing miR-382 and miR-21 expression (Aslan et al., 2020). A combination of DHA and ALA demonstrated antiangiogenic effects in CAM, resulting in decreased VEGF, VEGFR-2, and CD31 expression and a reduced overall number of vessels (Pal et al., 2019). Similarly, in an *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine-induced rat urinary bladder cancer model, daily administration of DHA and EPA led to reduced VEGF expression (Fadallah et al., 2022). Furthermore, DHA-enriched phosphatidylcholine exhibited antiangiogenic effects in CAM and HUVECs by reducing the number of microvessels, tube formation, and VEGFR-2 mRNA expression (Liu, Tian, et al., 2021). EPA also demonstrated

TABLE 2 Naturally occurring omega-3 fatty acids compounds in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular target	Effects	Ref(s)
17-Oxo-DHA	Standard	SKH1-Hrhr mice UVB-induced carcinogenesis in skin	20 nmol dissolved in 200 μL of acetone 30 min prior to each UVB exposure (4 days)	ND	↓ Numbers of vessels and hemoglobin accumulated in the skin	Kim et al. (2023)
DHA	Standard	BT-474 and MDA-MB-231 cells	100 μM under normoxic and hypoxic conditions (24 h)	HIF-1 α, TGF-β, SOX2, Snail1, VEGFR, miR-101, miR-199, miR-342, miR-382, and miR-21	↓ HIF-1α, TGF-β, SOX2, Snail1, Snail2, VEGFR, miR-101, miR-199, miR-342 ↑ miR-382 and miR-21	Aslan et al. (2020)
	Standard	HUVECS, MDA-MB-231 cells	50 μM (24 and 48 h)	VEGF-A	↓ VEGF expression, tube formation miR-34a, miR-125b, miR-221, miR-222 ↑ miR-9, miR-17-5p, miR-19a, miR-126, miR-130a, miR-132, miR-296, miR-378	Ghaffari-Makhmalbaf et al. (2021)
DHA and ALA	Standard	CAM	1–100 μM and 1 mM (48 h)	VEGF, VEGFR-2, CD31	↓ VEGF, VEGFR-2, CD31, and number of vessels	Pal et al. (2019)
DHA and EPA	Standard	BBN-induced rat bladder cancer	480 mg/kg/day (DHA) and 720 mg/kg/day (EPA) (dissolved in corn oil, gavage, 10 weeks)	VEGF	↓ VEGF expression	Fadallah et al. (2022)
DHA-PC	Isolated from *Squid oualaniensis*	HUVECs	50–100 μg/mL (24 h)	VEGFR-2	↓ Tube formation and VEGFR-2 mRNA expression	Liu, Tian, et al. (2021)
		CAM	10–30 μg/egg (24 h)		↓ No. of microvessels	
EPA	Standard	CAFs, HUVECs	30 μM (24 h, 48 and 72 h)	VEGF	↓ VEGFR and tube formation	Ando et al. (2019)

Abbreviations: ALA, α-Linoleic acid; BBN, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; CAF, cancer-associated fibroblasts; CAM, in vivo chick chorioallantoic membrane; CD31, cluster of differentiation 31; DHA, docosahexaenoic acid; DHA-PC, docosahexaenoic acid-enriched phosphatidylcholine; EPA, eicosapentaenoic acid; HIF-1α, hypoxia-inducible factor 1-α; HUVECs, human umbilical vein endothelial cells; miR, microRNA; ND, nondefined; No., number; SOX2, SRY-box 2; TGF-β, transforming growth factor-β; UVB, ultraviolet B; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

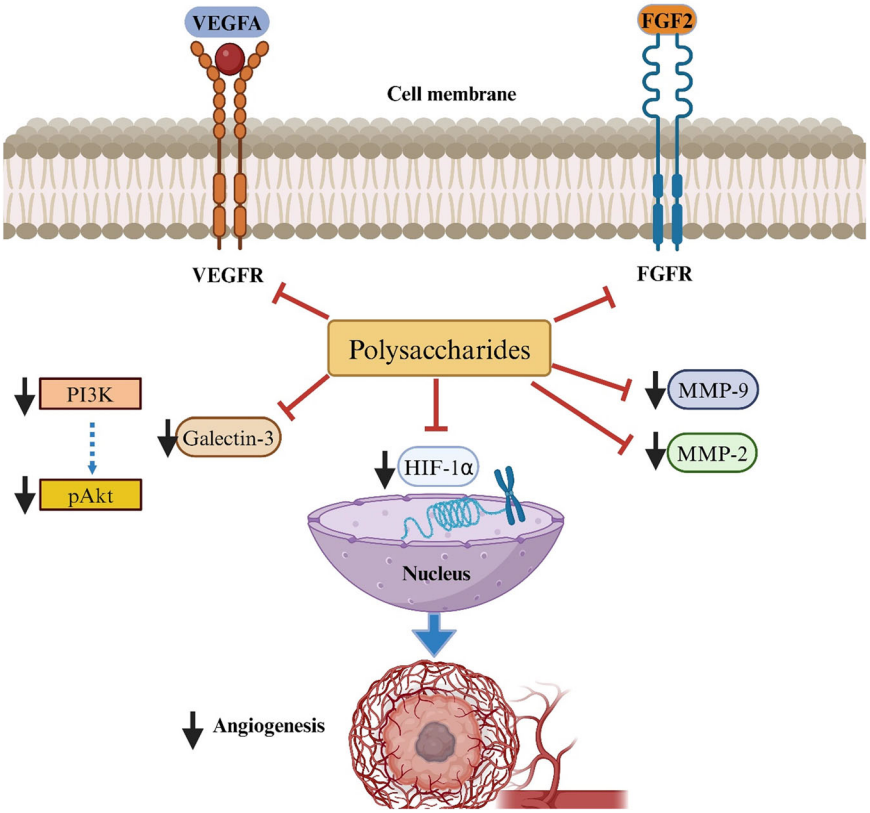

FIGURE 3 Mechanisms of polysaccharide action in cancer antiangiogenesis. The figure illustrates the inhibitory pathways of polysaccharides in cancer angiogenesis. The signaling cascades involve the interaction between VEGFA, VEGFR, FGF2, and FGFR, which are fundamental for angiogenesis. Polysaccharides modulate these interactions and downstream pathways (PI3k, Akt, Galectin-3, MMP-2, MMP-9), leading to reduced expression of HIF1α in the nucleus and ultimately decreasing angiogenesis in the tumor microenvironment. Abbreviations and Symbols: Akt, protein kinase B; FGF2, fibroblast growth factor 2; FGFR, fibroblast growth factor receptor; HIF1α, hypoxia-inducible factor 1-alpha; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; PI3k, phosphoinositide 3-kinase; VEGFA, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor. **Symbols**: ↓ decrease, ⊥ nhibition

antiangiogenic effects in HUVECs and cancer-associated fibroblasts, decreasing VEGFR expression and tube formation (Ando et al., 2019). Figure 4 highlights how Omega-3 fatty acids inhibit tumor angiogenesis by blocking VEGF signaling and modulating microRNA profiles, ultimately reducing tumor vascular development.

4.1.3 | Amino acids, peptides, and proteins

Aminoacids, the building blocks of proteins, provide energy, forming essential biomolecules such as hormones, neurotransmitters, and signaling molecules. The polymers of amino acids, peptides, and proteins intricately regulate various physiological and biochemical processes in the human body. Peptides, composed of two or more amino acids linked by peptide bonds, act as building blocks for proteins, with polypeptides forming longer, continuous, unbranched chains; bioactive peptides serve as sources of nitrogen and amino acids and also potentially regulate physiological functions (Harnedy & FitzGerald, 2011). Proteins, as important macronutrients, are a vital source of essential amino acids and energy, playing a critical role in numerous physiological processes within the human body (Cerna, 2011). Beyond their fundamental nutritional contributions, specific food proteins offer additional health benefits by releasing bioactive peptides (Tahergorabi & Hosseini, 2017). Despite these compounds' integral role in body function, there is a noticeable gap in research concerning their pharmacological use and potential impact on angiogenesis regulation (Medina & Quesada, 2014). Arginine, a dietary amino acid involved in several metabolic pathways, was investigated for its antiangiogenic capacity using nude mice xenografted with human colon cancer (SW480) cells, revealing significantly lower MMP-2, MMP-9, and VEGFR levels in tumors (Yeh et al., 2010). Regarding peptides, the pepsin-generated peptide lactoferricin, derived from bovine lactoferrin, demonstrated inhibition of tumor metastasis in mice with highly metastatic murine melanoma (B16-BL6) and lymphoma (L5178Y-ML25) cells, associated with a reduction in tumor-induced blood vessels and suppressed tumor growth (Yoo et al., 1997). Carnosine (β-alanyl-L-histidine), found in beef and fish, demonstrated significant inhibition of angiogenesis-related molecules, including VEGF, EGFR, and HIF-1α, when tested in human colorectal carcinoma (HCT-116) cells (Hsieh et al., 2022). Additionally, anticancer peptides have been isolated from marine species (Ahmed et al., 2022). Aplidine from *Aplidium albicans*, a toxic sea squirt, demonstrated inhibition of cell migration and invasiveness in ovarian cancer (1A9) cells by blocking VEGF-mediated effects and suppressing the production of MMP-2 and MMP-9 (Taraboletti et al., 2004). Interestingly, venoms also serve as a source of peptides for cancer therapy (S. Mirzaei et al., 2021), exemplified by the RK1 peptide, a 14-aminoacid peptide derived from *Buthus occitanus tunetanus*, which has demonstrated great potential in cancer therapy by suppressing migration and angiogenesis (Khamessi et al., 2018). Additionally, the peptide Tv1 found in the venom of the predatory marine snail *Terebra variegatavia* has demonstrated efficacy in downregulating cyclooxygenase-2 (COX-2) in BALB/c mice allografted with mouse liver carcinoma (BNL1MEA.7R.1) cells, thereby suppressing angiogenesis and metastasis (Anand et al., 2019). Among the proteins studied in the

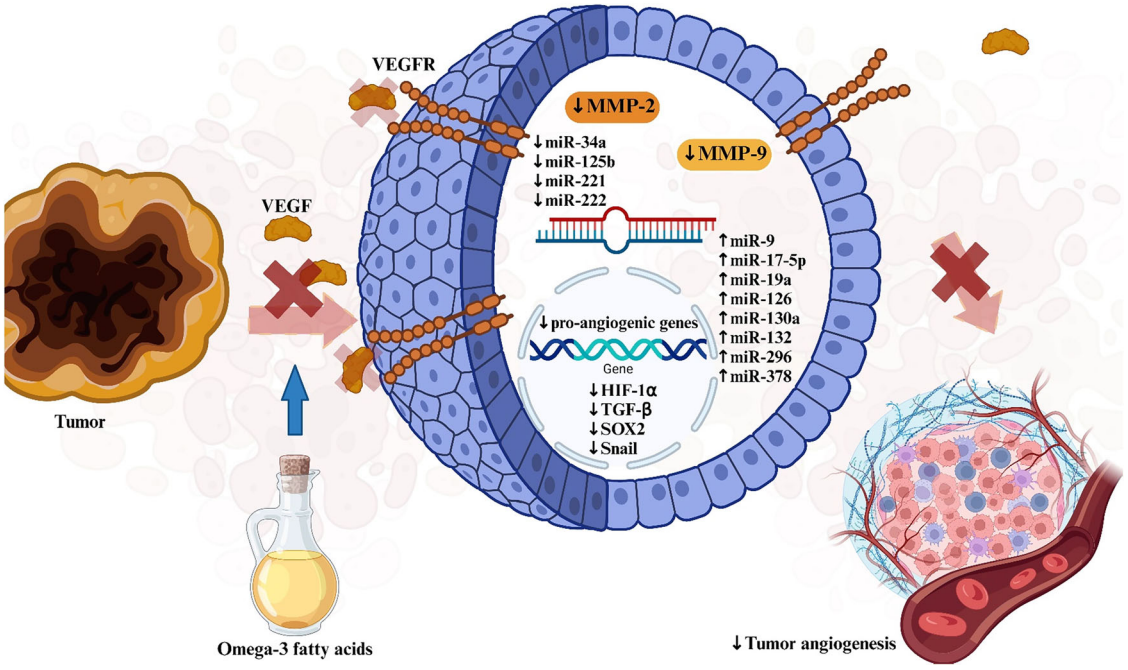

FIGURE 4 The role of omega-3 fatty acids in inhibiting tumor angiogenesis. The diagram outlines the antiangiogenic mechanisms of Omega-3 fatty acids on tumor growth. Omega-3 fatty acids inhibit the release of VEGF from the tumor, which subsequently prevents VEGF from binding to its receptor (VEGFR) on endothelial cells. This disruption hinders multiple downstream angiogenic pathways, including the decrease in expression of MMP-2 and MMP-9, which are essential for vascular remodeling. The figure also highlights the modulation of microRNA (miRNA) profiles by Omega-3 fatty acids, leading to the upregulation of antiangiogenic miRNAs and downregulation of proangiogenic miRNAs, which suppress key proangiogenic genes such as HIF-1α, TGF-β, SOX2, and Snail. Collectively, these effects result in reduced tumor angiogenesis. Abbreviations: HIF-1α, hypoxia-inducible factor 1-alpha; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Symbols: ↑ increase, ↓ decrease.

literature (Table 3), lactoferrin derived from cow milk demonstrated significant antiangiogenic effects. In BALB/c mice with xenografted human colorectal adenocarcinoma (HT29) cells, the administration of lactoferrin resulted in a notable decrease in the expression of vital angiogenic markers, including VEGFR2, VEGF-A, p-PI3K, p-AKT, and p-Erk1/2 (H. Y. Li et al., 2019). Additionally, in another study, lactoferrin administration to human melanoma (A375SM) cell line and C3H/HeN mice xenografted with human squamous cell carcinoma (SCCXII) cells resulted in significant reductions in *VEGF-A*, *FLT-1*, and *FLK-1* mRNA expression levels (Ayuningtyas et al., 2023). This protein further demonstrated inhibitory effects on p-p65 by binding to TRAF6, suppressing HIF-1α activation, and ultimately reducing microvessel density (Ayuningtyas et al., 2023). Interestingly, administering arresten derived from collagen has reduced tumor cell proliferation, vessel density, and local invasiveness in nude mice xenografted with tongue carcinoma (HSC-3) cells (Aikio et al., 2012). Furthermore, a protein (ZK002) isolated from *Deinagkistrodon acutus* venom has been found to exhibit antiangiogenic effects by decreasing tube length in HUVECs (Chan et al., 2023). Plants can also be a rich source of proteins with medicinal properties, especially anticancer (Boh, 2013). A plant-derived lectin from *Praecitrullus fistulosus* exhibited antiangiogenic properties in Swiss albino mice xenografted with Ehrlich ascites carcinoma cells and CAM by decreasing VEGF levels, microvessel density, and MMP activity (Madhu et al., 2019). Protein derivatives, including phycobiliprotein and glycoproteins, have also shown potential regarding antiangiogenesis cancer treatments (Saadaoui et al., 2020). C-phycocyanin, one of the most widely known phycobiliproteins and often found in cyanobacteria, simultaneously downregulated HIF-1 and MCP-1 expression and promoted MIP-1 expression, thereby reducing angiogenesis in a rat model of colon cancer (Saini & Sanyal, 2014). Direct therapeutic use may be challenging since proteins are large and poorly stable. Therefore, effective and targeted biodistribution requires an efficient delivery vehicle. One such example is a study by Marulanda et al. (2021), which delivered Slit3 proteins, common proteins in the human body, using alginate microbeads and found that angiogenesis was effectively downregulated in HUVECs and MECs.

4.2 | Secondary metabolites

4.2.1 | Polyphenols

Polyphenols constitute a varied category of secondary metabolites found abundantly in plants and, consequently, in plant-based foods and beverages (Niedzwiecki et al., 2016). Polyphenolic compounds can be broadly classified into two main categories: nonflavonoids, characterized by a single phenol ring, and flavonoids, distinguished by the presence of two phenol rings. Among these, flavonoids, encom-

TABLE 3 Naturally occurring peptide and proteins in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Structural class	Bioactive compounds	Origin	Cellular/animal model	Treatment	Molecular target	Effects	Ref(s)
Peptide	Carnosine	Standard	HCT-116 cells	0.5–15 mM (72 and 96 h)	VEGF, EGFR, HIF 1-α	↓ EGFR and VEGF expression	Hsieh et al. (2022)
	Tv1	Standard	BALB/c mice (Allo: BNL1MEA.7R.1 cells)	0.08–0.8 mg/kg (i.p., daily, 19 days)	COX-2	↓ COX-2	Anand et al. (2019)
Protein	Lactoferrin	Standard	BALB/c mice (Xen: HT29 cells)	100 mg/kg (p.o., every 2 days, 25 days)	VEGFR2, VEGFA, p-PI3K, p-AKT, p-Erk1/2	↓ VEGFR2, VEGFA, p-PI3K, p-AKT, p-Erk1/2 protein expression	H. Y. Li et al. (2019)
		ND	A375SM cells	0.6–6.0 μM (8 and 24 h)	VEGF-A, FLT-1, FLK-1	↓ *VEGF-A*, *FLT-1*, *FLK-1* expression, MVD Inhibits p-p65 by binding to TRAF6, suppresses HIF-1α activation	Ayuningtyas et al. (2023)
			C3H/HeN mice (Xen: SCCVII cells)	1.2–6.0 mM/kg/day (p.o., 4 weeks)			
	Lectin	Isolated from *Praecitrullus fistulosus*	Swiss albino mice (Xen: EAC cells), CAM	10 mg/kg	VEGF	↓ VEGF levels, MVD, and MMP activity	Madhu et al. (2019)
	ZK002	Isolated from *Deinagkistrodon acutus*	HUVECs	5 μM (3 and 6 h)	VEGF	↓ Tube length	Chan et al. (2023)

Abbreviations: CAM, in vivo chick chorioallantoic membrane; Erk, extracellular signal-regulated kinases; FAK, focal adhesion kinase; FGF, fibroblast growth factor; FLK, fms-related tyrosine kinase; FLT, fetal liver kinase; HIF-1α, hypoxia-inducible factor 1-α; HUVEC, human umbilical vein endothelial cells; i.p., intraperitoneal; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MVD, microvessel density; p.o., per os; PIGF, placenta growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Xen, xenograft. **Symbols**: ↓ decrease; ↑ increase.

passing anthocyanins, flavanols, flavones, flavonols, flavanones, and isoflavones, stand out as the most abundant polyphenols in our diet and existing in both free and conjugated forms in nature (Sharma et al., 2019; Sheikh et al., 2020). Nonflavonoid compounds comprise phenolic acids, stilbenes, and lignans. Many studies have explored the health advantages associated with polyphenols (Azevedo et al., 2024; Briguglio et al., 2020), highlighting their antioxidant or anticarcinogenic properties, especially by mediating the angiogenic process in tumors (Rahaman et al., 2023) (Table 4). Quercetin, a flavonoid found in fresh fruits, vegetables, and citrus fruits, has demonstrated anticancer properties by inhibiting tumor proliferation, invasion, metastasis, and angiogenesis. The anticancer mechanism of quercetin is controlled through several signaling pathways within the cancer cells, including apoptotic, p53, nuclear factor-kappa B (NF-κB), MAPK, JAK/STAT, PI3K/AKT, and Wnt/β-catenin pathways. Quercetin also controls the activity of oncogenic and tumor suppressor ncRNAs. Quercetin may inhibit angiogenesis by suppressing the VEGF and VEGFR expressions, critical regulators of angiogenesis (Pratheeshkumar et al., 2012; H. Shi et al., 2020). Quercetin also inhibits the activity of MMPs, which are enzymes that degrade the extracellular matrix and promote angiogenesis (Saragusti et al., 2010; Vijayababu et al., 2006). Anand et al. (2011) examined the effects of quercetin on solid tumors induced by Dalton's lymphoma ascites in Swiss albino mice. The results proved that administering quercetin directly into the tumor reduced its size/weight. Additionally, quercetin induced the death of cancer cells by reducing the levels of Hsp90 and Hsp70. The decrease in these two chaperones due to quercetin might activate caspase-3 in the treated tumors. Furthermore, it also diminished the expression of central angiogenic or proangiogenic factors, such as VEGF and HIF-1α. Another study also explored the antiangiogenic effects of quercetin in models in vitro, *ex vivo*, and in vivo (Pratheeshkumar et al., 2012). Their findings revealed that quercetin considerably suppressed microvessel sprouting at nontoxic concentrations and notably inhibited endothelial cell proliferation, migration, invasion, and tube formation—all critical steps in angiogenesis. Moreover, the matrigel plug and the chicken egg CAM assays confirmed that quercetin decreased *ex vivo* angiogenesis. Likewise, quercetin prevented the VEGFR2 phosphorylation induced by VEGF, as indicated by western blot analysis in HUVEC cells. Finally, quercetin, at a dosage of 20 mg/kg/day, noticeably diminished the size and weight of solid tumors in a prostate xenograft model, suggesting that quercetin prevents tumorigenesis by affecting angiogenesis. On the other hand, a recent study examined the antiangiogenic effect of quercetin on both endothelial cells and colorectal cancer cells (Uttarawichien et al., 2021b). The authors determined the tube formation ability of HUVECs by using HT-29 cells that received quercetin and were cocultured with HUVECs. After this treatment, the fluorescence assay and Western blot analysis were used to measure the VEGF-A and NF-κB p65 protein levels. Quercetin notably reduced the angiogenesis induced by HT-29 cells in HUVECs and inhibited the expression of NF κB p65 and VEGF-A proteins. Moreover, quercetin significantly lowered the expression and translocation of VEGFR-2 protein in HUVECs after coculturing with HT-29 cells that received a high dose of quercetin. Thus, the authors concluded that quercetin exerted its antiangiogenic effect by blocking VEGF-A related to the NF-κB signaling pathway in the HT-29 cells and by decreasing the expression and translocation of VEGFR-2 in HUVECs.

Luteolin is a natural compound tested for its antiangiogenic effects. It is a flavonoid with antiproliferative, antimetastatic, and antiangiogenic biological activities based on its antioxidative activity (neutralizing reactive oxygen species [ROS]) (Williams et al., 2004). Ambasta et al. (2015) conducted a study that demonstrated that luteolin inhibits cell growth at a dose of 20 μM compared to lectin and lupeol in HT-29 cell culture for 24 and 48 h. In the chick CAM assay, luteolin exposure after 24 and 48 h produced an effect dose-dependent and inhibited angiogenesis better than lectin and lupeol (Ambasta et al., 2015). Park et al. (2012) demonstrated that the exposure of 1-μM of luteolin inhibited in vitro angiogenesis in human retinal microvascular endothelial cells, and the administration of 0.1 and 1 μM of luteolin inhibits retinal neovascularization in oxygen-induced retinopathy without toxicity. According to the authors, the mechanism of action of luteolin would be related to inhibited VEGF expression by blockade of ROS production (Park et al., 2012). A strong relationship exists between increased ROS and angiogenesis and tumor growth through VEGFs (Ushio-Fukai & Nakamura, 2008; Xia et al., 2007). Another natural compound that inhibits tumor neovasculature formation in cancer conditions is curcumin, an active and nontoxic phenolic compound isolated from the rhizome of *Curcuma longa L* (H. Mirzaei et al., 2021). Fu et al. (2015) demonstrated that curcumin inhibits tumor growth accelerated by VEGF in a dose-dependent manner; moreover, it normalizes vasculature structures of livers and reduces tumor micro-vessel density. Li et al. (2022) also demonstrated the antiangiogenic effects of 2.5–100 μM curcumin in colon cancer cells incubated at 37°C for 24, 48, or 72 h. The results indicated that curcumin inhibited the proliferation of colon cancer in a dose-dependent manner and did not harm normal colon mucosa epithelial cells (Li et al., 2022).

Anthocyanins, prevalent water-soluble pigments in plants derived from anthocyanidins, can be found in several plant species' flowers, seeds, fruits, and leaves (Azevedo et al., 2022; Castañeda-Ovando et al., 2009; Tan et al., 2022). These compounds exhibit diverse biological activities, including antioxidant, immunomodulatory, antitumor, hepatoprotective, antiaging, and anti-inflammatory effects (Tan et al., 2022). Their antiangiogenic effects have been extensively investigated using various models, especially cell lines and CAM (Bagchi et al., 2004; Favot et al., 2003; Gupta et al., 2023; Huang et al., 2006; Rodrigo et al., 2006). Studies on human pulmonary adenocarcinoma (A549) cells have shown that delphinidin, an anthocyanidin, exhibits antiangiogenic effects in vitro and in vivo by downregulating EGF, CoCl2, HIF-1α, ERK, and VEGF gene expression (Kim et al., 2017). Cyanidin-3-glucoside also exhibits promising antiangiogenic properties in human breast cancer (MDA-MB-231) and cholangiocarcinoma (QBC399) cells, CAM, and HUVECs by effectively reducing tube formation and suppressing VEGF and HIF-1α expression (Ma & Ning, 2019; Xie et al., 2019).

Flavanols, another essential subclass of the flavonoid family, are molecules with biological activities of great interest, particularly anticancer effects (Kumar & Pandey, 2013). They are mainly found in broccoli, kale, apples, grapes, tomatoes, onion, red wine, olive oil, and

TABLE 4 Naturally occurring phenolic compounds in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Structural class	Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular target	Effects	Ref(s)
Anthocyanins	Cyanidin-3-glucoside	Standard	MDA-MB-231 cells, HUVECs	20 μM (24 h)	VEGF	↓ Tube formation, VEGF mRNA, and protein expression	Ma and Ning (2019)
			CAM	20 μM (5 days)		↓ Neovasculature formation	
		ND	QBC939 cells	50–200 μM (12 h)	VEGF and HIF-1α	↓ VEGF and HIF-1α mRNA expression	Xie et al. (2019)
Flavanols	EGCG	ND	SGC7901 cells	20–100 μg/mL	VEGF for 24, 48, and 72 h	↓ HIF-1α and VEGF proteins and VEGF mRNA expression	Fu et al. (2019)
	EGCG with vincristine sulfate	ND	BALB/c-nu/nu nude mice (Xen: KBV200 cells), CAM	BALB/c mice: 20 mg/kg (13 days); CAM: 80–230 mg/L (48 h)	VEGF	↓ VEGF protein expression, mRNA expression, and serum levels	L. Chen et al. (2020)
Flavanones	Hesperidin	ND	Mice (Allo: 4T1 cells)	5–40 mg/200 mL (24 days)	VEGF-A and VEGFR-2	↓ VEGF-A and VEGFR-2 mRNA expression and MMP-2, MMP-9, VEGF protein expression	Shakiba et al. (2023)
	Baicalin	ND	A549 cells and HUVECs	1–200 μM (24 h)	VEGF	↓ Tube formation, VEGF protein expression	Yan et al. (2020)
			Nude mice (Xen: A549 cells)	80 mg/kg (i.p., 30 days)		↓ VEGF, vimentin, and CD34 protein expression	
Flavonols	Quercetin	Standard	CLR-1730 and Eca109 cells	10 μg/mL (6 and 24 h)	MMP-2, MMP-9, VEGF-A	↓ Tube formation, MMP-2, MMP-9, and VEGF-A protein expression	Liu, Li, et al. (2021)
			HUVECs, HT-29 cells	5–10 μg/mL (24 h)	VEGF-A and VEGFR-2	↓ Tube formation, VEGF-A, and VEGFR-2 protein expression	Uttarawichien et al. (2021a)
			Swiss albino mice (Allo: EAC cells)	50 mg/kg (i.p., 15 days)	CD31	↓ New blood vessels and CD31 expression	Sannappa Gowda et al. (2023)

(Continues)

TABLE 4 (Continued)

Structural class	Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular target	Effects	Ref(s)
Hydroxybenzoic acid	Ellagic acid	Standard	C6 cells	100 mM (24 h, 48 and 72 h)	VEGF	↓ VEGF mRNA and protein expression	Çetin and Biltekin (2019)
			HeLa cells	57.8 μM (12 h, 24 and 48 h)	VEGF, MMP-2, and MMP-9	↓ MMP-2, MMP-9, TGF-β1, VEGF mRNA expression	Sarıbaş et al. (2023)
			Wistar rats (Allo: 4T1 cells)	50 mg/kg (p.o., 5 weeks)	TGF-α, TGF-β, VEGF	↓ TGF-α, TGF-β, VEGF mRNA expression	Ramadan et al. (2023)
Hydroxybenzoic acid and hydroxycinnamic acid	Gallic acid and caffeic acid	Standard	Swiss albino mouse (Allo: EAC cells)	40–80 mg/kg (i.p., on days 5, 7, 9, and 11 after cell inoculation)	VEGF, MMP-2, and MMP-9	↓ MVD and MMP-2, MMP-9, VEGF mRNA expression	Orsolic et al. (2020)
Stilbenes	Resveratrol	Standard	HUVECs	25–100 μM	ND	↓ Tube structures ↑ Capillary free area	Uvez et al. (2020)
			CAM	10-5-2.5 μg/pellet			
			Athymic mice (Xen: COLO205-luc cells)	6 μg/implant (3 weeks)	ND	↓ Hb percentages in tumor mass	Sudha et al. (2020)
			BALB/c mice (Allo: EAT cells)	50 mg/kg (i.g., 5 days and start 2 days after injecting cells)	HDAC, VEGF	↓ HDAC activity, VEGF expression, and no. of blood vessels	Kucan et al. (2023)

Abbreviations: Allo, allograft; CAM, in vivo chick chorioallantoic membrane; CD, cluster of differentiation; EGCG, epigallocatechin-3-Gallate; Hb, hemoglobin; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor 1-α; HUVECs, human umbilical vein endothelial cells; i.g., intragastric; i.p., intraperitoneal; MMP, matrix metalloproteinase; MVD, microvessel density; No., number; p.o., per os; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; Xen, xenograft.

citrus fruits (Mahmud et al., 2023). Epigallocatechin gallate, an example of flavanol, demonstrated antiangiogenic effects in human gastric cancer (SGC7901) cells alone and in BALB/c-nu/nu nude mice combined with vincristine sulfate through downregulation of VEGF at both protein and mRNA levels (L. Chen et al., 2020; Fu et al., 2019).

Flavanones, another subclass of flavonoids, are abundant in various plants' seeds, fruit skin, bark, and flowers (Panche et al., 2016). Numerous naturally occurring flavanones have been identified for their antioxidative, anti-inflammatory, and antibacterial properties (Manthey et al., 2001; Moulari et al., 2006). A previous study indicated that hesperidin, a flavanone glycoside from citrus species, suppresses metastasis, angiogenesis, and tumor growth in BALB/c mice xenografted with 4T1 cell lines by inducing a significant reduction in the gene expression of CD105, VEGF-A, VEGFR2, and COX-2 (Shakiba et al., 2023). Hesperidin can also inhibit tumor growth and invasion by inhibiting angiogenesis and metastasis by decreasing mast cell density, MMP-2, and MMP-9 expression in Swiss mice with Benzo(a)pyrene-induced lung cancer (Kamaraj et al., 2010). Baicalin, the main active chemical constituent of *Scutellaria baicalensis*, exhibited antiangiogenic effects both in vitro (human pulmonary adenocarcinoma [A549] cells and HUVECs) and in vivo (nude mice xenografted with human pulmonary adenocarcinoma (A549) cells), resulting in decreased tube formation and VEGF protein expression (Yan et al., 2020).

Flavonols such as myricetin (Kim et al., 2006), quercetin (Tan et al., 2003), kaempferol (Luo et al., 2009), and galangin (Huang et al., 2015), found in various fruits, vegetables, nuts, and beverages such as wine and tea, have been widely researched for their antiangiogenic properties (Khater et al., 2020). Quercetin, in particular, displayed antiangiogenic effects in human esophageal carcinoma (Eca109) and human colorectal adenocarcinoma (HT-29) cells by decreasing VEGF-A, VEGFR-2, MMP-2, and MMP-9 protein expression (Liu, Li, et al., 2021; Uttarawichien et al., 2021a). Quercetin exposure also reduced new vessel formation and CD31 expression in Swiss albino mice allografted with Ehrlich ascites carcinoma cells (Sannappa Gowda et al., 2023).

Isoflavones, such as genistein, daidzein, and equol, primarily found in legumes like soy, exhibit significant antiangiogenic properties (Krizova et al., 2019; Varinska et al., 2015). Genistein, identified as the primary isoflavone in soybeans, acts as a receptor-associated tyrosine kinase inhibitor, preventing excessive cell proliferation and abnormal angiogenesis (Akiyama et al., 1987). It interacts primarily with HIF-1α in breast cancer (MDA-MB231 and T-47D) cells (Mukund et al., 2019). In an oral squamous cell carcinoma (HSC-3) cell line, genistein downregulated VEGF, bFGF, and MMP-2 (Myoung et al., 2003). It also demonstrated anticancer effects in human thyroid cell lines (CAL-62, ACC 448, CGTH-W1, and ACC 360) by reducing cell viability and hTERT, VEGF-A, and NF-κB mRNA expression levels (Ozturk et al., 2018). In prostate cancer (LNCaP, PC-3, and DU-145) cells, Daidzein directly inhibited several angiogenesis genes (Rabiau et al., 2010). Equol inhibited angiogenesis in bovine brain capillary endothelial cells through the MAPK pathway, downregulating VEGF, FGF2, and extracellular regulated kinase1/2 (Bellou et al., 2012).

Phenolic acids, a nonflavonoid subcategory, are divided into hydroxybenzoic and hydroxycinnamic acids, characterized by hydroxylated aromatic rings (Tsakiroglou et al., 2019). Hydrobenzoic acids, such as vanillic acid, have shown the capacity to hinder angiogenesis and proliferation by inhibiting HIF-1 protein synthesis in a dose-dependent manner (Gong et al., 2019). Protocatechuic acid exhibited potent antiangiogenic activities in an in vitro study using HUVECs, blocking several cellular processes and inhibiting VEGFR2-dependent A/MMP-2 and ERK pathways (Hu et al., 2018). Gallic acid inhibited the growth and in vitro angiogenesis of two ovarian cancer (OVCAR-3 and A2780/CP70) cell lines by inhibiting VEGF secretion through AKT phosphorylation inhibition and HIF-1α expression while promoting PTEN expression (He et al., 2016). Ellagic acid is another antioxidant, a natural compound with antiangiogenic effects in cancer, attributed to growth inhibition and apoptosis-promoting activity (Vanella et al., 2013). Ellagic acid demonstrated antiangiogenic effects in rat glioma (C6) and human cervical carcinoma (HeLa) cells, leading to decreased VEGF mRNA and protein expression (Çetin & Biltekin, 2019; Ramadan et al., 2023; Sarıbaş et al., 2023). Vanella et al. (2013) evaluated the antiangiogenic effects of exposure to 25–50 μM of ellagic acid in the human prostatic cancer cell line LnCap. The authors reported that ellagic acid decreases VEGF, which poses antiproliferative and prodifferentiation properties via decreased eicosanoid synthesis (Vanella et al., 2013). Kowshik et al. (2014) tested the ellagic acid in a hamster model of oral oncogenesis; the researchers observed that it is a lead compound for anticancer therapeutics because it inhibits VEGF/VEGFR2 signaling a critical oncogenic cascade (Kowshik et al., 2014). Concerning hydroxycinnamic acids, ferulic acid inhibits endothelial cell tube formation and suppresses melanoma (A375, CHL-1, SK-MEL-2, B16F10) cell growth and angiogenesis through the FGFR1-mediated PI3K-AKT signaling pathway (Yang et al., 2015). The combination of hydroxybenzoic and hydroxycinnamic acids, specifically gallic and caffeic acids, exhibited antiangiogenic effects in a murine model allografted with Ehrlich ascites carcinoma cells, reducing microvessel density and downregulating VEGF, MMP-2, and MMP-9 mRNA expression (Orsolic et al., 2020).

Lignans, diphenolic plant compounds resulting from the dimerization of cinnamic acid residues, are found in various foods, fruits, vegetables, and cereals (Hazafa et al., 2022; Reuben et al., 2012). Flaxseed (*Linum usitatissimum*)-derived lignans, enterodiol, and enterolactone have shown inhibition of VEGF secretion in human breast cancer (MCF-7) cells (Bergman Jungestrom et al., 2007). Additionally, sesamin extracted from *Sesamum indicum* seeds suppressed VEGF expression in human breast cancer (MCF-7 and MDA-MB-231) cells by targeting HIF-1α, NF-κB, AKT, and p38 MAPK (Lee et al., 2011). Episesamin treatment in HCC cells led to significantly lower VEGF levels in an in vitro study (Freise et al., 2012).

Stilbenes also represent a large class of plant secondary polyphenols widely distributed in food and medicinal plants (Su et al., 2022). A notable example is resveratrol. Resveratrol is a natural polyphenol found in various plants and fruits, such as grapes, blueberries, cranberries, and peanuts. Resveratrol has multiple biological effects, including antioxidant, antiaging, anti-inflammatory, antiestrogenic, and

anticancer activities (Koushki et al., 2018). Resveratrol can inhibit angiogenesis by affecting various molecular pathways and cellular processes. This compound exerts its anticancer effects by preventing angiogenesis, which is vital for tumor growth and metastasis, as it provides nutrients and oxygen to the cancer cells and allows them to invade other tissues. Resveratrol inhibited VEGF expression in human ovarian cancer (A2780/CP70 and OVCAR-3) cells by reducing HIF-1α expression levels (Cao et al., 2004). In addition, resveratrol inhibited VEGF expression and cell proliferation in a human osteosarcoma (U20S) cell line (Liu et al., 2012). This phenolic compound was also shown to decrease tube structures in HUVECs, increase the capillary-free area in CAM, and reduce hemoglobin percentages within the tumor mass in BALB/c mice xenografted with Ehrlich ascites carcinoma cells (Kucan et al., 2023; Sudha et al., 2020; Uvez et al., 2020). Although resveratrol is the most well-known stilbene and has antiangiogenic effects in several models, other stilbenes, such as piceatannol, also show these properties. In BALB/c mice allografted with mammary carcinoma (4T1) cells, piceatannol treatment reduced the expression of transcription factors P-NF-κB, p65, P-STAT3, and HIF-1α, along with various proteins regulating angiogenesis (VEGF-A, VEGFR-2, VE-cadherin, CD31) (Song et al., 2015). Also, resveratrol can prevent the activation of VEGF receptor-2 (VEGFR-2) and the molecules it signals, such as Akt, ERK, and eNOS, which mediate the angiogenic activity of VEGF (W. H. Hu et al., 2019). Likewise, resveratrol can modify the function and expression of integrins, which mediate the interaction between the extracellular matrix and endothelial cells. Resveratrol can specifically inhibit the $\alpha v\beta 3$ integrin, which is highly expressed on activated endothelial cells and has a relevant role in angiogenesis (Ho et al., 2018). Resveratrol can interfere with the attachment of $\alpha v\beta 3$ integrin to vitronectin and fibronectin and prevent the development of focal adhesion complexes and cytoskeletal rearrangements required for endothelial cell migration and invasion. Resveratrol can decrease the production and action of molecules that cause inflammation, such as COX-2, prostaglandins, and interleukins, which can increase angiogenesis by promoting the expression of VEGF and other angiogenic factors (Zykova et al., 2008). Resveratrol can also stop the activation of NF-κB, which controls the expression of many genes related to inflammation and angiogenesis (Manna et al., 2000). Resveratrol can augment the amount and activity of enzymes that protect cells from harmful ROS and reduce oxidative stress (Xia et al., 2017). These enzymes include glutathione peroxidase, catalase, and superoxide dismutase. Finally, resveratrol can also modulate the signaling pathways sensitive to the balance of ROS, such as Nrf2 and AMPK, which can control the expression of genes associated with antioxidant defense, energy metabolism, and angiogenesis (Bitterman & Chung, 2015; Dhapola et al., 2024; Kim et al., 2018).

Resveratrol has been tested in different experimental models of angiogenesis and cancer. It has exhibited hopeful results in stopping the creation of new blood vessels and tumor growth. For example, a pioneer study investigated the antitumor properties of resveratrol on RT-2 gliomas in rats and its impact on angiogenesis (Tseng et al., 2004). Its experimental design involved treating RT-2 glioma cells with resveratrol, assaying cytotoxicity, measuring apoptosis by flow-activated cell sorter flow cytometry, and quantifying the VEGF expression by RT-PCR. Additionally, in vitro proliferation was assayed to explore the effects of resveratrol on the proliferation of ECV304 endothelial cells. The study found that resveratrol had a concentration- and time-dependent cytotoxic effect on glioma cells, causing apoptosis. Furthermore, the expression of VEGF in the glioma cells and the proliferation of ECV304 cells were inhibited by resveratrol in a concentration-dependent fashion. Immunohistochemical analyses showed that the s.c. gliomas from resveratrol-treated rats had fewer microvessel densities than those of control rats. Therefore, resveratrol demonstrated substantial cytotoxicity and apoptosis in glioma cells and inhibited angiogenesis in s.c. gliomas. Similarly, Trapp et al. (2010) performed experiments to evaluate the effects of resveratrol on angiogenesis in vitro in HMVECad endothelial cells. The authors assessed angiogenesis as a function of endothelial cell survival in a three-dimensional spheroidal coculture. When cocultured with WM3211, YUZAZ6, or A375 melanoma cells, resveratrol treatment (50 IM, 48 h) decreased endothelial cell viability. Interestingly, the combination of resveratrol with other compounds seems to improve the anticancer and antiangiogenic activities. In this regard, a study investigated the antiangiogenic properties of resveratrol and 5-Fluorouracil (5-FU), individually or in combination, in a B16 mouse melanoma model. The combined use of resveratrol and 5-FU was more successful in inhibiting cell growth than either drug used separately, and this antigrowth effect was linked to changes in the expression levels of AMPK, COX-2, vasodilator-stimulated phosphoprotein (VASP), and VEGF. Moreover, the combined treatment of resveratrol and 5-FU led to a reduction in tumor growth compared to the control group, and this reduction in growth was correlated with changes in the expression levels of VEGF, VASP, and AMPK. Immunohistochemical analysis of angiogenesis indicated that the combined treatment of resveratrol and 5-FU resulted in fewer microvascular vessels than the control group. These findings demonstrate that the combined treatment of resveratrol and 5-FU inhibited angiogenesis and cell growth in B16 mouse melanoma tumors.

It is necessary to highlight that some compounds, such as genistein and resveratrol, are endocrine-disrupting chemicals. This implies a dual role of these compounds, which can both prevent and promote cancer depending on the context (Modica et al., 2023). For example, genistein has shown the potential to reduce mammary cancer in rats (Bhat et al., 2021). However, it has also been associated with increased mammary tumors and uterine adenocarcinomas in animal models (Doerge et al., 2002; Newbold et al., 2001). Similarly, resveratrol, known for its chemopreventive properties, can also act through estrogenic pathways, potentially exacerbating hormone-dependent cancers (Abdal Dayem et al., 2016). Polyphenols have a chemical structure like that of estradiol. Therefore, they could join the estrogenic receptors (Henley & Korach, 2006) and alter the hormone functions related to cholesterol production and reproductive cycles in males and females. Specifically, the dual observed effect could be given to the relation between hormone activity in the organism, the type of cancer hormone-dependent, and the dose and affinity to estrogenic receptors of the compound (Henley & Korach, 2006; Modica et al., 2023).

4.2.2 | Terpenes and terpenoids

Terpenes, synthesized by plants and various organisms through the mevalonate pathway, are commonly present in essential oils, resins, and other plant-derived materials (Masyita et al., 2022). Distinguished by a specific carbon skeleton, terpenes display a diverse array of linear, branched, or cyclic structures. These compounds consist of basic hydrocarbons, whereas terpenoids represent a modified category of terpenes featuring diverse functional groups and oxidized methyl groups relocated or eliminated at various positions (Perveen, 2018). Terpenes or terpenoids are grouped as hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40). These compounds interact with specific biological targets, modulating signaling pathways critical to cellular processes (Wroblewska-Luczka et al., 2023). Notably, terpenes demonstrate potent antiangiogenic effects in cancer (Wroblewska-Luczka et al., 2023), as shown in Table 5.

Monoterpenes like thymoquinone, auraptene, and linalool also exhibited antiangiogenic effects. Thymoquinone inhibited MMP-2, MMP-9, and VEGF expression in DEN-intoxicated rats (Tadros et al., 2022), while auraptene, in CAM and human breast cancer (MCF-7) cells, reduced the number of blood vessels, as well as MMP-2, MMP-9, VEGFR-1, and VEGFR-2 expression levels (Charmforoshan et al., 2019). Linalool has been studied using several models, namely in B16F10, a murine melanoma cell line, CAM, aortic ring assay, and HDMECs, leading to inhibition of VEGF, MMP-2, and MMP-9 expression, as well as decreased vascular network formation (Becker et al., 2021; Pal et al., 2022).

Sesquiterpenes like β-caryophyllene (BCP), furanodiene, and artemisinin (ART) showed antiangiogenic properties in various models. BCP, found in plants, inhibited tube formation in HUVECs and reduced neovascularization in CAM (Dahham et al., 2021), while furanodiene, also of plant origin, decreased subintestinal vessel formation in zebrafish (Zhu et al., 2019). Extensive evaluation in HUVECs, osteosarcoma (MG-63) cells, as well as xenografts of osteosarcoma and breast cancer, has revealed ART as capable of modulating the expression of critical factors such as TSP-1, VEGF, HIF-1α, and Notch1 (J. Dong et al., 2020; Z. Li et al., 2019; Tsui et al., 2019; Yu et al., 2022). β-elemene, another sesquiterpene, exhibited antiangiogenic activity in hemangioma endothelial cells (HemECs) and BALB/c mice by downregulating ACE2, VEGFA, and HIF-1α (Z. Wang et al., 2023; Wang et al., 2021).

Leucosesterterpenone, a sesterterpene isolated from the Himalayan plant *Leucosceptrum canum*, is capable of inhibiting FGF-2-induced proliferation, migration in a wounding assay, chemotaxis, and tube formation with small vessel (human dermal) and large vessel (bovine aortic) endothelial cells (Hussain et al., 2008).

One noteworthy polycyclic diterpenoid is Taxol (paclitaxel), which promotes tubulin polymerization and shows remarkable efficacy in cancer chemotherapy (Koksal et al., 2011). This natural product, extracted from the bark of the Pacific yew tree *Taxus brevifolia*, is a widely used agent for the treatment of a variety of tumors, including lung, breast, head, neck, and ovarian cancers, as well as Kaposi's sarcoma (Hsiao et al., 2009; Li et al., 2012; Wang et al., 2009). This drug has been widely studied regarding its antiangiogenic properties (Bocci et al., 2013). Recent studies focus on low-dose paclitaxel administrations (Shetti et al., 2019), combinations with other natural compounds (Mahmoud et al., 2021), and even new encapsulation formulations to improve its delivery (Clemente et al., 2019).

Regarding sesquiterpenoids, such as curcumol, these compounds displayed antiangiogenic effects by decreasing VEGF-A and TSP1 protein levels in human pulmonary adenocarcinoma (A549) and human non-small-cell lung cancer (H1975) cells and BALB/c mice xenografted with human pulmonary adenocarcinoma (A549) cells (Ma et al., 2022). Additionally, it reduced HIF-1α, p-ERK, p-JNK, p-p38, p-mTOR, p-p70S6K, p-4EBP1, and p-eIF4E in human HCC (Hep3B) cells (Zuo et al., 2020). Diterpenoids, including eurifoloid Q, suppressed angiogenesis by targeting VEGFR/AKT in rat aortic rings and HUVECs (Qi et al., 2020). Anotherditerpenoind is Tanshinone I, Tanshinone IIA, and Cryptotanshinone compounds of the herb *Salvia miltiorrhiza*, which efficiently inhibit antiangiogenesis in tumor metastasis in hypoxic or normoxic conditions, acting in vitro (lung cancer and osteosarcoma cells) and in vivo, and induced the impairment of VEGF expression to suppress the cancer growth (Zhou et al., 2020; Zhu et al., 2016).

Triterpenoids, such as oleanolic and ursolic acids, exhibited antiangiogenic effects by downregulating VEGFR, HIF-1α, and MMP-2 mRNAs in DMBA-induced HCC in Swiss mice, several tumor cell lines (A549, H460, and CAKI-1 cells), and HUVECs (Cai et al., 2023; Hosny et al., 2021; Kang et al., 2021). A hexane extract from *Azadirachta indica* containing lupeol, isomeldenin, nimocinol, gedunin, and nimbidinin also reduced VEGFR, HIF-1, and MMP-2 mRNA expression in DEN-induced HCC Wistar rats (Akinloye et al., 2021).

4.2.3 | Carotenoids

Carotenoids, the most common tetraterpenes in nature, are ubiquitous pigments in photosynthetic bacteria, algae, and plants (Ademowo et al., 2024; Maoka, 2020). These compounds play an important role in photosynthesis, displaying red, yellow, or orange hues while contributing to photoprotection and cell membrane stabilization. Chemically, carotenoids are divided into carotenes (pure hydrocarbons containing no oxygen) and xanthophylls (oxygenated carotenes). Typically composed of eight isoprene units, most carotenoids feature a 40-carbon backbone with a standard structure comprising a polyene chain with nine conjugated double bonds and terminal groups (Maoka, 2020). The effects of several carotenoids (astaxanthin,7′,8,8′-tetrahydro-β,β-carotene, betacarotene-15,15′-epoxide, diatoxanthin, crocetin, crocin, and fucoxanthin) have been the focus of extensive research, particularly assessing their antiangiogenic properties in cancer (Table 6).

Astaxanthin, a plant-derived xanthophyll, has shown promising antiangiogenic effects in various *in vitro* and in vivo models. In human prostate cancer (LNCaP) cells, astaxanthin demonstrated a decrease in VEGF-A expression (Erzurumlu, Catakli, & Dogan, 2023). Additionally, in colon cancer (HCT116) cells, astaxanthin exhibited an upregulation of miR-29a-3p expression (Kim et al., 2019). Furthermore, in a DMBA-induced breast carcinoma model in Wistar rats, a combination

TABLE 5 Naturally occurring plant terpenes/terpenoids compounds in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Structural class	Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular targets	Effects	Ref(s)
Diterpenoid	Eurifoloid Q	Isolated from *Euphorbia neriifolia*	Rat aortic ring	12.5–50 μg/mL (7 days)	VEGFR/AKT	↓ p-AKT and VEGFR expressions	Qi et al. (2020)
			HUVECs	50 μg/mL (24 h)		↓ New blood vessel growth	
Monoterpene	Auraptene	Purified from *Ferula Szowitsiana*	MCF-7 cells	62.5–250 μg/mL (10 and 24 h)	VEGF	↓ MMP-2, ↓MMP-9, ↓VEGFR-1, ↓VEGFR-2	Charmforoshan et al. (2019)
			CAM	125–1000 μg/mL (12 days)		↓ No. of blood vessels	
	Linalool	Standard	B16F10 cells	0.4–0.8 mM (24 h)	VEGF	↓ MMP-2, ↓MMP-9, ↓VEGF, ↓vimentin ↓mRNA ↑ E-cadherin	Pal et al. (2022)
			CAM	0.4–0.8 mM (8 days)		↓ Vascular network	
			HDMECs	2 mM (24 h)	TRPM8	↓ Tube formation, intracellular ATP levels ↑ p-ERK/ERK levels TRPM8 activation	Becker et al. (2021)
			Rat aortic ring	0.25–2 mM (6 days)		↓ Area of sprouting	
	Thymoquinone	Standard	DEN-intoxicated rats	5 mg/kg (p.o., 7 days)	miR-1-3p	↓ MMP-2, ↓MMP-9, ↓VEGF ↑ TIMP3, miR-1-3p	Tadros et al. (2022)
Sesquiterpene	ART	ND	HUVECs, MG-63 cells	24 μM	TSP-1	↑ TSP-1, ↑p-p38 ↑p-CREBf	Z. Li et al. (2019)
		Standard	BALB/c mice (Xen: MDA-MB-231 cells)	50–200 mg/kg (gavage, 21 days)	VEGF, HIF-1α, Notch1	↓ VEGF, ↓ HIF-1α (20 mg/kg), ↓ Notch1, ↓ Jagged1, ↓ Dll4 (50–200 mg/kg)	J. Dong et al. (2020)
		ND	Cal27 and HN31 cells, HUVECs	25–100 μM (24 h)	VEGF	↓ VEGF, ↓ IL-8, ↓ MIF ↓ mRNA, ↓ tube formation (100 μM), ↓ VEGFR1 and R2	Yu et al. (2022)
			Nude mice (Xen: Cal27 cells)	50 mg/kg (i.p., 21 days)		↓ IL-8, ↓ MIF, ↓ VEGF	
		Standard	HUVECs, MDA-MB-231 cells	10 μM (24 h)	VEGF	↓ Tube formation	Tsui et al. (2019)
			BALB/c nude mice (Xen: MDA-MB-231)	100 mg/kg (i.v., 14 days)		↓ CREB, ↓ PGC1α, ↓ VEGF	
	BCP	Standard	HUVECs	10–20 μM (48 h)	VEGF	↓ VEGF, ↓ neovascularization	Dahham et al. (2021)
			CAM	10–20 μM (48 h)		↓ Tube formation	

(Continues)

TABLE 5 (Continued)

Structural class	Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular targets	Effects	Ref(s)
	Furanodiene	ND	Zebrafish (Xen: JF-305 cells)	4.1–12.2 μM (24 h)	ND	↓ SIVs	Zhu et al. (2019)
	β-elemene	ND	HemECs	5–160 μg/mL (24 h)	ACE2, HIF-1*α*	↓ ACE2, ↓ HIF-1*α*, ↓ VEGFA (40–160 μg/mL)	Wang et al. (2021)
			BALB/c mice (Xen: HemECs)	20–160 mg/kg (i.p., 30 days)			
		Standard	HemECs	75 μg/mL (24 h)	HIF-1-*α*/VEGFA	↓ Tube formation, ↓ HIF-1-*α*, ↓ VEGFA, ↓ p-AKT/AKT, ↓ p-Erk/Erk, ↓ CD31 expression	Z. Wang et al. (2023)
			BALB/c mice (Xen: HemECs)	75 mg/kg (i.p., 30 days)			
Sesquiterpenoid	Curcumol	Standard	A549 and H1975 cells	400 μM (24 h)	VEGF, SP1, miR-125b-5p	↓ VEGFA, ↓ SP1 protein level, ↓ CD31 ↑ miR-125b-5p	Ma et al. (2022)
			BALB/c mice (Xen: A549 cells)	40–80 mg/kg (gavage, 25 days)			
			Hep3B cells	3–30 μM (24 h)	HIF-1*α*	↓ HIF-1*α*, ↓ p-ERK, ↓ p-JNK, ↓ p-p38, ↓ p-mTOR, ↓ p-p70S6K, ↓ p-4EBP1, ↓ p-eIF4E	Zuo et al. (2020)
Triterpenoid	23(E)-eupha-8,23–diene-3*β*,25-diol-7-one	Isolated from *Euphorbia neriifolia*	HUVECs	12.5–50 μg/mL (7 days)	VEGFR/AKT	↓ VEGFR, ↓ p-AkT	Qi et al. (2020)
			Rat aortic ring	50 μg/mL (24 h)		↓ New blood vessel growth	
	Lupeol, isomeldenin, nimocinol, gedunin, nimbidinin	Hexane extract from *Azadirachta indica*	DEN-induced hepatocellular carcinoma in Wistar rats	30–50 mg/kg (p.o., 2 weeks)	VEGF, HIF-1	↓ VEGFR, ↓ HIF-1*α*, ↓ MMP-2 mRNA expression	Akinloye et al. (2021)
	Oleanolic acid	Standard	DMBA-induced hepatocellular carcinoma in Swiss mice	75 mg/kg (dissolved in olive oil, gavage, 4 weeks)	VEGF	↓ VEGF	Hosny et al. (2021)
	Ursolic acid	Standard	A549 and H460 cells, HUVECs	10–20 μM (12 and 24 h)	STAT3, VEGF	↓ Tube formation, ↓ MMP-2, ↓ p-STAT3, ↓ VEGF	Kang et al. (2021)
		ND	CAKI-1 cells, HUVECs	5–80 μmol/L (24 h)	VEGF	↓ Tube formation, ↓ VEGF	Cai et al. (2023)

Abbreviations: ACE2, angiotensin-converting enzyme 2; ART, artemisinin; BCP, *β*-caryophyllene; CD31, cluster of differentiation 31; CREB, cAMP-responsive element binding protein-1; DEN, diethylnitrosamine; DMBA, 7,12-Dimethylbenz[a]anthracene; Erk, extracellular signal-regulated kinases; HDMECs, human dermal microvascular endothelial cells; HemECs, human hemangioma endothelial cells; HIF-1*α*, hypoxia-inducible factor 1-*α*; HUVEC, human umbilical vein endothelial cells; i.p., intraperitoneal; i.v., intravenous; IL-8, interleukin-8; JNK, c-Jun N-terminal kinase; MIF, macrophage migration inhibitory factor; miRNA, microRNA; MMP, matrix metalloproteinase; ND, nondefined; No., number; p.o., per os; PGC1*α*, peroxisome proliferator-activated receptor-gamma coactivator-1 *α*; SIVs, subintestinal vessels; SP1, specificity protein 1; TRPM, transient receptor potential cation channel subfamily M (melastatin) Member; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor; Xen, xenograft.

TABLE 6 Naturally occurring carotenoids compounds in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Structural class	Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular target	Effects	Ref(s)
Xanthophyll	Astaxanthin	Standard	LNCaP cells	10–250 μM (24 h)	VEGF-A	↓ VEGF-A expression	Erzurumlu et al. (2023)
			HCT116 cells	50–100 μM (24 h)	miR-29a-3p	↑ miR-29a-3p expression	Kim et al. (2019)
	Astaxanthin, 7,7′,8,8′-tetrahydro-β,β-carotene and β-carotene-15,15′-epoxide	Isolated from *Spondias mombin*	DMBA-induced breast carcinoma in Wistar rats	100–200 mg/kg (p.o., 4 weeks)	EGFR, HIF-1, MMP-2, VEGF, VEGFR	↓ Tumor size and EGFR, HIF-1, MMP-2, VEGF, VEGFR mRNA expression ↑ CHD-1 expression	Metibemu et al. (2021)
	Diatoxanthin	ND	DU145 and PC3 cells	4.41–441 pM (24 h)	MMP-1 and MMP-9	↓ MMP-1 and MMP-9 expression	Sansone et al. (2023)
Apocarotenoid dicarboxylic acid	Crocetin	ND	HUVECs, Hs-746T cells	30–100 μM (24 h)	ND	↓ Tube formation and vasculogenic mimicry formation	Zang et al. (2021)
Hydrophilic carotenoids	Crocin	Standard	Athymic nude mice (NCR nu/nu) (Xen: HT-29 cells)	50–150 mg/kg (gavage, five times per week)	ND	↓ Tumor volume and no. of vessels	Bakshi et al. (2022)
Epoxycarotenol	Fucoxanthin	Standard	CMT-U27 cells, HUVECs	5–20 μM (18 h)	Ang-2	↑ Ang-2	Jang et al. (2021)
			MDA-MB-231 and MDA-MB-468 cells	1.56–300 μM (24 h)	VEGF-A, VEGF-C	↓ VEGF-A and VEGF-C mRNA expression	Ahmed et al. (2023)
		Isolated from *Phaeodactylum tricornutum*	CAM (with GBM1 cells)	10–150 μM (24 h)	ND	↓ No. and area of vessels	Lopes et al. (2020)
		Isolated from *Undaria pinnatifida*	MDA-MB-231	25–100 μM (12 h, 24 and 48 h)	VEGF-C and VEGFR-3	↓ VEGF-C and VEGFR-3 protein and mRNA levels	Wang et al. (2019)
			BALB/c nu/nu mice (Xen: MDA-MB-231 cells)	100–500 μM (injected at the tumor periphery daily, 26 days)		↓ VEGFR-3 protein expression, lymphatic vessel numbers, tumor volume, and weight	

Abbreviations: Ang-2, angiopoietin-2; CAM, in vivo chick chorioallantoic membrane; DMBA, 7,12-Dimethylbenz[a]anthracene; EGFR, epidermal growth factor receptor; HIF-1α, hypoxia-inducible factor 1-α; HUVECs, human umbilical vein endothelial cells; miR, microRNA; MMP, matrix metalloproteinase; ND, nondefined; No., number; p.o., per os: VEGF, vascular endothelial growth factor; VEGFR, vascular growth factor receptor; Xen, xenograft.

of astaxanthin, 7,7′,8,8′-tetrahydro-β,β-carotene and betacarotene-15,15′-epoxide led to a significant reduction in the expression of vital angiogenesis-related markers, including VEGF, VEGFR, EGFR, HIF-1α, and MMP-2 (Metibemu et al., 2021). Other carotenoids, such as diatoxanthin and crocetin, have also demonstrated antiangiogenic properties. Diatoxanthin, in human prostate cancer (PC3 and DU145) cells, decreased MMP-1 and MMP-9 expression (Sansone et al., 2023). At the same time, crocetin, an apocarotenoid dicarboxylic acid, demonstrated antiangiogenic effects in gastric cancer (Hs-746T) cells and HUVECs, leading to a reduction in tube formation and vasculogenic mimicry (Zang et al., 2021). Hydrophilic carotenoids, such as crocin, have also shown promise in inhibiting tumor growth and angiogenesis. In athymic nude mice xenografted with human colorectal adenocarcinoma (HT-29) cells, crocin administration decreased the number of vessels and tumor volume (Bakshi et al., 2022). Additionally, fucoxanthin, an epoxycarotenol, exhibited antiangiogenic effects in various models, including female dog mammary gland carcinoma (CMT-U27), human breast cancer (MDA-MB-231 and MDA-MB-468) cells, CAM with glioblastoma (GBM1) cells, and BALB/c nu/nu mice xenografted with human breast cancer (MDA-MB-231) cells. In these studies, angiogenesis was hindered by decreased expression of VEGF-A, VEGF-C, and VEGFR-3 protein and mRNA levels but also reduced lymphatic vessel number and area, tumor volume, and weight (Ahmed et al., 2023; Jang et al., 2021; Lopes et al., 2020; Wang et al., 2019).

Although some studies report carotenoids in animals, these are primarily acquired from food or undergo partial modification through metabolic reactions, as animals generally do not synthesize them *de novo* (Maoka, 2011). Marine animals, including sponges, mollusks, and crustaceans, exhibit structural diversity in their carotenoids, which often derive from β-carotene, fucoxanthin, peridinin, diatoxanthin, alloxanthin, and astaxanthin (Maoka, 2011). New structural carotenoids discovered in marine animals offer valuable information about function, food chains, and metabolic pathways, most likely sourced from seaweeds or microalgae (Meresse et al., 2020).

4.2.4 | Cannabinoids

Cannabinoids, classified as terpenophenolic compounds with a C21 backbone, display diverse chemical structures primarily influenced by variations in isoprenyl groups, side chains, and the resorcinyl core. Based on their chemical composition, cannabinoids can be categorized into 11 distinct classes, namely, cannabichromene, cannabidiol (CBD), cannabielsoin, cannabigerol, cannabicyclol, cannabinol (CBN), cannabinodiol, cannabitriol, (−)-Δ8-trans-tetrahydrocannabinol (Δ8-THC), (−)-Δ9-trans-tetrahydrocannabinol (Δ9-THC), and miscellaneous-type cannabinoids (Radwan et al., 2021). While several compounds in these subclasses exhibit anticancer activity (Daris et al., 2019; Silva-Reis et al., 2023), three classes (CBD, CBN, and THC) have been extensively studied and shown to impact angiogenesis in cancer (Table 8). CBD, a nonpsychotropic phytocannabinoid isolated from *Cannabis sativa*, has been extensively studied regarding its anticancer properties, especially by mediating angiogenesis (Ramer et al., 2014). This compound inhibited sprout formation in human pulmonary adenocarcinoma (A549) cells cocultured in HUVECs and treated with CBD (Ramer et al., 2014). More recently, CBD was reported to exhibit antiangiogenic properties in various models. It induced a reduction in VEGF, a key regulator of angiogenesis, in BALB/c mice xenografted with the murine colorectal carcinoma (CT26) cells; it caused a decrease in VEGF, a key regulator of angiogenesis (Honarmand et al., 2018). In human breast cancer (MCF-7) cells, CBD contributed to the downregulation of HIF-1α and VEGF (Jo et al., 2021). In human prostatic adenocarcinoma (LNCaP) cells, CBD reduced N-cadherin and VEGF levels (Erzurumlu, Catakli, & Sezer, 2023), while in athymic nu/J mice xenografted with lung adenocarcinoma (NCI-H1437) cells, it reduced the levels of VEGF and P-selectin (Salles et al., 2023). THC, another cannabinoid compound, inhibited vascularization in A549 xenografted tumors in SCID mice (Preet et al., 2008). In ErbB2-MMTV-neu mice with metastatic mammary cancer, THC treatment resulted in antiangiogenic effects through the downregulation of AKT (Caffarel et al., 2010). Furthermore, CBN, another cannabinoid, was described to exhibit antiangiogenic effects in neuroblastoma cell lines (IMR-5 and SK-N-AS), including decreased p-AKT, downregulated E2F1 expression, and increased miR-34a expression (Wang et al., 2022). Extracts containing CBD, THC, and THCA also reduce CAM's VEGF and L-arginine-induced vessel formation (Bala et al., 2019).

4.2.5 | Alkaloids

Alkaloids, nitrogen-containing compounds produced by plants, fungi, and bacteria (Dey et al., 2020), have diverse biological effects and historical uses in traditional medicine (Ziegler & Facchini, 2008). They can be classified based on nitrogen atoms and categorized by chemical properties and sources (Yan et al., 2021). Some alkaloids exhibit promising anticancer properties, particularly in angiogenesis modulation (Table 7).

Capsaicin is a natural product of Capsicum species; it induces excitation of nociceptive terminals implicated in pain sensation (Min et al., 2004). It has demonstrated carcinogens' and mutagens' properties in *vitro* and in vivo assay systems. in vitro, 1−25 μM for 48 h of capsaicin (IC_{50}: 5 μM) inhibited VEGF-induced proliferation, DNA synthesis, chemotactic motility, and capillary-like tube formation of primary cultured human endothelial cells (Min et al., 2004). Also, it protects against experimentally induced mutagenesis and tumorigenesis and induces apoptosis in immortalized or malignant cell lines (Surh, 1999). Pyun et al. (2008) demonstrated that the pretreatment for 30 min of 1, 5, 10, or 25 μmol/L of capsiate (a capsaicin analog) in primary cultured human endothelial cells inhibited VEGF-induced proliferation, chemotactic motility, and capillary-like tube formation. Their study also exposed that the exposure of capsiate (5 or 25 μmol/L) to aortic segments from 6-week-old Sprague-Dawley rats (*ex vivo* study) inhibits VEGF-induced vessel sprouting. In an in vivo study with C57BL/6 mice, exposure for 7 days to 0.6 mL of Matrigel containing VEGF (100 ng) and 60 μg of capsiate inhibited the formation of new blood vessels (Pyun et al., 2008).

TABLE 7 Naturally occurring cannabinoids derived from *Cannabis sativa* in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular targets	Effects	Ref(s)
CBD	ND	BALB/c mice (Xen: CT26 cells)	1–5 mg/kg (i.p., three times a week, 7 weeks)	VEGF	↓ VEGF	Honarmand et al. (2018)
	Standard	MCF-7 cells	2 μM (1–24 h)	HIF-1α	↓ HIF-1α and VEGF	Jo et al. (2021)
	Formulation ApelinDx	Athymic nu/J mice (Xen: NCI-H1437 cells)	6.4 mg/day (inhaled, 3 weeks)	P-selectin, VEGF	↓ P-selectin and VEGF	Salles et al. (2023)
	ND extract	LNCaP cells	1–20 nM (24 h)	N- and E-cadherin, VEGF	↓ N-cadherin and VEGF ↑ E-cadherin	Erzurumlu et al. (2023)
CBD, THC, THCA	Hexane, DCM, and MeOH extracts	CAM	40 μg (11 days)	VEGF	↓ VEGF and L-arginine-induced vessel formation	Bala et al. (2019)
CBN	ND	IMR-5 and SK-N-AS cells	15–20 μM (24 and 48 h)	miR-34a, PFKFB3	↓ Tube formation, p-AKT and E2F1 ↑ miR-34a expression	Wang et al. (2022)

Abbreviations: CAM, in vivo chick chorioallantoic membrane; CBD, cannabidiol; CBN, cannabinol; DCM, dichloromethane; E2F1, E2 transcription factor 1; HIF-1α, hypoxia-inducible factor 1-α; i.p., intraperitoneal; MeOH, methanol; ND, nondefined; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; VEGF, vascular endothelial growth factor; Xen, xenograft.

Noscapine, a benzylisoquinoline alkaloid from plants in the *Papaveraceae* family, has shown reduced HIF-1α and HIF-1-regulated gene products in ovarian cancer (C13K) cell lines (Alasvand et al., 2019). This antiangiogenic activity has also been observed in various other cell lines (Chougule et al., 2011; Newcomb et al., 2008) and in Nu/Nu mice xenografted with human non-small-lung cancer (H460) cells (Jackson et al., 2008). Berberine is another alkaloid that has been the focus of several studies, being found to decrease VEGF expression levels in human cervical cancer (SiHa) and human HCC (HepG2) cells (Chu et al., 2014; Jie et al., 2011). Sanguinarine, found in multiple plants including *Bocconia frutescens*, *Chelidonium majus*, *Macleya cordata*, *Poppy fumaria*, and *Sanguinaria canadensis*, has also undergone extensive study in the past, mainly focusing on its antiangiogenic effects in diverse cell lines such as murine B16 melanoma (4A5) cells (De Stefano et al., 2009), human pulmonary adenocarcinoma (A549) cells (Xu et al., 2013), human breast cancer (MCF-7) (Dong et al., 2013), and human pancreatic cancer (BxPC-3 and MIA PaCa-2) (Singh et al., 2015).

Camptothecin, isolated from *Camptotheca acuminata*, showed antiangiogenic effects in CAM (Wang et al., 2003) and resulted in reduced blood vessel density in an orthotopic metastatic human colon cancer (HCT-116) cell line in ND-GFP nude mice (Yong et al., 2007). Notably, four analogs of camptothecin—topotecan, irinotecan, belotecan, and trastuzumab deruxtecan—have been approved and are currently employed in cancer chemotherapy (Montanino et al., 2021).

Recent research has delved into other alkaloids, including evodiamine, present in a variety of herbs, such as *Evodia rutaecarpa* and *Euonymus europaeus*, which has displayed a notable reduction of angiogenesis-related factors in colorectal cancer (SW480 and HCT116) cell lines (Zeng et al., 2021). In human prostate cancer (PC-3 and DU145) cells, evodiamine was shown to increase Sema3A (Yu et al., 2023) and reduce VEGF levels (Hwang et al., 2020). Similarly, sophoridine, derived from herbs such as *Sophora alopecuroides* L., *Euchresta japonica* Benth, and *Sophora moocrorftinan*, has shown a decrease in VEGFR in human breast cancer (MDA-MB-231 and BT549) cell lines (Xue et al., 2022). Crinamine, an alkaloid isolated from *Crinum asiaticum* bulbs, demonstrated antiangiogenic effects by inhibiting VEGF-A in human cervical cancer (SiHa) cells (Khumkhrong et al., 2019). Also, tetramethylpyrazine, an alkaloid isolated from the medicinal herb *Ligusticum chuanxiong*, demonstrated inhibitory effects on VEGF and CD31 expression in HUVECs and BALB/c nude mice xenografted with ovarian cancer (A2780) cells (Zou et al., 2019). Harmaline, a major β-carboline alkaloid present in the seeds and roots of *Peganum harmala*, exhibits a downregulation of VEGF, MMP-2, and VEGFR2 in a human breast cancer (4T1) cell line, as well as in BALB/c mice xenografted with this same cell line (Rashidi et al., 2022). Lycorine, the primary active alkaloid of most *Amaryllidaceae* plants, demonstrates inhibition of PDGFRα in HUVECs (Lv et al., 2022). Solanidine, an alkaloid isolated from *Solanum dulcamara* L., has revealed inhibitory effects on HIF-1α, VEGF-A, MMP-2, and MMP-9 expression levels in murine Lewis lung carcinoma and human pulmonary adenocarcinoma (A549) cell lines (Sherapura et al., 2023).

Although most alkaloids studied in the literature come from plant sources, quinadoline B, an alkaloid derived from fungi, has also been found to have antiangiogenic effects in a murine model with allografted melanoma (B16F10) cells, leading to a notable reduction in CD31 expression (Guo et al., 2023).

TABLE 8 Naturally occurring alkaloids in tumor angiogenesis: Sources, experimental models, and antiangiogenic molecular mechanisms.

Bioactive compounds	Origin	Cellular/animal models	Treatment	Molecular target	Effects	Ref(s)
Crinamine	Isolated from *Crinum asiaticum* bulbs	SiHa cells	4–16 μM (8 h)	VEGF-A	↓ VEGF-A	Khumkhrong et al. (2019)
Cyclovirobuxine	Standard	ACHN and 786-O cells	20–60 μM (48 h)	Vimentin	↓ Vimentin	Liu, Lv, et al. (2021)
		Nude mice (Xen: 786-O cells)	0.5 mg/kg (i.p., 7 days)			
Evodiamine	Standard	DU145 and PC-3 cells	10 μM (48 h)	Sema3A	↑ Sema3A	Yu et al. (2023)
		HCT116 and SW480 cells	0.375–12.0 μM (24 h)	HIF-1α, MMP-2, MMP-9, VEGF	↓ HIF-1α, MMP-2, MMP-9, VEGF	Zeng et al. (2021)
		DU145 and PC-3 cells	1–10 μM (36 h)	VEGF	↓ VEGF	Hwang et al. (2020)
Harmaline	Standard	BALB/c mice (Xen: 4T1 cells)	10–30 mg/kg (i.p., 35 days)	MMP-2, VEGF, VEGFR2	↓ VEGF ↓ MMP-2, VEGFR2	Rashidi et al. (2022)
Harmine	Standard	HUVECs, RT4 cells	10 μM (24 h)	VEGFR2	↓ VEGFR2	Hai-Rong et al. (2019)
		BALB/c nude mice (Xen: RT4 cells)	10 mg/kg (i.p., 30 days)			
Ligustrazine	ND	BALB/c nude mice (Xen: H1299 cells)	70 mg/kg (i.p., 6 weeks)	Wnt/β-catenin signaling pathway	↓ Wnt/β-catenin signaling pathway	Y. Dong et al. (2020)
Lycorine	Standard	HUVECs	6–12 μM (24 h)	PDGFRα	↓ PDGFRα	Lv et al. (2022)
Oxostephanine	Isolated from *Stephania dielsiana* leaves	OVCAR-8 and HeLa cells	0.2–25 μM (24 h)	Aurora kinases	↓ Aurora kinases	Tran et al. (2022)
Quinadoline B	Isolated from *Aspergillus clavutus* LZD32-24	C57/BL6J mice (Allo: B16F10 cells)	10 mg/kg (i.p., 18 days)	CD31, VEGFR	↓ CD31	Guo et al. (2023)
Sanguinarine	Standard	MDA-MB-231 and MDA-MB-468 cells	5 μM (24 h)	IKBKE	↓ IKBKE	Messeha et al. (2022)
Solanidine	Standard	A549 and LLC cells	4–8 μM (48 h)	HIF-1α, MMP-2, MMP-9, VEGF-A	↓ HIF-1α, MMP-2, MMP-9, VEGF-A	Sherapura et al. (2023)
Sophoridine	Standard	BT549 and MDA-MB-231 cells	20–80 μM (24 h)	VEGFR	↓ VEGFR	Xue et al. (2022)
Tetramethylpyrazine	Standard	HUVECs	100 μM (48 h)	CD31, VEGF	↓ CD31, VEGF	Zou et al. (2019)
		BALB/c nude mice (Xen: A2780 cells)	60 mg/kg (tail vein injection, every 2 days, 12 days)			

Abbreviations: CD31, cluster of differentiation 31; HIF-1α, hypoxia-inducible factor-1 α; i.p., intraperitoneal; IKBKE, inhibitor of nuclear factor kappa B kinase subunit epsilon; IL-8, interleukin-8; MMP, matrix metalloproteinase; PDGFR, platelet-derived growth factor receptor; Sema3A, semaphorin-3A; VEGF-A, vascular endothelial growth factor-A; VEGFR, vascular endothelial growth factor receptor.

Other alkaloids such as oxostephanine, harmine, sanguinarine, ligustrazine, and cyclovirobuxine have also shown varying degrees of antiangiogenic effects in diverse cancer cell lines and animal models, targeting molecules such as Aurora kinases, VEGFR-2, IKBKE, Wnt/β-catenin signaling pathway, and vimentin (Y. Dong et al., 2020; Hai-Rong et al., 2019; Liu, Lv, et al., 2021; Messeha et al., 2022; Tran et al., 2022).

4.2.6 | Ginsenosides

Ginsenosides are natural compounds extracted from the root of the Ginseng plant. Ginsenoside-Rg3 has demonstrated in vitro and in vivo antiangiogenic effects in cancer models (Nakhjavani et al., 2019; Zhang et al., 2024). A study conducted by Yue et al. (2006) exposed that this compound inhibits HUVEC proliferation at IC_{50} 10 nM, demonstrating its capacity to suppress angiogenesis by inhibiting vascular proliferation.

5 | COMBINED NATURAL PRODUCTS WITH ANTIANGIOGENIC DRUGS IN CANCER

Nowadays, combinatorial therapy between natural compounds and antiangiogenic drugs for cancer treatments has become increasingly significant. This increase could be due to administering multiple chemotherapeutics targeting different biochemical pathways, enhancing efficacy and safety (Naeem et al., 2022). Various studies have successfully combined phytochemicals with conventional drugs. For example, Ginsenoside Rg3 is known for inhibiting tumor cells' adhesion, invasion, and proliferation and forming tumor neovascularization (Hong et al., 2020). In a study involving a cervical cancer-bearing nude mouse model, ginsenoside Rg3 was administered orally at 5 mg/kg and evaluated for 5 weeks. The experimental design included a cisplatin-positive control group and a combined treatment group. Jia et al. (2024) performed an immunohistochemical analysis to determine the expression levels of CD31 and PCNA in tumor tissues and apoptosis. Their results indicated that ginsenoside Rg3, both alone and in combination with cisplatin, significantly inhibited the growth of Hela cell-transplanted tumors in nude mice (Jia et al., 2024). Cisplatin (5, 10, and 15 μM) was also evaluated with piperine (20 and 30 μM) in the MCF-7 cell line for 24 h. A synergistically inhibited cell viability of MCF-7 breast cancer cells more than piperine and cisplatin used alone was observed. At concentrations of 5 μM cisplatin and 20 μM piperine, a synergistic effect is observed in inducing apoptosis (Fattah et al., 2021). In another study by Shen et al. noscapine administration increases cisplatin's sensitivity by modulating the cell cycle and inducing apoptosis in cisplatin-resistant ovarian SKOV3 cells in mice. Curcumin is one of the most tested compounds in combination with other conventional anticancer drugs (Shen et al., 2015). Its administration increases the doxorubicin's antitumor activity by inducing apoptosis in neuroblastoma SH-SY5Y cells via upregulation of p21 p53 and TIMP1 and downregulation of MMP2 (Namkaew et al., 2018). Combined therapies offer some advantages. For example, (i) diminishing the toxicities linked with chemotherapeutics drugs such as doxorubicin and cisplatin. (ii) Overcoming chemoresistance can reduce adverse events by employing lower doses of drugs while maintaining the same efficacy and, in some cases, achieving better pharmacological effects through synergism (Ng et al., 2022).

6 | PROS AND CONS OF USING NATURAL PRODUCTS

Natural compounds offer distinct advantages in drug discovery due to their diverse range and ability to target multiple signaling pathways in angiogenesis (Khalid et al., 2016). These compounds are readily available in our daily diet, cost-effective compared to other drugs, efficiently absorbed from the gastrointestinal tract, and provide long-lasting effects suitable for extended prevention and treatment (Khalid et al., 2016). Additionally, they typically exhibit minimal side effects. Combining natural compounds with classic antineoplastic drugs can mitigate the latter's toxicity, improving patients' quality of life (Mohi-Ud-Din et al., 2023; Naeem et al., 2022) (Figure 5). For example, Daumone (a natural product secreted by *Caenorhabditis elegans*) is a biodegradable glycolipid with low toxicity that enhances the hybrid system's solubility and activity (Ricci et al., 2011). This synergistic approach also holds the potential for minimizing side effects associated with prolonged drug administration and has also been found to augment drug efficacy (Ng et al., 2022). Currently, an expanding field of research is focused on synthesizing bifunctional conjugates of natural products. This approach addresses the limitations of developing new and more effective cancer treatments. These conjugates enhance the selectivity of natural products for cancer cells, reducing their toxicity (Sflakidou et al., 2022). For example, in the phase I clinical trial, EC145, a conjugate of folic acid and the vinca alkaloid desacetylvinblastine hydrazide, was determined to have an acceptable toxicity profile. However, some symptoms were presented, such as constipation, nausea, fatigue, and vomiting (Lorusso et al., 2012). The evaluation of natural compounds such as curcumin and triptolide, which have strong liver and kidney toxicities, has demonstrated that curcumin exerts synergistic anticancer effects in ovarian cancer and decreases the side effects of triptolide (Liu et al., 2018).

Despite these benefits, several challenges must be addressed: their limited bioavailability, aqueous solubility, chemical complexity, susceptibility to degradation, and low absorption rates (Lu et al., 2023; Shanmugam et al., 2017). To address these limitations enhancing the therapeutic potential of natural products, various formulation strategies, including liposomes, micelles, nanoparticles, and solid dispersions, have been explored, aiming to improve the solubility and stability of natural products, ultimately enhancing their bioavailability and target specificity (Baranwal et al., 2023; Mahran et al., 2017). Likewise, a research opportunity is to explore the natural compounds with antiangiogenesis activity in clinical trials to determine their effects as anticancer compounds.

Other challenging issues when using natural compounds are the potential drawbacks, including adverse effects, contraindications, and

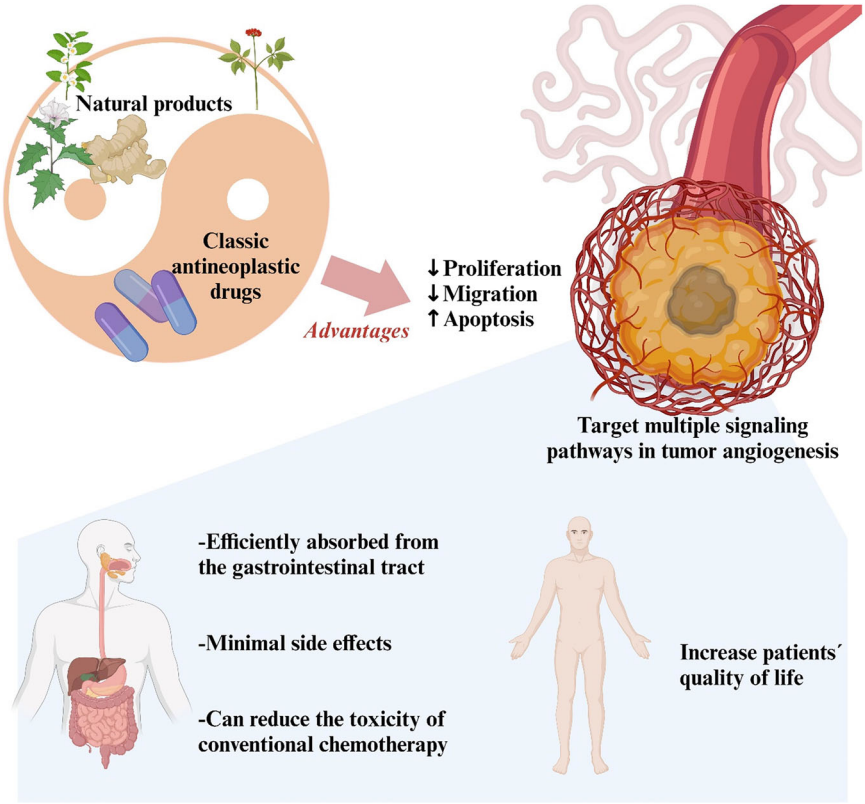

FIGURE 5 Benefits of combining natural products with conventional chemotherapeutic drugs in cancer therapy.

interactions with other medications. For example, orally administered resveratrol supplements are generally considered safe at doses of up to 1500 mg daily for up to 3 months. However, caution is warranted when exceeding this dosage, as higher amounts may result in adverse effects such as nausea, diarrhea, vomiting, and even liver dysfunction. Notably, resveratrol has the potential to interact with medications that undergo hepatic metabolism, particularly those processed by the cytochrome P450 1A2 (CYP1A2), CYP3A, and CYP2E1. These interactions may impact drug efficacy or safety (Piver et al., 2001). Consequently, individuals concurrently taking medications metabolized by these enzymes could suffer from harmful complications. Additionally, it is essential to note that resveratrol may increase the risk of bruising and bleeding when used concomitantly with anticoagulants or antiplatelet agents in individuals with bleeding disorders. Likewise, quercetin may have potentially hazardous interactions with several drugs, including warfarin and cyclosporine. For example, quercetin may amplify the effects of warfarin, increasing the bleeding risk (Poór et al., 2017). Moreover, quercetin may influence the metabolism of cyclosporine, a medication commonly prescribed to prevent organ transplant rejection; quercetin could alter its effects and side effects by slowing down its breakdown (Hsiu et al., 2002). Thus, the parallel administration of quercetin with these medications might require caution and close medical monitoring. Similarly, other natural compounds may have adverse effects or important implications when coadministered with conventional drugs. For instance, high doses of epigallocatechin gallate could produce liver dysfunction and/or interact with medications for cholesterol or blood pressure (Z. Shi et al., 2020; Zeng et al., 2022). Likewise, genistein may influence hormone-dependent cancers due to their structural resemblance to endogenous hormones. In summary, although many natural compounds are promising for cancer treatment, it is evident that there are potential risks associated with the unregulated use of natural medicines alongside conventional therapeutic medications. Thus, a comprehensive evaluation and monitoring of possible side effects associated with these natural compounds is warranted to guarantee their safe and effective integration for cancer treatment.

7 | CLINICAL STUDIES OF NATURAL PRODUCTS AS ANTIANGIOGENIC AGENTS

Significant attention has been given lately to finding natural chemopreventive substances that can inhibit, retard, or reverse multistage carcinogenesis because its antitumor, anti-inflammatory, and antiangiopathy bioactivities often used in clinical applications. We could not detect direct clinical trials of natural products targeting an antiangiogenesis mechanism in cancer. International clinical registries reveal that most molecules extracted from natural products related to an antiangiogenesis mechanism are being evaluated, looking for a mechanism of malignant cell death, treatment of cancer-related symptoms such as pain, inflammation, or, in the greatest proportion, as adjuvants. In the public information of clinical trials, the need for data such as purity of the compounds or the combination of extracts, in addition to the type of source of natural origin variables intrinsic to natural products, may be convenient. We are still in the initial stage of evaluating clinical trials, and we will need more time and more support work to

advance the in vivo knowledge of antiangiogenesis mechanisms. We can corroborate the above in that most of the studies on the related topic began in 2010, and in most of them, there is still no definitive public result. However, it highlights and motivates the interest that they are natural products that could offer a high benefit at a low cost and with almost no adverse effects. Most of the reports of clinical trials with natural products for tumors are in phase 1. One aspect that we observe that highlights its importance is that most interventions do not consider further intervention or modification to the route of administration and the type of pharmaceutical dosage form to guarantee adequate pharmacology. Therefore, the clinical result may be undervalued in most studies, hence the discrepancy in in vitro-in vivo correlations.

In this section (Table 9), we provide information regarding clinical studies made with natural products shown to have antiangiogenic effects in vivo and in vitro.

In human trials, the therapeutic potential of curcumin in cancer patients has been evaluated. From June 2014 to July 2016, a double-blind, randomized phase II study was carried out. This study evaluated the effect of curcumin plus docetaxel (a chemotherapy drug) 6 g/day for 7 days every 3 weeks in 50 patients with metastatic castration-resistant prostate cancer (mCRPC). The authors evaluated data on the time to progression, overall survival, prostate-specific antigen, response, safety, curcumin absorption, and patients' quality of life at 6 months. No statistical significance was observed between the curcumin and placebo groups in any evaluated variable at 6 months. These results underline that curcumin was ineffective in improving the studied parameters in mCRPC patients. The study was discontinued due to curcumin ineffectiveness (Passildas-Jahanmohan et al., 2021). Also, an open-label phase I trial was conducted to assess the feasibility and tolerability of administering docetaxel with curcumin among people with breast cancer. The inclusion criteria were: (i) postmenopausal women or men, (ii) histologically confirmed metastatic or regionally recurrent advanced breast cancer, and (iii) patients who had received anthracycline-based adjuvant chemotherapy. For six cycles, 100 mg/m^2 of docetaxel was administered to patients as a 1-h intravenous infusion every 3 weeks. Curcumin was orally applied at 500 mg/day for seven consecutive cycles and gradually increased until dose-limiting toxicity was observed. This study also evaluated the effect of curcumin on VEGFs and tumor markers. The maximal tolerated dose of curcumin was determined to be 8000 mg/day. Regarding the VEGF, it significantly decreased by −30% between baseline and cycle no. 3. Worth mentioning that VEGF overexpression is clinically associated with larger tumor size, increased metastasis, and poor prognosis in metastatic breast cancer patients (Sweeney et al., 2001). The clinical trial authors recommend the dose of 6000 mg/day of curcumin for 7 days in sequence, every 3 weeks, with the standard dose of docetaxel.

Another natural compound that has been studied for treating cancer is genistein. A phase II randomized clinical trial was conducted between May 2009 and January 2011. This study assessed the appropriate efficacy of genistein in blocking enzymes for cancer cell growth and tumor blood flow among patients with primary adenocarcinoma of the pancreas. Also, its effect on angiogenesis-related factors. Patients were randomly divided into two groups: the oral genistein group, with a 3-week time frame, and another group that received no specific therapy and carried out surgical resection in the third week from enrolment. Currently, the results have not been posted on ClinicalTrials.gov. Ginsenoside Rg3 was used in Shanghai, China, in a study conducted from December 2020 until December 2023 on patients with unresectable HCC. Ginsenoside Rg3 is a ginseng leachate extract that can inhibit angiogenesis, reduce the expression of programmed cell death ligand 1 (PD-L1), and block the binding of programmed cell death 1 and PD-L1. This study was directed to compare the efficacy and safety of transcatheter arterial chemoembolization combined with the antiangiogenic targeted drugs and ginsenoside Rg3 versus transcatheter arterial chemoembolization alone. Although antiangiogenic targeted drugs and ginsenoside Rg3 synergize with transcatheter arterial chemoembolization in this clinical trial, no results are posted on ClinicalTrials.gov for this study (Table 9). In summary, the studies discussed above demonstrated that natural compounds have the potential to inhibit angiogenesis, which is essential to cancer progression. However, most clinical trials that have tested the natural compounds have not been finished, so it is necessary to give continuity to trials, especially to know the probable side effects and doses for different cancer conditions.

8 | CHALLENGES AND FUTURE DIRECTIONS

The effects of natural products as antiangiogenic compounds are limited and inconclusive. Indeed, the results are contradictory in some cases; for example, the capsaicin that is antiangiogenic. However, high capsaicin pepper use is a risk factor for developing stomach and liver cancer; even capsaicin is considered a carcinogen (Archer & Jones, 2002). So, the evidence suggests that capsaicin has a dual role in carcinogenic and mutagenic processes. A challenge in using natural compounds as antiangiogenic agents is the standardization of the doses, routes of administration, types of tissues affected, and people's habits since it has been established that consuming natural compounds in the diet involves the risk of developing cancer (Archer & Jones, 2002). These challenges affect the reproducibility of the study and, therefore, of results. Also, translating preclinical findings into clinical studies is difficult due to limitations and discrepancies in bioavailability and compound specificity. Only a small fraction of the administered dose reaches the systemic circulation, and the bioavailability of antiangiogenic compounds varies depending on the administration way (Sohn et al., 2021). The parenteral route offers superior absorption and bioavailability compared to the oral route (Stielow et al., 2023). The oral administration of these compounds alters their composition because they could suffer modification within the gastrointestinal system, rendering them susceptible to inactivation (Stielow et al., 2023).

In humans, the homogenization of natural dietary compounds is complex; therefore, evaluating an interest compound's pure effect is difficult. An additional complication arises from the fact that certain bioactive agents, such as amino acids and proteins, have diverse

TABLE 9 Clinical studies of natural products as modulators of angiogenesis in cancer therapy, data obtained from ClinicalTrials.gov.

NCT Number	Title	Status	Conditions	Interventions	Study type/Phase	Population	Results
NCT03317613	Efficacy of Capsaicin Patch (Qutenza®) in Cancer Patients With Neuropathic Pain (CAPSONCO)	Completed	Cancer patients with neuropathic pain	Qutenza (8% capsaicin patch)	Interventional/Phase 2	-Patients at least 18 years old. -Patient presenting neuropathic pain secondary to an anticancerous treatment. -Patient presenting a neuropathic pain in Four Questions score superior or equal to 4 out of 10. -Patient presenting a skin without lesion at the painful area.	No data were reported or published in this study.
NCT02095717	Multicenter Study Comparing Taxotere Plus Curcumin Versus Taxotere Plus Placebo Combination in First-line Treatment of Prostate Cancer Metastatic Castration-Resistant	Completed	Prostate cancer metastatic castration resistant	Drug: Curcumin Drug: Placebo Drug: Taxotere	Interventional/Phase 2	Patients older than 18 years. Life expectancy > 3 months. Patient in hormonal blockade based on surgical castration by orchiectomy or pulpectomy.	Curcumin was not efficacious, and the study was discontinued.
–	Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer	Completed	Advanced or metastatic breast cancer	Curcumin orally for 7 consecutive days by cycle	Phase I	Postmenopausal women or men with histologically confirmed metastatic or regionally recurrent advanced breast cancer and patients who had received anthracycline-based adjuvant chemotherapy.	VEGF decreased around −30% between baseline and cycle no. 3.

(Continues)

TABLE 9 (Continued)

NCT Number	Title	Status	Conditions	Interventions	Study type/Phase	Population	Results
NCT00882765	Genistein in Treating Patients With Pancreatic Cancer That Can Be Removed by Surgery	Closed	Pancreatic cancer	Dietary supplement: Genistein Given orally	Interventional/Phase 2	Adults over the age of 18. About resectable pancreatic mass, known or presumed to be primary pancreatic adenocarcinoma. Negative pregnancy test before initiation of treatment and adequate contraception throughout treatment.	The study has been closed due to no accrual.
NCT04523467	Anti-angiogenic Targeted Drugs Plus Rg3 to Improve the Efficacy of TACE for Unresectable Hepatocellular Carcinoma	Ongoing	Hepatocellular carcinoma	Drug: Antiangiogenic targeted drugs Drug: Ginsenoside Rg3	Interventional/ Not applicable	Aged 18–75 Unresectable hepatocellular carcinoma patients clinically diagnosed or confirmed by histopathology and/or cytology. At least one measurable lesion.	–
NCT02782949	Curcumin in Preventing Gastric Cancer in Patients With Chronic Atrophic Gastritis or Gastric Intestinal Metaplasia	Active, not recruiting	Gastric cancer	Drug: Curcumin Other: Placebo	Interventional/Phase 2	21 years and older. Histologically confirmed chronic multifocal atrophic gastritis and/or gastric intestinal metaplasia.	Study in the process of information analysis with completion of the study estimated for 2025-04-01.
NCT02411565	Fermented Wheat Germ Extract in Women With Ovarian Cancer	Terminated	Ovarian cancer	Drug: Fermented wheat germ extract Drug: Placebo	Interventional/Early Phase 1	Women with suspected epithelial ovarian, fallopian tube, or primary peritoneal carcinoma scheduled to undergo surgical exploration with no prior treatment for the cancer. 18 years and older.	Giving fermented wheat germ extract before surgery may be safe and may improve quality of life by decreasing the symptoms associated with ovarian, fallopian tube, or peritoneal cancer.

(Continues)

TABLE 9 (Continued)

NCT Number	Title	Status	Conditions	Interventions	Study type/Phase	Population	Results
NCT00668707	Adjuvant Melatonin for Prevention of Lung Cancer Recurrence and Mortality (AMPLCaRe)	Completed	Lung cancer	Dietary supplement: Melatonin Dietary supplement: Placebo	Interventional, Phase 3	Clinical diagnosis of non-small-cell lung cancer. Eligible for surgical resection. 18 years and older.	25% increase in 5-year disease-free survival with melatonin treatment in advanced cancer (stage III/IV).
NCT03292822	Effects of (Licochalcone A) and Paclitaxel on Human Oral Squamous Cell Carcinoma Cell Line	Completed	Human oral squamous cell carcinoma cell line	Dietary supplement: Licochalcone A Drug: Paclitaxel	Interventional, Phase 1	All head and neck squamous cell carcinoma cell lines, child, adult, older adult.	There is no data reported so far. The authors relate the possible activity of Licochalcone-A with an increase in the expression of TRAIL mediated by MAPK induced by ERK1/2 and p38, in addition to an increase in proapoptotic and apoptotic factors.
NCT06148038	CBD for Breast Cancer Primary Tumors	Not yet recruiting	Breast cancer primary tumors	Drug: CBD oral Other: Control	Interventional, Phase 1	Histologically confirmed invasive breast cancer (stages I, II, or III) or DCIS with primary tumor(s) ≥ 0.8 cm on mammogram, ultrasound, MRI, or physical exam. 18 years of age or older.	There is no data reported so far. Study Start Date (Estimated): 2024-05-31.
NCT00256334	Resveratrol for Patients With Colon Cancer	Completed	Colon cancer	Drug: Resveratrol	Interventional, Phase 1	Patients diagnosed with colon cancer by colonoscopic biopsy and tissue obtained under UCI04-05. 18 years and older.	There is no data reported so far. The authors relate the possible activity of resveratrol by inhibition of the Wnt pathway in colon cancer.

functions in regulating biochemical and physiological processes in the human body and serve as a source of energy. Therefore, providing a detailed report of people's diets in the clinical trials could be beneficial in considering another factor that could alter, bias, or confound the results.

A notable comment in most studies in vitro that tested natural compounds as antiangiogenic is the use of high concentrations of compounds in cell culture systems and not in animal models. So, there exists a need for further in-depth studies in animal models and epidemiology studies with humans to precisely delineate the effects of natural compounds on antiangiogenesis in cancer. As a result of this review, we observed that in most articles that tested natural compounds as modulators of angiogenic effects, the decrease of VEGF is its primary effect. It was postulated that VEGF-blocking by phytochemicals has emerged as an attractive strategy for cancer prevention and therapeutics (Kowshik et al., 2014). VEGF is the most essential angiogenic signal protein that stimulates tumor neoangiogenesis. This protein also increases vascular endothelial cells' mitogenic and has survival properties (Dvorak, 2005; Roberts & Palade, 1997). Therefore, a limitation is that there is a lack of studies that test the synergic or additive effects between the natural compounds with antiangiogenic effects (diet or as a supplement) and the antiangiogenic therapy for cancers, as bevacizumab (Avastin), small molecule tyrosine kinase inhibitors (sunitinib, sorafenib, and pazopanib), soluble VEGF decoy receptor (aflibercept), and humanized monoclonal antibody of VEGFR2 (ramucirumab). Finally, it is essential to highlight that some natural compounds, such as genistein, could favor cancer hormone-dependent because of their chemical similitude with endogen hormones. It has been reported that consuming genistein may have the opposite effect for patients with a high ERα/ERβ ratio diagnosed with breast cancer who are undergoing anticancer treatment (Pons et al., 2016). Thus, although the natural compounds discussed in this article seem promising alternatives for cancer treatment, the use of these substances carries potential risks. Therefore, a thorough evaluation and ongoing monitoring of these natural compounds' possible side effects and contraindications are essential to ensure their safe and effective integration into cancer treatment protocols.

9 | CONCLUSION

This review presents a portfolio of diverse bioactive compounds with antiangiogenic molecular mechanisms. Interestingly, preclinical evidence reveals an encouraging outlook for controlling different types of cancer through an antiangiogenesis mechanism. Therefore, natural products as modulators of angiogenesis in cancer could be adjuvant treatments to classic antineoplastic drugs. However, some clinical trials are underway, but no confirmatory evidence exists to support the information suggested from the preclinical data. Then, as occurs with the advance of research in the translation of the knowledge of different bioactive compounds, the impact of clinical studies may require greater robustness in the studies for some biocompounds from extraction, purification, characterization, demonstration of the reproducibility of the previous processes, safety, and efficacy to guarantee an adequate clinical trial and, therefore, more clinical trials in development.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. That is revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors wish to confirm that there are no known conflict of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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REFERENCES

Abdal Dayem, A., Choi, H., Yang, G.-M., Kim, K., Saha, S., & Cho, S.-G. (2016). The anti-cancer effect of polyphenols against breast cancer and cancer stem cells: Molecular mechanisms. *Nutrients*, *8*, 581. https://doi.org/10.3390/nu8090581

Abdollah, M. R. A., Ali, A. A., Elgohary, H. H., & Elmazar, M. M. (2023). Antiangiogenic drugs in combination with seaweed fucoidan: A mechanistic in vitro and in vivo study exploring the VEGF receptor and its downstream signaling molecules in hepatic cancer. *Frontiers in Pharmacology*, *14*, 1108992. https://doi.org/10.3389/fphar.2023.1108992

Ademowo, O. S., Oyebode, O., Edward, R., Conway, M. E., Griffiths, H. R., & Dias, I. H. K. (2024). Effects of carotenoids on mitochondrial dysfunction. *Biochemical Society Transactions*, *52*(1), 65–74. https://doi.org/10.1042/BST20230193

Ahmad, M. M., Chatha, S. A. S., Iqbal, Y., Hussain, A. I., Khan, I., & Xie, F. (2022). Recent trends in extraction, purification, and antioxidant activity evaluation of plant leaf-extract polysaccharides. *Biofuels, Bioproducts and Biorefining*, *16*(6), 1820–1848. https://doi.org/10.1002/bbb.2405

Ahmed, S., Khan, H., Fakhri, S., Aschner, M., & Cheang, W. S. (2022). Therapeutic potential of marine peptides in cervical and ovarian cancers. *Molecular and Cellular Biochemistry*, *477*(2), 605–619. https://doi.org/10.1007/s11010-021-04306-y

Ahmed, S. A., Mendonca, P., Messeha, S. S., & Soliman, K. F. A. (2023). Anticancer effects of fucoxanthin through cell cycle arrest, apoptosis induction, and angiogenesis inhibition in triple-negative breast can-

cer cells. *Molecules (Basel, Switzerland)*, *28*(18). https://doi.org/10.3390/molecules28186536

Aikio, M., Alahuhta, I., Nurmenniemi, S., Suojanen, J., Palovuori, R., Teppo, S., Sorsa, T., Lopez-Otin, C., Pihlajaniemi, T., Salo, T., Heljasvaara, R., & Nyberg, P. (2012). Arresten, a collagen-derived angiogenesis inhibitor, suppresses invasion of squamous cell carcinoma. *PLoS ONE*, *7*(12), e51044. https://doi.org/10.1371/journal.pone.0051044

Akinloye, O. A., Akinloye, D. I., Lawal, M. A., Shittu, M. T., & Metibemu, D. S. (2021). Terpenoids from *Azadirachta indica* are potent inhibitors of Akt: Validation of the anticancer potentials in hepatocellular carcinoma in male Wistar rats. *Journal of Food Biochemistry*, *45*(1), e13559. https://doi.org/10.1111/jfbc.13559

Akiyama, T., Ishida, J., Nakagawa, S., Ogawara, H., Watanabe, S., Itoh, N., Shibuya, M., & Fukami, Y. (1987). Genistein, a specific inhibitor of tyrosine-specific protein kinases. *Journal of Biological Chemistry*, *262*(12), 5592–5595. https://doi.org/10.1016/s0021-9258(18)45614-1

Alasvand, M., Assadollahi, V., Ambra, R., Hedayati, E., Kooti, W., & Peluso, I. (2019). Antiangiogenic effect of alkaloids. *Oxidative Medicine and Cellular Longevity*, *2019*, 9475908. https://doi.org/10.1155/2019/9475908

Ambasta, R. K., Jha, S. K., Kumar, D., Sharma, R., Jha, N. K., & Kumar, P. (2015). Comparative study of anti-angiogenic activities of luteolin, lectin and lupeol biomolecules. *Journal of Translational Medicine*, *13*, 307. https://doi.org/10.1186/s12967-015-0665-z

Anand, K., Asthana, P., Kumar, A., Ambasta, R. K., & Kumar, P. (2011). Quercetin mediated reduction of angiogenic markers and chaperones in DLA-induced solid tumours. *Asian Pacific Journal of Cancer Prevention*, *12*(11), 2829–2835. https://www.ncbi.nlm.nih.gov/pubmed/22393949

Anand, P., Filipenko, P., Huaman, J., Lyudmer, M., Hossain, M., Santamaria, C., Huang, K., Ogunwobi, O. O., & Holford, M. (2019). Selective inhibition of liver cancer cells using venom peptide. *Marine Drugs*, *17*(10), 587. https://doi.org/10.3390/md17100587

Ando, N., Hara, M., Shiga, K., Yanagita, T., Takasu, K., Nakai, N., Maeda, Y., Hirokawa, T., Takahashi, H., Ishiguro, H., Matsuo, Y., & Takiguchi, S. (2019). Eicosapentaenoic acid suppresses angiogenesis via reducing secretion of IL-6 and VEGF from colon cancer-associated fibroblasts. *Oncology Reports*, *42*(1), 339–349. https://doi.org/10.3892/or.2019.7141

Archer, V. E., & Jones, D. W. (2002). Capsaicin pepper, cancer and ethnicity. *Medical Hypotheses*, *59*(4), 450–457. https://doi.org/10.1016/s0306-9877(02)00152-4

Aslan, C., Maralbashi, S., Kahroba, H., Asadi, M., Soltani-Zangbar, M. S., Javadian, M., Shanehbandi, D., Baradaran, B., Darabi, M., & Kazemi, T. (2020). Docosahexaenoic acid (DHA) inhibits pro-angiogenic effects of breast cancer cells via down-regulating cellular and exosomal expression of angiogenic genes and microRNAs. *Life Sciences*, *258*, 118094. https://doi.org/10.1016/j.lfs.2020.118094

Augustin, H. G., & Koh, G. Y. (2022). Antiangiogenesis: Vessel regression, vessel normalization, or both? *Cancer Research*, *82*(1), 15–17. https://doi.org/10.1158/0008-5472.CAN-21-3515

Ayuningtyas, N. F., Chea, C., Ando, T., Saninggar, K. E., Tanimoto, K., Inubushi, T., Maishi, N., Hida, K., Shindoh, M., Miyauchi, M., & Takata, T. (2023). Bovine lactoferrin suppresses tumor angiogenesis through NF-kappaB pathway inhibition by binding to TRAF6. *Pharmaceutics*, *15*(1), 165. https://doi.org/10.3390/pharmaceutics15010165

Azevedo, T., Ferreira, T., Ferreira, J., Teixeira, F., Ferreira, D., Silva-Reis, R., Neuparth, M. J., Pires, M. J., Pinto, M. d. L., Gil da Costa, R. M., Bastos, M. M. S. M., Medeiros, R., Félix, L., Venâncio, C., Dias, M. I., Gaivão, I., Barros, L., & Oliveira, P. A. (2022). Supplementation of an anthocyanin-rich elderberry (*Sambucus nigra* L.) extract in FVB/n mice: A healthier alternative to synthetic colorants. *Applied Sciences*, *12*(23). https://doi.org/10.3390/app122311928

Azevedo, T., Silva, J., Faustino-Rocha, A. I., Valada, A., Anjos, L., Moura, T., Ferreira, R., Santos, M., Pires, M. J., Neuparth, M. J., Peixoto, F., Silvestre-Ferreira, A. C., Gama, A., Seixas, F., Finimundy, T. C., Barros, L., Matos, M., & Oliveira, P. A. (2024). The role of natural compounds in rat mammary cancer: The beneficial effects of *Santolina chamaecyparissus* L. aqueous extract. *Veterinarska Stanica*, *55*(1), 45–61. https://doi.org/10.46419/vs.55.1.3

Bae, H., Lee, J. Y., Yang, C., Song, G., & Lim, W. (2020). Fucoidan derived from fucus vesiculosus inhibits the development of human ovarian cancer via the disturbance of calcium homeostasis, endoplasmic reticulum stress, and angiogenesis. *Marine Drugs*, *18*(1), 45. https://doi.org/10.3390/md18010045

Bagchi, D., Sen, C. K., Bagchi, M., & Atalay, M. (2004). Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula. *Biochemistry (Mosc)*, *69*(1), 75–80. 71 p preceding 75. https://doi.org/10.1023/b:biry.0000016355.19999.93

Bakshi, H. A., Quinn, G. A., Nasef, M. M., Mishra, V., Aljabali, A. A. A., El-Tanani, M., Serrano-Aroca, A., Webba Da Silva, M., McCarron, P. A., & Tambuwala, M. M. (2022). Crocin inhibits angiogenesis and metastasis in colon cancer via TNF-alpha/NF-kB/VEGF pathways. *Cells*, *11*(9), 1502. https://doi.org/10.3390/cells11091502

Bala, A., Rademan, S., Kevin, K. N., Maharaj, V., & Matsabisa, M. G. (2019). UPLC-MS analysis of *Cannabis sativa* using tetrahydrocannabinol (THC), cannabidiol (CBD), and tetrahydrocannabinolic acid (THCA) as marker compounds: Inhibition of breast cancer cell survival and progression. *Natural Product Communications*, *14*(8). https://doi.org/10.1177/1934578x19872907

Baranwal, J., Barse, B., Di Petrillo, A., Gatto, G., Pilia, L., & Kumar, A. (2023). Nanoparticles in cancer diagnosis and treatment. *Materials (Basel)*, *16*(15), 5354. https://doi.org/10.3390/ma16155354

Batlle, R., Andres, E., Gonzalez, L., Llonch, E., Igea, A., Gutierrez-Prat, N., Berenguer-Llergo, A., & Nebreda, A. R. (2019). Regulation of tumor angiogenesis and mesenchymal-endothelial transition by p38alpha through TGF-beta and JNK signaling. *Nature Communications*, *10*(1), 3071. https://doi.org/10.1038/s41467-019-10946-y

Becker, V., Hui, X., Nalbach, L., Ampofo, E., Lipp, P., Menger, M. D., Laschke, M. W., & Gu, Y. (2021). Linalool inhibits the angiogenic activity of endothelial cells by downregulating intracellular ATP levels and activating TRPM8. *Angiogenesis*, *24*(3), 613–630. https://doi.org/10.1007/s10456-021-09772-y

Bellou, S., Karali, E., Bagli, E., Al-Maharik, N., Morbidelli, L., Ziche, M., Adlercreutz, H., Murphy, C., & Fotsis, T. (2012). The isoflavone metabolite 6-methoxyequol inhibits angiogenesis and suppresses tumor growth. *Molecular Cancer*, *11*, 35. https://doi.org/10.1186/1476-4598-11-35

Bergman Jungestrom, M., Thompson, L. U., & Dabrosin, C. (2007). Flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo. *Clinical Cancer Research*, *13*(3), 1061–1067. https://doi.org/10.1158/1078-0432.CCR-06-1651

Bhat, S. S., Prasad, S. K., Shivamallu, C., Prasad, K. S., Syed, A., Reddy, P., Cull, C. A., & Amachawadi, R. G. (2021). Genistein: A potent anti-breast cancer agent. *Current Issues in Molecular Biology*, *43*(3), 1502–1517. https://doi.org/10.3390/cimb43030106

Bitterman, J. L., & Chung, J. H. (2015). Metabolic effects of resveratrol: Addressing the controversies. *Cellular and Molecular Life Sciences*, *72*(8), 1473–1488. https://doi.org/10.1007/s00018-014-1808-8

Bocci, G., Di Paolo, A., & Danesi, R. (2013). The pharmacological bases of the antiangiogenic activity of paclitaxel. *Angiogenesis*, *16*(3), 481–492. https://doi.org/10.1007/s10456-013-9334-0

Boh, B. (2013). *Ganoderma lucidum*: A potential for biotechnological production of anti-cancer and immunomodulatory drugs. *Recent Patents on Anti-Cancer Drug Discovery*, *8*(3), 255–287. https://doi.org/10.2174/1574891x113089990036

Bordeleau, F., Mason, B. N., Lollis, E. M., Mazzola, M., Zanotelli, M. R., Somasegar, S., Califano, J. P., Montague, C., LaValley, D. J., Huynh, J., Mencia-Trinchant, N., Negron Abril, Y. L., Hassane, D. C., Bonassar, L. J., Butcher, J. T., Weiss, R. S., & Reinhart-King, C. A. (2017). Matrix stiffening promotes a tumor vasculature phenotype. *Proceedings of the National Academy of Sciences*, *114*(3), 492–497. https://doi.org/10.1073/pnas.1613855114

Briguglio, G., Costa, C., Pollicino, M., Giambò, F., Catania, S., & Fenga, C. (2020). Polyphenols in cancer prevention: New insights (Review). *International Journal of Functional Nutrition*, *1*(2), 9. https://doi.org/10.3892/ijfn.2020.9

Caffarel, M. M., Andradas, C., Mira, E., Perez-Gomez, E., Cerutti, C., Moreno-Bueno, G., Flores, J. M., Garcia-Real, I., Palacios, J., Manes, S., Guzman, M., & Sanchez, C. (2010). Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Molecular Cancer*, *9*, 196. https://doi.org/10.1186/1476-4598-9-196

Cai, C., Zhi, Y., Xie, C., Geng, S., Sun, F., Ji, Z., Zhang, P., Wang, H., & Tang, J. (2023). Ursolic acid-downregulated long noncoding RNA ASMTL-AS1 inhibits renal cell carcinoma growth via binding to HuR and reducing vascular endothelial growth factor expression. *Journal of Biochemical and Molecular Toxicology*, *37*(8), e23389. https://doi.org/10.1002/jbt.23389

Cao, Z., Fang, J., Xia, C., Shi, X., & Jiang, B. H. (2004). trans-3,4,5'-Trihydroxystibene inhibits hypoxia-inducible factor 1alpha and vascular endothelial growth factor expression in human ovarian cancer cells. *Clinical Cancer Research*, *10*(15), 5253–5263. https://doi.org/10.1158/1078-0432.CCR-03-0588

Carmeliet, P., & Jain, R. K. (2011). Molecular mechanisms and clinical applications of angiogenesis. *Nature*, *473*(7347), 298–307. https://doi.org/10.1038/nature10144

Castañeda-Ovando, A., Pacheco-Hernández, M. d. L., Páez-Hernández, M. E., Rodríguez, J. A., & Galán-Vidal, C. A. (2009). Chemical studies of anthocyanins: A review. *Food Chemistry*, *113*(4), 859–871. https://doi.org/10.1016/j.foodchem.2008.09.001

Cerna, M. (2011). Seaweed proteins and amino acids as nutraceuticals. *Advances in Food and Nutrition Research*, *64*, 297–312. https://doi.org/10.1016/B978-0-12-387669-0.00024-7

Çetin, A., & Biltekin, B. (2019). Combining ellagic acid with temozolomide mediates the cadherin switch and angiogenesis in a glioblastoma model. *World Neurosurgery*, *132*, e178–e184. https://doi.org/10.1016/j.wneu.2019.08.228

Chan, B. D., Wong, W. Y., Lee, M. M., Yue, P. Y., Dai, X., Tsim, K. W., Hsiao, W. W., Li, M., Li, X. Y., & Tai, W. C. (2023). Isolation and characterization of ZK002, a novel dual function snake venom protein from *Deinagkistrodon acutus* with anti-angiogenic and anti-inflammatory properties. *Frontiers in Pharmacology*, *14*, 1227962. https://doi.org/10.3389/fphar.2023.1227962

Charmforoshan, E., Karimi, E., Oskoueian, E., Es-Haghi, A., & Iranshahi, M. (2019). Inhibition of human breast cancer cells (MCF-7 cell line) growth via cell proliferation, migration, and angiogenesis by auraptene of *Ferula szowitsiana* root extract. *Journal of Food Measurement and Characterization*, *13*(4), 2644–2653. https://doi.org/10.1007/s11694-019-00185-6

Chen, G., He, L., Zhang, P., Zhang, J., Mei, X., Wang, D., Zhang, Y., Ren, X., & Chen, Z. (2020). Encapsulation of green tea polyphenol nanospheres in PVA/alginate hydrogel for promoting wound healing of diabetic rats by regulating PI3K/AKT pathway. *Materials Science & Engineering C-Materials for Biological Applications*, *110*, 110686. https://doi.org/10.1016/j.msec.2020.110686

Chen, L., Guo, X., Hu, Y., Li, L., Liang, G., & Zhang, G. (2020). Epigallocatechin-3-gallate sensitises multidrug-resistant oral carcinoma xenografts to vincristine sulfate. *FEBS Open Bio*, *10*(7), 1403–1413. https://doi.org/10.1002/2211-5463.12905

Chen, X., Sun, L., Wei, X., Lu, H., Tan, Y., Sun, Z., & Jiang, J. (2021). Antitumor effect and molecular mechanism of fucoidan in NSCLC. *BMC Complementary Medicine and Therapies*, *21*(1), 25. https://doi.org/10.1186/s12906-020-03191-0

Cheng, W., Cheng, Z., Weng, L., Xing, D., & Zhang, M. (2021). Asparagus polysaccharide inhibits the hypoxia-induced migration, invasion and angiogenesis of hepatocellular carcinoma cells partly through regulating HIF1alpha/VEGF expression via MAPK and PI3K signaling pathway. *Journal of Cancer*, *12*(13), 3920–3929. https://doi.org/10.7150/jca.51407

Cho, M. H., Li, Y., Lo, P. C., Lee, H., & Choi, Y. (2020). Fucoidan-based theranostic nanogel for enhancing imaging and photodynamic therapy of cancer. *Nano-Micro Letters*, *12*(1), 47. https://doi.org/10.1007/s40820-020-0384-8

Cholewski, M., Tomczykowa, M., & Tomczyk, M. (2018). A comprehensive review of chemistry, sources and bioavailability of omega-3 fatty acids. *Nutrients*, *10*(11), 1662. https://doi.org/10.3390/nu10111662

Choueiri, T. K., & Kaelin, W. G., Jr. (2020). Targeting the HIF2-VEGF axis in renal cell carcinoma. *Nature Medicine*, *26*(10), 1519–1530. https://doi.org/10.1038/s41591-020-1093-z

Chougule, M. B., Patel, A. R., Jackson, T., & Singh, M. (2011). Antitumor activity of noscapine in combination with doxorubicin in triple negative breast cancer. *PLoS ONE*, *6*(3), e17733. https://doi.org/10.1371/journal.pone.0017733

Chu, S. C., Yu, C. C., Hsu, L. S., Chen, K. S., Su, M. Y., & Chen, P. N. (2014). Berberine reverses epithelial-to-mesenchymal transition and inhibits metastasis and tumor-induced angiogenesis in human cervical cancer cells. *Molecular Pharmacology*, *86*(6), 609–623. https://doi.org/10.1124/mol.114.094037

Chung, A. S., Lee, J., & Ferrara, N. (2010). Targeting the tumour vasculature: Insights from physiological angiogenesis. *Nature Reviews Cancer*, *10*(7), 505–514. https://doi.org/10.1038/nrc2868

Clemente, N., Argenziano, M., Gigliotti, C. L., Ferrara, B., Boggio, E., Chiocchetti, A., Caldera, F., Trotta, F., Benetti, E., Annaratone, L., Ribero, S., Pizzimenti, S., Barrera, G., Dianzani, U., Cavalli, R., & Dianzani, C. (2019). Paclitaxel-loaded nanosponges inhibit growth and angiogenesis in melanoma cell models. *Frontiers in Pharmacology*, *10*, 776. https://doi.org/10.3389/fphar.2019.00776

Dahham, S. S., Tabana, Y., Asif, M., Ahmed, M., Babu, D., Hassan, L. E., Ahamed, M. B. K., Sandai, D., Barakat, K., Siraki, A., & Majid, A. (2021). beta-Caryophyllene induces apoptosis and inhibits angiogenesis in colorectal cancer models. *International Journal of Molecular Sciences*, *22*(19), 10550. https://doi.org/10.3390/ijms221910550

Daly, C., Eichten, A., Castanaro, C., Pasnikowski, E., Adler, A., Lalani, A. S., Papadopoulos, N., Kyle, A. H., Minchinton, A. I., Yancopoulos, G. D., & Thurston, G. (2013). Angiopoietin-2 functions as a Tie2 agonist in tumor models, where it limits the effects of VEGF inhibition. *Cancer Research*, *73*(1), 108–118. https://doi.org/10.1158/0008-5472.CAN-12-2064

Daris, B., Tancer Verboten, M., Knez, Z., & Ferk, P. (2019). Cannabinoids in cancer treatment: Therapeutic potential and legislation. *Bosnian Journal of Basic Medical Sciences*, *19*(1), 14–23. https://doi.org/10.17305/bjbms.2018.3532

de Heer, E. C., Jalving, M., & Harris, A. L. (2020). HIFs, angiogenesis, and metabolism: Elusive enemies in breast cancer. *Journal of Clinical Investigation*, *130*(10), 5074–5087. https://doi.org/10.1172/JCI137552

de Jesus Raposo, M. F., de Morais, A. M., & de Morais, R. M. (2015). Marine polysaccharides from algae with potential biomedical applications. *Marine Drugs*, *13*(5), 2967–3028. https://doi.org/10.3390/md13052967

De Palma, M., Biziato, D., & Petrova, T. V. (2017). Microenvironmental regulation of tumour angiogenesis. *Nature Reviews Cancer*, *17*(8), 457–474. https://doi.org/10.1038/nrc.2017.51

De Stefano, I., Raspaglio, G., Zannoni, G. F., Travaglia, D., Prisco, M. G., Mosca, M., Ferlini, C., Scambia, G., & Gallo, D. (2009). Antiproliferative and antiangiogenic effects of the benzophenanthridine alkaloid sanguinarine in melanoma. *Biochemical Pharmacology*, *78*(11), 1374–1381. https://doi.org/10.1016/j.bcp.2009.07.011

Deshpande, R., Mansara, P., & Kaul-Ghanekar, R. (2016). Alpha-linolenic acid regulates Cox2/VEGF/MAP kinase pathway and decreases the expression of HPV oncoproteins E6/E7 through restoration of p53 and Rb expression in human cervical cancer cell lines. *Tumour Biology*, *37*(3), 3295–3305. https://doi.org/10.1007/s13277-015-4170-z

Dey, P., Kundu, A., Kumar, A., Gupta, M., Lee, B. M., Bhakta, T., Dash, S., & Kim, H. S. (2020). Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). *Recent advances in natural products analysis*, 505–567). https://doi.org/10.1016/b978-0-12-816455-6.00015-9

Dhapola, R., Beura, S. K., Sharma, P., Singh, S. K., & HariKrishnaReddy, D. (2024). Oxidative stress in Alzheimer's disease: Current knowledge of signaling pathways and therapeutics. *Molecular Biology Reports*, *51*(1), 48. https://doi.org/10.1007/s11033-023-09021-z

Diéras, V., Wildiers, H., Jassem, J., Dirix, L. Y., Guastalla, J. P., Bono, P., Hurvitz, S. A., Goncalves, A., Romieu, G., Limentani, S. A., Jerusalem, G., Lakshmaiah, K. C., Roche, H., Sanchez-Rovira, P., Pienkowski, T., Segui Palmer, M. A., Li, A., Sun, Y. N., Pickett, C. A., & Slamon, D. J. (2015). Trebananib (AMG 386) plus weekly paclitaxel with or without bevacizumab as first-line therapy for HER2-negative locally recurrent or metastatic breast cancer: A phase 2 randomized study. *Breast (Edinburgh, Scotland)*, *24*(3), 182–190. https://doi.org/10.1016/j.breast.2014.11.003

Ding, J., Jia, W., Cui, Y., Jin, J., Zhang, Y., Xu, L., & Liu, Y. (2020). Anti-angiogenic effect of a chemically sulfated polysaccharide from *Phellinus ribis* by inhibiting VEGF/VEGFR pathway. *International Journal of Biological Macromolecules*, *154*, 72–81. https://doi.org/10.1016/j.ijbiomac.2020.03.068

Doerge, D. R., Twaddle, N. C., Banks, E. P., Jefferson, W. N., & Newbold, R. R. (2002). Pharmacokinetic analysis in serum of genistein administered subcutaneously to neonatal mice. *Cancer Letters*, *184*(1), 21–27. https://doi.org/10.1016/s0304-3835(02)00200-8

Dong, J., Chen, Y., Yang, W., Zhang, X., & Li, L. (2020). Antitumor and anti-angiogenic effects of artemisinin on breast tumor xenografts in nude mice. *Research in Veterinary Science*, *129*, 66–69. https://doi.org/10.1016/j.rvsc.2020.01.005

Dong, X. Z., Zhang, M., Wang, K., Liu, P., Guo, D. H., Zheng, X. L., & Ge, X. Y. (2013). Sanguinarine inhibits vascular endothelial growth factor release by generation of reactive oxygen species in MCF-7 human mammary adenocarcinoma cells. *BioMed Research International*, *2013*, 517698. https://doi.org/10.1155/2013/517698

Dong, Y., Yang, Y., Wei, Y., Gao, Y., Jiang, W., & Wang, G. (2020). Ligustrazine eases lung cancer by regulating PTEN and Wnt/beta-catenin pathway. *Translational Cancer Research*, *9*(3), 1742–1751. https://doi.org/10.21037/tcr.2020.03.26

Donnem, T., Reynolds, A. R., Kuczynski, E. A., Gatter, K., Vermeulen, P. B., Kerbel, R. S., Harris, A. L., & Pezzella, F. (2018). Non-angiogenic tumours and their influence on cancer biology. *Nature Reviews Cancer*, *18*(5), 323–336. https://doi.org/10.1038/nrc.2018.14

Dvorak, H. F. (2005). Angiogenesis: Update 2005. *Journal of Thrombosis and Haemostasis*, *3*(8), 1835–1842. https://doi.org/10.1111/j.1538-7836.2005.01361.x

Erzurumlu, Y., Catakli, D., & Dogan, H. K. (2023). Potent carotenoid astaxanthin expands the anti-cancer activity of cisplatin in human prostate cancer cells. *Journal of Natural Medicines*, *77*(3), 572–583. https://doi.org/10.1007/s11418-023-01701-1

Erzurumlu, Y., Catakli, D., & Sezer, S. (2023). Cannabidiol negatively regulates androgenic signal in prostate cancer cells and fine-tunes the tumorigenesis by modulating endoplasmic reticulum-associated degradation, unfolded protein response, and autophagy. *Revista Brasileira de Farmacognosia*, *33*(2), 316–325. https://doi.org/10.1007/s43450-023-00360-3

Fadallah, M., Zahran, M. H., El-Assmy, A. M., Barakat, N. M., Khater, S., Awadalla, A., Ahmed, A. E., Ibrahiem, E., & Shokeir, A. A. (2022). Omega-3 polyunsaturated fatty acids: A modified approach for chemo-prevention of bladder cancer in a rat model and molecular studies of antineoplastic mechanisms. *Molecular Biology Reports*, *49*(7), 6357–6365. https://doi.org/10.1007/s11033-022-07445-7

Fantin, A., Vieira, J. M., Plein, A., Denti, L., Fruttiger, M., Pollard, J. W., & Ruhrberg, C. (2013). NRP1 acts cell autonomously in endothelium to promote tip cell function during sprouting angiogenesis. *Blood*, *121*(12), 2352–2362. https://doi.org/10.1182/blood-2012-05-424713

Fattah, A., Morovati, A., Niknam, Z., Mashouri, L., Asadi, A., Rizi, S. T., Abbasi, M., Shakeri, F., & Abazari, O. (2021). The synergistic combination of cisplatin and piperine induces apoptosis in MCF-7 cell line. *Iranian Journal of Public Health*, *50*(5), 1037–1047. https://doi.org/10.18502/ijph.v50i5.6121

Favot, L., Martin, S., Keravis, T., Andriantsitohaina, R., & Lugnier, C. (2003). Involvement of cyclin-dependent pathway in the inhibitory effect of delphinidin on angiogenesis. *Cardiovascular Research*, *59*(2), 479–487. https://doi.org/10.1016/s0008-6363(03)00433-4

Freise, C., Trowitzsch-Kienast, W., Ruehl, M., Erben, U., Seehofer, D., Kim, K. Y., Zeitz, M., & Somasundaram, R. (2012). (+)-Episesamin exerts anti-neoplastic effects in human hepatocellular carcinoma cell lines via suppression of nuclear factor-kappa B and inhibition of MMP-9. *Investigational New Drugs*, *30*(6), 2087–2095. https://doi.org/10.1007/s10637-011-9762-x

Fu, J. D., Yao, J. J., Wang, H., Cui, W. G., Leng, J., Ding, L. Y., & Fan, K. Y. (2019). Effects of EGCG on proliferation and apoptosis of gastric cancer SGC7901 cells via down-regulation of HIF-1alpha and VEGF under a hypoxic state. *European Review for Medical and Pharmacological Sciences*, *23*(1), 155–161. https://doi.org/10.26355/eurrev_201901_16759

Fu, Z., Chen, X., Guan, S., Yan, Y., Lin, H., & Hua, Z. C. (2015). Curcumin inhibits angiogenesis and improves defective hematopoiesis induced by tumor-derived VEGF in tumor model through modulating VEGF-VEGFR2 signaling pathway. *Oncotarget*, *6*(23), 19469–19482. https://doi.org/10.18632/oncotarget.3625

Garcia, J., Hurwitz, H. I., Sandler, A. B., Miles, D., Coleman, R. L., Deurloo, R., & Chinot, O. L. (2020). Bevacizumab (Avastin(R)) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treatment Reviews*, *86*, 102017. https://doi.org/10.1016/j.ctrv.2020.102017

Gavalas, N. G., Tsiatas, M., Tsitsilonis, O., Politi, E., Ioannou, K., Ziogas, A. C., Rodolakis, A., Vlahos, G., Thomakos, N., Haidopoulos, D., Terpos, E., Antsaklis, A., Dimopoulos, M. A., & Bamias, A. (2012). VEGF directly suppresses activation of T cells from ascites secondary to ovarian cancer via VEGF receptor type 2. *British Journal of Cancer*, *107*(11), 1869–1875. https://doi.org/10.1038/bjc.2012.468

Gerald, D., Chintharlapalli, S., Augustin, H. G., & Benjamin, L. E. (2013). Angiopoietin-2: An attractive target for improved antiangiogenic tumor therapy. *Cancer Research*, *73*(6), 1649–1657. https://doi.org/10.1158/0008-5472.CAN-12-4697

Geudens, I., & Gerhardt, H. (2011). Coordinating cell behaviour during blood vessel formation. *Development (Cambridge, England)*, *138*(21), 4569–4583. https://doi.org/10.1242/dev.062323

Ghaffari-Makhmalbaf, P., Sayyad, M., Pakravan, K., Razmara, E., Bitaraf, A., Bakhshinejad, B., Goudarzi, P., Yousefi, H., Pournaghshband, M., Nemati, F., Fahimi, H., Rohollah, F., Hasanzad, M., Hashemi, M., Mousavi, S. H., & Babashah, S. (2021). Docosahexaenoic acid reverses the promoting effects of breast tumor cell-derived exosomes on endothelial cell migration and angiogenesis. *Life Sciences*, *264*, 118719. https://doi.org/10.1016/j.lfs.2020.118719

Goggins, E., Mironchik, Y., Kakkad, S., Jacob, D., Wildes, F., Bhujwalla, Z. M., & Krishnamachary, B. (2023). Reprogramming of VEGF-mediated extracellular matrix changes through autocrine signaling. *Cancer Biology & Therapy*, *24*(1), 2184145. https://doi.org/10.1080/15384047.2023.2184145

Gong, J., Zhou, S., & Yang, S. (2019). Vanillic acid suppresses HIF-1alpha expression via inhibition of mTOR/p70S6K/4E-BP1 and Raf/MEK/ERK pathways in human colon cancer HCT116 cells. *International Journal of Molecular Sciences*, *20*(3), 465. https://doi.org/10.3390/ijms20030465

Gopinath, V., Saravanan, S., Al-Maleki, A. R., Ramesh, M., & Vadivelu, J. (2018). A review of natural polysaccharides for drug delivery applications: Special focus on cellulose, starch and glycogen. *Biomedicine & Pharmacotherapy*, *107*, 96–108. https://doi.org/10.1016/j.biopha.2018.07.136

Guo, R., Chen, M., Ding, Y., Yang, P., Wang, M., Zhang, H., He, Y., & Ma, H. (2022). Polysaccharides as potential anti-tumor biomacromolecules—A review. *Frontiers in Nutrition*, *9*, 838179. https://doi.org/10.3389/fnut.2022.838179

Guo, X., Fan, A., Qi, X., Liu, D., Huang, J., & Lin, W. (2023). Indoloquinazoline alkaloids suppress angiogenesis and inhibit metastasis of melanoma cells. *Bioorganic Chemistry*, *141*, 106873. https://doi.org/10.1016/j.bioorg.2023.106873

Gupta, N., Singh, S., Chauhan, D., Srivastava, R., & Singh, V. K. (2023). Exploring the anticancer potentials of polyphenols: A comprehensive review of patents in the last five years. *Recent Patents on Anti-Cancer Drug Discovery*, *18*(1), 3–10. https://doi.org/10.2174/1574892817666220512220036

Hai-Rong, C., Xiang, H., & Xiao-Rong, Z. (2019). Harmine suppresses bladder tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. *Bioscience Reports*, *39*(5), BSR20190155. https://doi.org/10.1042/BSR20190155

Hanahan, D. (2022). Hallmarks of cancer: New dimensions. *Cancer Discovery*, *12*(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

Harnedy, P. A., & FitzGerald, R. J. (2011). Bioactive proteins, peptides, and amino acids from macroalgae(1). *Journal of Phycology*, *47*(2), 218–232. https://doi.org/10.1111/j.1529-8817.2011.00969.x

Hazafa, A., Iqbal, M. O., Javaid, U., Tareen, M. B. K., Amna, D., Ramzan, A., Piracha, S., & Naeem, M. (2022). Inhibitory effect of polyphenols (phenolic acids, lignans, and stilbenes) on cancer by regulating signal transduction pathways: A review. *Clinical & Translational Oncology*, *24*(3), 432–445. https://doi.org/10.1007/s12094-021-02709-3

He, Z., Chen, A. Y., Rojanasakul, Y., Rankin, G. O., & Chen, Y. C. (2016). Gallic acid, a phenolic compound, exerts anti-angiogenic effects via the PTEN/AKT/HIF-1alpha/VEGF signaling pathway in ovarian cancer cells. *Oncology Reports*, *35*(1), 291–297. https://doi.org/10.3892/or.2015.4354

Henley, D. V., & Korach, K. S. (2006). Endocrine-disrupting chemicals use distinct mechanisms of action to modulate endocrine system function. *Endocrinology*, *147*, (6 Supp), S25–S32. https://doi.org/10.1210/en.2005-1117

Herrera-Bravo, J., Belén, L. H., Reyes, M. E., Silva, V., Fuentealba, S., Paz, C., Loren, P., Salazar, L. A., Sharifi-Rad, J., & Calina, D. (2024). Thymol as adjuvant in oncology: Molecular mechanisms, therapeutic potentials, and prospects for integration in cancer management. *Naunyn-Schmiedebergs Archives of Pharmacology*, Advance online publication. https://doi.org/10.1007/s00210-024-03196-3

Ho, Y., Sh Yang, Y. C., Chin, Y. T., Chou, S. Y., Chen, Y. R., Shih, Y. J., Whang-Peng, J., Changou, C. A., Liu, H. L., Lin, S. J., Tang, H. Y., Lin, H. Y., & Davis, P. J. (2018). Resveratrol inhibits human leiomyoma cell proliferation via crosstalk between integrin $\alpha v\beta 3$ and IGF-1R. *Food and Chemical Toxicology*, *120*, 346–355. https://doi.org/10.1016/j.fct.2018.07.030

Hodi, F. S., Lawrence, D., Lezcano, C., Wu, X., Zhou, J., Sasada, T., Zeng, W., Giobbie-Hurder, A., Atkins, M. B., Ibrahim, N., Friedlander, P., Flaherty, K. T., Murphy, G. F., Rodig, S., Velazquez, E. F., Mihm, M. C. Jr., Russell, S., DiPiro, P. J., Yap, J. T., … McDermott, D. (2014). Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunology Research*, *2*(7), 632–642. https://doi.org/10.1158/2326-6066.CIR-14-0053

Honarmand, M., Namazi, F., Mohammadi, A., & Nazifi, S. (2018). Can cannabidiol inhibit angiogenesis in colon cancer? *Comparative Clinical Pathology*, *28*(1), 165–172. https://doi.org/10.1007/s00580-018-2810-6

Hong, S., Cai, W., Huang, Z., Wang, Y., Mi, X., Huang, Y., Lin, Z., & Chen, X. (2020). Ginsenoside Rg3 enhances the anticancer effect of 5-FU in colon cancer cells via the PI3K/AKT pathway. *Oncology Reports*, *44*(4), 1333–1342. https://doi.org/10.3892/or.2020.7728

Hosny, S., Sahyon, H., Youssef, M., & Negm, A. (2021). Oleanolic acid suppressed DMBA-induced liver carcinogenesis through induction of mitochondrial-mediated apoptosis and autophagy. *Nutrition and Cancer*, *73*(6), 968–982. https://doi.org/10.1080/01635581.2020.1776887

Hsiao, J. R., Leu, S. F., & Huang, B. M. (2009). Apoptotic mechanism of paclitaxel-induced cell death in human head and neck tumor cell lines. *Journal of Oral Pathology & Medicine*, *38*(2), 188–197. https://doi.org/10.1111/j.1600-0714.2008.00732.x

Hsieh, S. L., Li, J. H., Dong, C. D., Chen, C. W., & Wu, C. C. (2022). Carnosine suppresses human colorectal cancer cell proliferation by inducing necroptosis and autophagy and reducing angiogenesis. *Oncology Letters*, *23*(2), 44. https://doi.org/10.3892/ol.2021.13162

Hsiu, S.-L., Hou, Y.-C., Wang, Y.-H., Tsao, C.-W., Su, S.-F., & Chao, P.-D. L. (2002). Quercetin significantly decreased cyclosporin oral bioavailability in pigs and rats. *Life Sciences*, *72*(3), 227–235. https://doi.org/10.1016/S0024-3205(02)02235-X

Hsu, W. J., Lin, M. H., Kuo, T. C., Chou, C. M., Mi, F. L., Cheng, C. H., & Lin, C. W. (2020). Fucoidan from *Laminaria japonica* exerts antitumor effects on angiogenesis and micrometastasis in triple-negative breast cancer cells. *International Journal of Biological Macromolecules*, *149*, 600–608. https://doi.org/10.1016/j.ijbiomac.2020.01.256

Hu, J., Lin, S., Huang, J. J., & Cheung, P. C. K. (2018). Mechanistic study of the in vitro and in vivo inhibitory effects of protocatechuic acid and syringic acid on VEGF-induced angiogenesis. *Journal of Agricultural and Food Chemistry*, *66*(26), 6742–6751. https://doi.org/10.1021/acs.jafc.8b01534

Hu, W. H., Duan, R., Xia, Y. T., Xiong, Q. P., Wang, H. Y., Chan, G. K., Liu, S. Y., Dong, T. T., Qin, Q. W., & Tsim, K. W. (2019). Binding of resveratrol to vascular endothelial growth factor suppresses angiogenesis by inhibiting the receptor signaling. *Journal of Agricultural and Food Chemistry*, *67*(4), 1127–1137. https://doi.org/10.1021/acs.jafc.8b05977

Hu, W. W., Lin, C. H., & Hong, Z. J. (2019). The enrichment of cancer stem cells using composite alginate/polycaprolactone nanofibers. *Carbohydrate Polymers*, *206*, 70–79. https://doi.org/10.1016/j.carbpol.2018.10.087

Huang, C., Li, J., Song, L., Zhang, D., Tong, Q., Ding, M., Bowman, L., Aziz, R., & Stoner, G. D. (2006). Black raspberry extracts inhibit benzo(a)pyrene diol-epoxide-induced activator protein 1 activation and VEGF transcription by targeting the phosphotidylinositol 3-kinase/Akt pathway. *Cancer Research*, *66*(1), 581–587. https://doi.org/10.1158/0008-5472.CAN-05-1951

Huang, H., Chen, A. Y., Rojanasakul, Y., Ye, X., Rankin, G. O., & Chen, Y. C. (2015). Dietary compounds galangin and myricetin suppress ovarian cancer cell angiogenesis. *Journal of Functional Foods*, *15*, 464–475. https://doi.org/10.1016/j.jff.2015.03.051

Hussain, S., Slevin, M., Matou, S., Ahmed, N., Choudhary, M. I., Ranjit, R., West, D., & Gaffney, J. (2008). Anti-angiogenic activity of sesterterpenes; Natural product inhibitors of FGF-2-induced angiogenesis. *Angiogenesis*, *11*(3), 245–256. https://doi.org/10.1007/s10456-008-9108-2

Hwang, S. T., Um, J. Y., Chinnathambi, A., Alharbi, S. A., Narula, A. S., Namjoshi, O. A., Blough, B. E., & Ahn, K. S. (2020). Evodiamine mitigates cellular growth and promotes apoptosis by targeting the c-Met pathway in prostate cancer cells. *Molecules (Basel, Switzerland)*, *25*(6), 1320. https://doi.org/10.3390/molecules25061320

Iqbal, M. J., Kabeer, A., Abbas, Z., Siddiqui, H. A., Calina, D., Sharifi-Rad, J., & Cho, W. C. (2024). Interplay of oxidative stress, cellular communication and signaling pathways in cancer. *Cell Communication and Signaling*, *22*(1), 7. https://doi.org/10.1186/s12964-023-01398-5

Jackson, T., Chougule, M. B., Ichite, N., Patlolla, R. R., & Singh, M. (2008). Antitumor activity of noscapine in human non-small cell lung cancer xenograft model. *Cancer Chemotherapy and Pharmacology*, *63*(1), 117–126. https://doi.org/10.1007/s00280-008-0720-z

Jakobsson, L., Franco, C. A., Bentley, K., Collins, R. T., Ponsioen, B., Aspalter, I. M., Rosewell, I., Busse, M., Thurston, G., Medvinsky, A., Schulte-Merker, S., & Gerhardt, H. (2010). Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting. *Nature Cell Biology*, *12*(10), 943–953. https://doi.org/10.1038/ncb2103

Jang, H., Choi, J., Park, J. K., Won, G., & Seol, J. W. (2021). Fucoxanthin exerts anti-tumor activity on canine mammary tumor cells via tumor cell apoptosis induction and angiogenesis inhibition. *Animals (Basel)*, *11*(6), 1512. https://doi.org/10.3390/ani11061512

Jia, S., Li, L., Yu, C., & Peng, F. (2024). Natural products' antiangiogenic roles in gynecological cancer. *Frontiers in Pharmacology*, *15*, 1353056. https://doi.org/10.3389/fphar.2024.1353056

Jie, S., Li, H., Tian, Y., Guo, D., Zhu, J., Gao, S., & Jiang, L. (2011). Berberine inhibits angiogenic potential of Hep G2 cell line through VEGF down-regulation in vitro. *Journal of Gastroenterology and Hepatology*, *26*(1), 179–185. https://doi.org/10.1111/j.1440-1746.2010.06389.x

Jo, M. J., Kim, B. G., Kim, W. Y., Lee, D. H., Yun, H. K., Jeong, S., Park, S. H., Kim, B. R., Kim, J. L., Kim, D. Y., Lee, S. I., & Oh, S. C. (2021). Cannabidiol suppresses angiogenesis and stemness of breast cancer cells by down-regulation of hypoxia-inducible factors-1alpha. *Cancers (Basel)*, *13*(22), 5667. https://doi.org/10.3390/cancers13225667

Ju, H., Yu, C., Zhang, X.-D., Liu, W., Wu, Y.-C., Gong, P.-X., Li, H.-H., Liu, Y., & Li, H.-J. (2023). Recent trends in anti-cancer activities of terrestrial plants-based polysaccharides: A review. *Carbohydrate Polymer Technologies and Applications*, *6*, 100341. https://doi.org/10.1016/j.carpta.2023.100341

Kalpathy-Cramer, J., Chandra, V., Da, X., Ou, Y., Emblem, K. E., Muzikansky, A., Cai, X., Douw, L., Evans, J. G., Dietrich, J., Chi, A. S., Wen, P. Y., Stufflebeam, S., Rosen, B., Duda, D. G., Jain, R. K., Batchelor, T. T., & Gerstner, E. R. (2017). Phase II study of tivozanib, an oral VEGFR inhibitor, in patients with recurrent glioblastoma. *Journal of Neuro-Oncology*, *131*(3), 603–610. https://doi.org/10.1007/s11060-016-2332-5

Kamaraj, S., Anandakumar, P., Jagan, S., Ramakrishnan, G., & Devaki, T. (2010). Modulatory effect of hesperidin on benzo(a)pyrene induced experimental lung carcinogenesis with reference to COX-2, MMP-2 and MMP-9. *European Journal of Pharmacology*, *649*(1–3), 320–327. https://doi.org/10.1016/j.ejphar.2010.09.017

Kang, D. Y., Sp, N., Lee, J. M., & Jang, K. J. (2021). Antitumor effects of ursolic acid through mediating the inhibition of STAT3/PD-L1 signaling in non-small cell lung cancer cells. *Biomedicines*, *9*(3), 297. https://doi.org/10.3390/biomedicines9030297

Kerbel, R., & Folkman, J. (2002). Clinical translation of angiogenesis inhibitors. *Nature Reviews Cancer*, *2*(10), 727–739. https://doi.org/10.1038/nrc905

Khalid, E. B., Ayman, E. E., Rahman, H., Abdelkarim, G., & Najda, A. (2016). Natural products against cancer angiogenesis. *Tumour Biology*, *37*(11), 14513–14536. https://doi.org/10.1007/s13277-016-5364-8

Khamessi, O., Ben Mabrouk, H., ElFessi-Magouri, R., & Kharrat, R. (2018). RK1, the first very short peptide from *Buthus occitanus tunetanus* inhibits tumor cell migration, proliferation and angiogenesis. *Biochemical and Biophysical Research Communications*, *499*(1), 1–7. https://doi.org/10.1016/j.bbrc.2018.01.133

Khan, K. A., & Kerbel, R. S. (2018). Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. *Nature Reviews Clinical Oncology*, *15*(5), 310–324. https://doi.org/10.1038/nrclinonc.2018.9

Khater, M., Greco, F., & Osborn, H. M. I. (2020). Antiangiogenic activity of flavonoids: A systematic review and meta-analysis. *Molecules (Basel, Switzerland)*, *25*(20), 4712. https://doi.org/10.3390/molecules25204712

Khatua, S., Nandi, S., Nag, A., Sen, S., Chakraborty, N., Naskar, A., Gürer, E. S., Calina, D., Acharya, K., & Sharifi-Rad, J. (2024). Homoharringtonine: Updated insights into its efficacy in hematological malignancies, diverse cancers and other biomedical applications. *European Journal of Medical Research*, *29*(1), 269. https://doi.org/10.1186/s40001-024-01856-x

Khumkhrong, P., Piboonprai, K., Chaichompoo, W., Pimtong, W., Khongkow, M., Namdee, K., Jantimaporn, A., Japrung, D., Asawapirom, U., Suksamrarn, A., & Iempridee, T. (2019). Crinamine induces apoptosis and inhibits proliferation, migration, and angiogenesis in cervical cancer SiHa cells. *Biomolecules*, *9*(9), 494. https://doi.org/10.3390/biom9090494

Kim, E. N., Lim, J. H., Kim, M. Y., Ban, T. H., Jang, I. A., Yoon, H. E., Park, C. W., Chang, Y. S., & Choi, B. S. (2018). Resveratrol, an Nrf2 activator, ameliorates aging-related progressive renal injury. *Aging (Albany NY)*, *10*(1), 83–99. https://doi.org/10.18632/aging.101361

Kim, H. Y., Kim, Y. M., & Hong, S. (2019). Astaxanthin suppresses the metastasis of colon cancer by inhibiting the MYC-mediated downregulation of microRNA-29a-3p and microRNA-200a. *Scientific Reports*, *9*(1), 9457. https://doi.org/10.1038/s41598-019-45924-3

Kim, J. D., Liu, L., Guo, W., & Meydani, M. (2006). Chemical structure of flavonols in relation to modulation of angiogenesis and immune-endothelial cell adhesion. *Journal of Nutritional Biochemistry*, *17*(3), 165–176. https://doi.org/10.1016/j.jnutbio.2005.06.006

Kim, M. H., Jeong, Y. J., Cho, H. J., Hoe, H. S., Park, K. K., Park, Y. Y., Choi, Y. H., Kim, C. H., Chang, H. W., Park, Y. J., Chung, I. K., & Chang, Y. C. (2017). Delphinidin inhibits angiogenesis through the suppression of HIF-1alpha and VEGF expression in A549 lung cancer cells. *Oncology Reports*, *37*(2), 777–784. https://doi.org/10.3892/or.2016.5296

Kim, S. H., Lee, S. E., Kim, S. J., Fang, X., Hur, J., Sozen, E., Ozer, N. K., Kim, K. P., & Surh, Y. J. (2023). Protective effects of an electrophilic metabolite of docosahexaenoic acid on UVB-induced oxidative cell death, dermatitis, and carcinogenesis. *Redox Biology*, *62*, 102666. https://doi.org/10.1016/j.redox.2023.102666

Kitic, D., Miladinovic, B., Randjelovic, M., Szopa, A., Seidel, V., Prasher, P., Sharma, M., Fatima, R., Arslan Ateşşahin, D., Calina, D., & Sharifi-Rad, J. (2024). Anticancer and chemopreventive potential of *Morinda citrifolia* L. bioactive compounds: A comprehensive update. *Phytotherapy Research*, *38*(4), 1932–1950. https://doi.org/10.1002/ptr.8137

Koch, S., Tugues, S., Li, X., Gualandi, L., & Claesson-Welsh, L. (2011). Signal transduction by vascular endothelial growth factor receptors. *Biochemical Journal*, *437*(2), 169–183. https://doi.org/10.1042/BJ20110301

Koh, G. Y. (2013). Orchestral actions of angiopoietin-1 in vascular regeneration. *Trends in Molecular Medicine*, *19*(1), 31–39. https://doi.org/10.1016/j.molmed.2012.10.010

Koksal, M., Jin, Y., Coates, R. M., Croteau, R., & Christianson, D. W. (2011). Taxadiene synthase structure and evolution of modular architecture in terpene biosynthesis. *Nature*, *469*(7328), 116–120. https://doi.org/10.1038/nature09628

Koushki, M., Amiri-Dashatan, N., Ahmadi, N., Abbaszadeh, H. A., & Rezaei-Tavirani, M. (2018). Resveratrol: A miraculous natural compound for diseases treatment. *Food Science & Nutrition*, *6*(8), 2473–2490. https://doi.org/10.1002/fsn3.855

Kowshik, J., Giri, H., Kishore, T. K., Kesavan, R., Vankudavath, R. N., Reddy, G. B., Dixit, M., & Nagini, S. (2014). Ellagic acid inhibits VEGF/VEGFR2, PI3K/Akt and MAPK signaling cascades in the hamster cheek pouch carcinogenesis model. *Anti-Cancer Agents in Medicinal Chemistry*, *14*(9), 1249–1260. https://doi.org/10.2174/1871520614666140723114217

Krizova, L., Dadakova, K., Kasparovska, J., & Kasparovsky, T. (2019). Isoflavones. *Molecules (Basel, Switzerland)*, *24*(6). https://doi.org/10.3390/molecules24061076

Krueger, J., Liu, D., Scholz, K., Zimmer, A., Shi, Y., Klein, C., Siekmann, A., Schulte-Merker, S., Cudmore, M., Ahmed, A., & le Noble, F. (2011). Flt1 acts as a negative regulator of tip cell formation and branching morphogenesis in the zebrafish embryo. *Development (Cambridge, England)*, *138*(10), 2111–2120. https://doi.org/10.1242/dev.063933

Kucan, D., Orsolic, N., Odeh, D., Ramic, S., Jakopovic, B., Knezevic, J., & Jazvinscak Jembrek, M. (2023). The role of hyperthermia in potentiation of anti-angiogenic effect of cisplatin and resveratrol in mice bearing solid form of Ehrlich ascites tumour. *International Journal of Molecular Sciences*, *24*(13), 11073. https://doi.org/10.3390/ijms241311073

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: An overview. *ScientificWorldJournal*, *2013*, 162750. https://doi.org/10.1155/2013/162750

Kuonqui, K., Campbell, A. C., Sarker, A., Roberts, A., Pollack, B. L., Park, H. J., Shin, J., Brown, S., Mehrara, B. J., & Kataru, R. P. (2023). Dysregulation of lymphatic endothelial VEGFR3 signaling in disease. *Cells*, *13*(1), 68. https://doi.org/10.3390/cells13010068

Lee, C. C., Liu, K. J., Wu, Y. C., Lin, S. J., Chang, C. C., & Huang, T. S. (2011). Sesamin inhibits macrophage-induced vascular endothelial growth factor and matrix metalloproteinase-9 expression and proangiogenic activity in breast cancer cells. *Inflammation*, *34*(3), 209–221. https://doi.org/10.1007/s10753-010-9226-z

Lee, M. S., Ryoo, B. Y., Hsu, C. H., Numata, K., Stein, S., Verret, W., Hack, S. P., Spahn, J., Liu, B., Abdullah, H., Wang, Y., He, A. R., Lee, K. H., & GO30140 investigators. (2020). Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): An open-label, multicentre, phase 1b study. *Lancet Oncology*, *21*(6), 808–820. https://doi.org/10.1016/S1470-2045(20)30156-X

Li, G., Zhao, J., Peng, X., Liang, J., Deng, X., & Chen, Y. (2012). Radiation/paclitaxel treatment of p53-abnormal non-small cell lung cancer xenograft tumor and associated mechanism. *Cancer Biotherapy & Radiopharmaceuticals*, *27*(4), 227–233. https://doi.org/10.1089/cbr.2011.1154

Li, H. Y., Yang, H. G., Li, P., Wang, Y. Z., Huang, G. X., Xing, L., Wang, J. Q., & Zheng, N. (2019). Effect of heat treatment on the antitumor activity of lactoferrin in human colon tumor (HT29) model. *Journal of Agricultural and Food Chemistry*, *67*(1), 140–147. https://doi.org/10.1021/acs.jafc.8b05131

Li, P., Pu, S., Lin, C., He, L., Zhao, H., Yang, C., Guo, Z., Xu, S., & Zhou, Z. (2022). Curcumin selectively induces colon cancer cell apoptosis and S cell cycle arrest by regulates Rb/E2F/p53 pathway. *Journal of Molecular Structure*, *1263*, 133180. https://doi.org/10.1016/j.molstruc.2022.133180

Li, Q., Wang, Y., Jia, W., Deng, H., Li, G., Deng, W., Chen, J., Kim, B. Y. S., Jiang, W., Liu, Q., & Liu, J. (2020). Low-dose anti-angiogenic therapy sensitizes breast cancer to PD-1 blockade. *Clinical Cancer Research*, *26*(7), 1712–1724. https://doi.org/10.1158/1078-0432.CCR-19-2179

Li, R., Song, X., Guo, Y., Song, P., Duan, D., & Chen, Z. S. (2021). Natural products: A promising therapeutics for targeting tumor angiogenesis. *Frontiers in Oncology*, *11*, 772915. https://doi.org/10.3389/fonc.2021.772915

Li, Y., Wang, X., Ma, X., Liu, C., Wu, J., & Sun, C. (2021). Natural polysaccharides and their derivates: A promising natural adjuvant for tumor immunotherapy. *Frontiers in Pharmacology*, *12*, 621813. https://doi.org/10.3389/fphar.2021.621813

Li, Z., Ding, X., Wu, H., & Liu, C. (2019). Artemisinin inhibits angiogenesis by regulating p38 MAPK/CREB/TSP-1 signaling pathway in osteosarcoma. *Journal of Cellular Biochemistry*, *120*(7), 11462–11470. https://doi.org/10.1002/jcb.28424

Liu, L., Xiong, X., Shen, M., Ru, D., Gao, P., Zhang, X., Huang, C., Sun, Y., Li, H., & Duan, Y. (2018). Co-delivery of triptolide and curcumin for ovarian cancer targeting therapy via mPEG-DPPE/CaP nanoparticle. *Journal of Biomedical Nanotechnology*, *14*(10), 1761–1772. https://doi.org/10.1166/jbn.2018.2633

Liu, Y., Li, C. L., Xu, Q. Q., Cheng, D., Liu, K. D., & Sun, Z. Q. (2021). Quercetin inhibits invasion and angiogenesis of esophageal cancer cells. *Pathology, Research and Practice*, *222*, 153455. https://doi.org/10.1016/j.prp.2021.153455

Liu, Y., Lv, H., Li, X., Liu, J., Chen, S., Chen, Y., Jin, Y., An, R., Yu, S., & Wang, Z. (2021). Cyclovirobuxine inhibits the progression of clear cell renal cell carcinoma by suppressing the IGFBP3-AKT/STAT3/MAPK-Snail signalling pathway. *International Journal of Biological Sciences*, *17*(13), 3522–3537. https://doi.org/10.7150/ijbs.62114

Liu, Y., Tian, Y., Guo, Y., Yan, Z., Xue, C., & Wang, J. (2021). DHA-enriched phosphatidylcholine suppressed angiogenesis by activating PPARgamma and modulating the VEGFR2/Ras/ERK pathway in human umbilical vein endothelial cells. *Food Science and Biotechnology*, *30*(12), 1543–1553. https://doi.org/10.1007/s10068-021-00990-0

Liu, Z.-L., Chen, H.-H., Zheng, L.-L., Sun, L.-P., & Shi, L. (2023). Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Signal Transduction and Targeted Therapy*, *8*(1), 198. https://doi.org/10.1038/s41392-023-01460-1

Liu, Z., Li, Y., & Yang, R. (2012). Effects of resveratrol on vascular endothelial growth factor expression in osteosarcoma cells and cell proliferation. *Oncology Letters*, *4*(4), 837–839. https://doi.org/10.3892/ol.2012.824

Lohela, M., Bry, M., Tammela, T., & Alitalo, K. (2009). VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. *Current Opinion in Cell Biology*, *21*(2), 154–165. https://doi.org/10.1016/j.ceb.2008.12.012

Lopes, F. G., Oliveira, K. A., Lopes, R. G., Poluceno, G. G., Simioni, C., Gabriel, D. S. P., Bauer, C. M., Maraschin, M., Derner, R. B., Garcez, R. C., Tasca, C. I., & Nedel, C. B. (2020). Anti-cancer effects of fucoxanthin on human glioblastoma cell line. *Anticancer Research*, *40*(12), 6799–6815. https://doi.org/10.21873/anticanres.14703

Lorusso, P. M., Edelman, M. J., Bever, S. L., Forman, K. M., Pilat, M., Quinn, M. F., Li, J., Heath, E. I., Malburg, L. M., Klein, P. J., Leamon, C. P., Messmann, R. A., & Sausville, E. A. (2012). Phase I study of folate conjugate EC145 (Vintafolide) in patients with refractory solid tumors. *Journal of Clinical Oncology*, *30*(32), 4011–4016. https://doi.org/10.1200/JCO.2011.41.4946

Lozac'h, N. (1986). Extension of Rules A-1.1 and A-2.5 concerning numerical terms used in organic chemical nomenclature (Recommendations 1986). *Pure and Applied Chemistry*, *58*(12), 1693–1696. https://doi.org/10.1351/pac198658121693

Lu, X., Friedrich, L. J., & Efferth, T. (2023). Natural products targeting tumour angiogenesis. *British Journal of Pharmacology*. Advance online publication. https://doi.org/10.1111/bph.16232

Luo, H., Rankin, G. O., Liu, L., Daddysman, M. K., Jiang, B. H., & Chen, Y. C. (2009). Kaempferol inhibits angiogenesis and VEGF expression through both HIF dependent and independent pathways in human ovarian cancer cells. *Nutrition and Cancer*, *61*(4), 554–563. https://doi.org/10.1080/01635580802666281

Lv, F., Li, X., & Wang, Y. (2022). Lycorine inhibits angiogenesis by docking to PDGFRalpha. *BMC Cancer*, *22*(1), 873. https://doi.org/10.1186/s12885-022-09929-y

Ma, C., Tang, X., Tang, Q., Wang, S., Zhang, J., Lu, Y., Wu, J., & Han, L. (2022). Curcumol repressed cell proliferation and angiogenesis via SP1/mir-125b-5p/VEGFA axis in non-small cell lung cancer. *Frontiers in Pharmacology*, *13*, 1044115. https://doi.org/10.3389/fphar.2022.1044115

Ma, H., Qiu, P., Xu, H., Xu, X., Xin, M., Chu, Y., Guan, H., Li, C., & Yang, J. (2019). The inhibitory effect of propylene glycol alginate sodium sulfate on fibroblast growth factor 2-mediated angiogenesis and invasion in murine melanoma B16-F10 cells in vitro. *Marine Drugs*, *17*(5). https://doi.org/10.3390/md17050257

Ma, X., & Ning, S. (2019). Cyanidin-3-glucoside attenuates the angiogenesis of breast cancer via inhibiting STAT3/VEGF pathway. *Phytotherapy Research*, *33*(1), 81–89. https://doi.org/10.1002/ptr.6201

Madhu, C. S., Balaji, K. S., Shankar, J., & Sharada, A. C. (2019). Antitumor effects of chitin specific lectin from *Praecitrullus fistulosus* by targeting angiogenesis and apoptosis. *Biochemical and Biophysical Research Communications*, *518*(2), 381–387. https://doi.org/10.1016/j.bbrc.2019.08.067

Mahmoud, M. A., Okda, T. M., Omran, G. A., & Abd-Alhaseeb, M. M. (2021). Rosmarinic acid suppresses inflammation, angiogenesis, and improves paclitaxel induced apoptosis in a breast cancer model via NF3 kappaB-p53-caspase-3 pathways modulation. *Journal of Applied Biomedicine*, *19*(4), 202–209. https://doi.org/10.32725/jab.2021.024

Mahmud, A. R., Ema, T. I., Siddiquee, M. F., Shahriar, A., Ahmed, H., Mosfeq-Ul-Hasan, M., Rahman, N., Islam, R., Uddin, M. R., & Mizan, M. F. R. (2023). Natural flavonols: Actions, mechanisms, and potential therapeutic utility for various diseases. *Beni-Suef University Journal of Basic and Applied Sciences*, *12*(1), 47. https://doi.org/10.1186/s43088-023-00387-4

Mahran, R. I., Hagras, M. M., Sun, D., & Brenner, D. E. (2017). Bringing curcumin to the clinic in cancer prevention: A review of strategies to enhance bioavailability and efficacy. *AAPS Journal*, *19*(1), 54–81. https://doi.org/10.1208/s12248-016-0003-2

Majidpoor, J., & Mortezaee, K. (2021). Angiogenesis as a hallmark of solid tumors—Clinical perspectives. *Cellular Oncology*, *44*(4), 715–737. https://doi.org/10.1007/s13402-021-00602-3

Manna, S. K., Mukhopadhyay, A., & Aggarwal, B. B. (2000). Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: Potential role of reactive oxygen intermediates and lipid peroxidation. *Journal of Immunology*, *164*(12), 6509–6519. https://doi.org/10.4049/jimmunol.164.12.6509

Manthey, J. A., Grohmann, K., & Guthrie, N. (2001). Biological properties of citrus flavonoids pertaining to cancer and inflammation. *Current Medicinal Chemistry*, *8*(2), 135–153. https://doi.org/10.2174/0929867013373723

Maoka, T. (2011). Carotenoids in marine animals. *Marine Drugs*, *9*(2), 278–293. https://doi.org/10.3390/md9020278

Maoka, T. (2020). Carotenoids as natural functional pigments. *Journal of Natural Medicines*, *74*(1), 1–16. https://doi.org/10.1007/s11418-019-01364-x

Marech, I., Leporini, C., Ammendola, M., Porcelli, M., Gadaleta, C. D., Russo, E., De Sarro, G., & Ranieri, G. (2016). Classical and non-classical proangiogenic factors as a target of antiangiogenic therapy in tumor microenvironment. *Cancer Letters*, *380*(1), 216–226. https://doi.org/10.1016/j.canlet.2015.07.028

Marulanda, K., Brokaw, D., Gambarian, M., Pareta, R., McQuilling, J. P., Opara, E. C., & McLean, S. E. (2021). Controlled delivery of Slit3 proteins from alginate microbeads inhibits in vitro angiogenesis. *Journal of Surgical Research*, *264*, 90–98. https://doi.org/10.1016/j.jss.2021.01.025

Masyita, A., Mustika Sari, R., Dwi Astuti, A., Yasir, B., Rahma Rumata, N., Emran, T. B., Nainu, F., & Simal-Gandara, J. (2022). Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. *Food Chemistry: X*, *13*, 100217. https://doi.org/10.1016/j.fochx.2022.100217

Medina, M. A., & Quesada, A. R. (2014). Dietary proteins and angiogenesis. *Nutrients*, *6*(1), 371–381. https://doi.org/10.3390/nu6010371

Meng, Y. M., Jiang, X., Zhao, X., Meng, Q., Wu, S., Chen, Y., Kong, X., Qiu, X., Su, L., Huang, C., Wang, M., Liu, C., & Wong, P. P. (2021). Hexokinase 2-driven glycolysis in pericytes activates their contractility leading to tumor blood vessel abnormalities. *Nature Communications*, *12*(1), 6011. https://doi.org/10.1038/s41467-021-26259-y

Meresse, S., Fodil, M., Fleury, F., & Chenais, B. (2020). Fucoxanthin, a marine-derived carotenoid from brown seaweeds and microalgae: A promising bioactive compound for cancer therapy. *International Journal of Molecular Sciences*, *21*(23), 9273. https://doi.org/10.3390/ijms21239273

Messeha, S. S., Zarmouh, N. O., Antonie, L., & Soliman, K. F. A. (2022). Sanguinarine inhibition of TNF-alpha-induced CCL2, IKBKE/NF-kappaB/ERK1/2 signaling pathway, and cell migration in human triple-negative breast cancer cells. *International Journal of Molecular Sciences*, *23*(15), 8329. https://doi.org/10.3390/ijms23158329

Metibemu, D. S., Akinloye, O. A., Akamo, A. J., Okoye, J. O., Ojo, D. A., Morifi, E., & Omotuyi, I. O. (2021). VEGFR-2 kinase domain inhibition as a scaffold for anti-angiogenesis: Validation of the anti-angiogenic effects of carotenoids from *Spondias mombin* in DMBA model of breast carcinoma in Wistar rats. *Toxicology Reports*, *8*, 489–498. https://doi.org/10.1016/j.toxrep.2021.02.011

Min, J. K., Han, K. Y., Kim, E. C., Kim, Y. M., Lee, S. W., Kim, O. H., Kim, K. W., Gho, Y. S., & Kwon, Y. G. (2004). Capsaicin inhibits in vitro and in vivo angiogenesis. *Cancer Research*, *64*(2), 644–651. https://doi.org/10.1158/0008-5472.can-03-3250

Mirzaei, H., Bagheri, H., Ghasemi, F., Khoi, J. M., Pourhanifeh, M. H., Heyden, Y. V., Mortezapour, E., Nikdasti, A., Jeandet, P., Khan, H., & Sahebkar, A. (2021). Anti-cancer activity of curcumin on multiple myeloma. *Anti-Cancer Agents in Medicinal Chemistry*, *21*(5), 575–586. https://doi.org/10.2174/1871520620666200918113625

Mirzaei, S., Fekri, H. S., Hashemi, F., Hushmandi, K., Mohammadinejad, R., Ashrafizadeh, M., Zarrabi, A., & Garg, M. (2021). Venom peptides in cancer therapy: An updated review on cellular and molecular aspects. *Pharmacological Research*, *164*, 105327. https://doi.org/10.1016/j.phrs.2020.105327

Modica, R., Benevento, E., & Colao, A. (2023). Endocrine-disrupting chemicals (EDCs) and cancer: New perspectives on an old relationship. *Journal of Endocrinological Investigation*, *46*(4), 667–677. https://doi.org/10.1007/s40618-022-01983-4

Mohammed, A. S. A., Naveed, M., & Jost, N. (2021). Polysaccharides; Classification, chemical properties, and future perspective applications in fields of pharmacology and biological medicine (a review of current applications and upcoming potentialities). *Journal of Polymers and the Environment*, *29*(8), 2359–2371. https://doi.org/10.1007/s10924-021-02052-2

Mohi-Ud-Din, R., Chawla, A., Sharma, P., Mir, P. A., Potoo, F. H., Reiner, Ž., Reiner, I., Ateşşahin, D. A., Sharifi-Rad, J., Mir, R. H., & Calina, D. (2023). Repurposing approved non-oncology drugs for cancer therapy: A comprehensive review of mechanisms, efficacy, and clinical prospects. *European Journal of Medical Research*, *28*(1), 345. https://doi.org/10.1186/s40001-023-01275-4

Montanino, A., Manzo, A., Carillio, G., Palumbo, G., Esposito, G., Sforza, V., Costanzo, R., Sandomenico, C., Botti, G., Piccirillo, M. C., Cascetta, P., Pascarella, G., La Manna, C., Normanno, N., & Morabito, A. (2021). Angiogenesis inhibitors in small cell lung cancer. *Frontiers in Oncology*, *11*, 655316. https://doi.org/10.3389/fonc.2021.655316

Mortezaee, K. (2021). Redox tolerance and metabolic reprogramming in solid tumors. *Cell Biology International*, *45*(2), 273–286. https://doi.org/10.1002/cbin.11506

Motzer, R. J., Penkov, K., Haanen, J., Rini, B., Albiges, L., Campbell, M. T., Venugopal, B., Kollmannsberger, C., Negrier, S., Uemura, M., Lee, J. L., Vasiliev, A., Miller, W. H. Jr., Gurney, H., Schmidinger, M., Larkin, J., Atkins, M. B., Bedke, J., Alekseev, B., & Choueiri, T. K. (2019). Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine*, *380*(12), 1103–1115. https://doi.org/10.1056/NEJMoa1816047

Moulari, B., Pellequer, Y., Lboutounne, H., Girard, C., Chaumont, J. P., Millet, J., & Muyard, F. (2006). Isolation and in vitro antibacterial activity of astilbin, the bioactive flavanone from the leaves of *Harungana madagascariensis* Lam. ex Poir. (*Hypericaceae*). *Journal of Ethnopharmacology*, *106*(2), 272–278. https://doi.org/10.1016/j.jep.2006.01.008

Mukund, V., Saddala, M. S., Farran, B., Mannavarapu, M., Alam, A., & Nagaraju, G. P. (2019). Molecular docking studies of angiogenesis target protein HIF-1alpha and genistein in breast cancer. *Gene*, *701*, 169–172. https://doi.org/10.1016/j.gene.2019.03.062

Myoung, H., Hong, S. P., Yun, P. Y., Lee, J. H., & Kim, M. J. (2003). Anticancer effect of genistein in oral squamous cell carcinoma with respect to angiogenesis and in vitro invasion. *Cancer Science*, *94*(2), 215–220. https://doi.org/10.1111/j.1349-7006.2003.tb01422.x

Naeem, A., Hu, P., Yang, M., Zhang, J., Liu, Y., Zhu, W., & Zheng, Q. (2022). Natural products as anticancer agents: Current status and future perspectives. *Molecules (Basel, Switzerland)*, *27*(23), 8367. https://doi.org/10.3390/molecules27238367

Nakayama, M., Nakayama, A., van Lessen, M., Yamamoto, H., Hoffmann, S., Drexler, H. C., Itoh, N., Hirose, T., Breier, G., Vestweber, D., Cooper, J. A., Ohno, S., Kaibuchi, K., & Adams, R. H. (2013). Spatial regulation of VEGF receptor endocytosis in angiogenesis. *Nature Cell Biology*, *15*(3), 249–260. https://doi.org/10.1038/ncb2679

Nakhjavani, M., Hardingham, J. E., Palethorpe, H. M., Tomita, Y., Smith, E., Price, T. J., & Townsend, A. R. (2019). Ginsenoside Rg3: Potential molecular targets and therapeutic indication in metastatic breast cancer. *Medicines (Basel)*, *6*(1), 17. https://doi.org/10.3390/medicines6010017

Namkaew, J., Jaroonwitchawan, T., Rujanapun, N., Saelee, J., & Noisa, P. (2018). Combined effects of curcumin and doxorubicin on cell death and cell migration of SH-SY5Y human neuroblastoma cells. *In Vitro Cellular & Developmental Biology Animal*, *54*(9), 629–639. https://doi.org/10.1007/s11626-018-0288-9

Newbold, R. R., Banks, E. P., Bullock, B., & Jefferson, W. N. (2001). Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Research*, *61*(11), 4325–4328. https://www.ncbi.nlm.nih.gov/pubmed/11389053

Newcomb, E. W., Lukyanov, Y., Alonso-Basanta, M., Esencay, M., Smirnova, I., Schnee, T., Shao, Y., Devitt, M. L., Zagzag, D., McBride, W., & Formenti, S. C. (2008). Antiangiogenic effects of noscapine enhance radioresponse

for GL261 tumors. *International Journal of Radiation and Oncology in Biology and Physics*, *71*(5), 1477–1484. https://doi.org/10.1016/j.ijrobp.2008.04.020

Ng, C. X., Affendi, M. M., Chong, P. P., & Lee, S. H. (2022). The potential of plant-derived extracts and compounds to augment anticancer effects of chemotherapeutic drugs. *Nutrition and Cancer*, *74*(9), 3058–3076. https://doi.org/10.1080/01635581.2022.2069274

Niedzwiecki, A., Roomi, M. W., Kalinovsky, T., & Rath, M. (2016). Anticancer efficacy of polyphenols and their combinations. *Nutrients*, *8*(9), 552. https://doi.org/10.3390/nu8090552

Nishida, N., Yano, H., Nishida, T., Kamura, T., & Kojiro, M. (2006). Angiogenesis in cancer. *Vascular Health and Risk Management*, *2*(3), 213–219. https://doi.org/10.2147/vhrm.2006.2.3.213

Oliveira, C., Granja, S., Neves, N. M., Reis, R. L., Baltazar, F., Silva, T. H., & Martins, A. (2019). Fucoidan from *Fucus vesiculosus* inhibits new blood vessel formation and breast tumor growth in vivo. *Carbohydrate Polymers*, *223*, 115034. https://doi.org/10.1016/j.carbpol.2019.115034

Orsolic, N., Kunstic, M., Kukolj, M., Odeh, D., & Ancic, D. (2020). Natural phenolic acid, product of the honey bee, for the control of oxidative stress, peritoneal angiogenesis, and tumor growth in mice. *Molecules (Basel, Switzerland)*, *25*(23), 5583. https://doi.org/10.3390/molecules25235583

Ouyang, Y., Qiu, Y., Liu, Y., Zhu, R., Chen, Y., El-Seedi, H. R., Chen, X., & Zhao, C. (2021). Cancer-fighting potentials of algal polysaccharides as nutraceuticals. *Food Research International*, *147*, 110522. https://doi.org/10.1016/j.foodres.2021.110522

Ozturk, S. A., Alp, E., Yar Saglam, A. S., Konac, E., & Menevse, E. S. (2018). The effects of thymoquinone and genistein treatment on telomerase activity, apoptosis, angiogenesis, and survival in thyroid cancer cell lines. *Journal of Cancer Research & Therapy*, *14*(2), 328–334. https://doi.org/10.4103/0973-1482.202886

Pal, P., Hales, K., Petrik, J., & Hales, D. B. (2019). Pro-apoptotic and anti-angiogenic actions of 2-methoxyestradiol and docosahexaenoic acid, the biologically derived active compounds from flaxseed diet, in preventing ovarian cancer. *Journal of Ovarian Research*, *12*(1), 49. https://doi.org/10.1186/s13048-019-0523-3

Pal, P., Jana, S., Biswas, I., Mandal, D. P., & Bhattacharjee, S. (2022). Biphasic effect of the dietary phytochemical linalool on angiogenesis and metastasis. *Molecular and Cellular Biochemistry*, *477*(4), 1041–1052. https://doi.org/10.1007/s11010-021-04341-9

Palhares, L., Barbosa, J. S., Scortecci, K. C., Rocha, H. A. O., Brito, A. S., & Chavante, S. F. (2020). In vitro antitumor and anti-angiogenic activities of a shrimp chondroitin sulfate. *International Journal of Biological Macromolecules*, *162*, 1153–1165. https://doi.org/10.1016/j.ijbiomac.2020.06.100

Pan, T. J., Li, L. X., Zhang, J. W., Yang, Z. S., Shi, D. M., Yang, Y. K., & Wu, W. Z. (2019). Antimetastatic effect of fucoidan-sargassum against liver cancer cell invadopodia formation via targeting integrin alphaVbeta3 and mediating alphaVbeta3/Src/E2F1 signaling. *Journal of Cancer*, *10*(20), 4777–4792. https://doi.org/10.7150/jca.26740

Panche, A. N., Diwan, A. D., & Chandra, S. R. (2016). Flavonoids: An overview. *Journal of Nutritional Science*, *5*, e47. https://doi.org/10.1017/jns.2016.41

Park, S. W., Cho, C. S., Jun, H. O., Ryu, N. H., Kim, J. H., Yu, Y. S., & Kim, J. S. (2012). Anti-angiogenic effect of luteolin on retinal neovascularization via blockade of reactive oxygen species production. *Investigative Ophthalmology & Visual Science*, *53*(12), 7718–7726. https://doi.org/10.1167/iovs.11-8790

Passildas-Jahanmohan, J., Eymard, J. C., Pouget, M., Kwiatkowski, F., Van Praagh, I., Savareux, L., Atger, M., Durando, X., Abrial, C., Richard, D., Ginzac Couvé, A., Thivat, E., Monange, B., Chollet, P., & Mahammedi, H. (2021). Multicenter randomized phase II study comparing docetaxel plus curcumin versus docetaxel plus placebo in first-line treatment of metastatic castration-resistant prostate cancer. *Cancer Medicine*, *10*(7), 2332–2340. https://doi.org/10.1002/cam4.3806

Perveen, S. (2018). Introductory Chapter: Terpenes and terpenoids. In *Terpenes and terpenoids*. https://doi.org/10.5772/intechopen.79683

Phng, L. K., Potente, M., Leslie, J. D., Babbage, J., Nyqvist, D., Lobov, I., Ondr, J. K., Rao, S., Lang, R. A., Thurston, G., & Gerhardt, H. (2009). Nrarp coordinates endothelial Notch and Wnt signaling to control vessel density in angiogenesis. *Developmental Cell*, *16*(1), 70–82. https://doi.org/10.1016/j.devcel.2008.12.009

Piver, B., Berthou, F., Dreano, Y., & Lucas, D. (2001). Inhibition of CYP3A, CYP1A and CYP2E1 activities by resveratrol and other non volatile red wine components. *Toxicology Letters*, *125*(1), 83–91. https://doi.org/10.1016/S0378-4274(01)00418-0

Pons, D. G., Nadal-Serrano, M., Torrens-Mas, M., Oliver, J., & Roca, P. (2016). The phytoestrogen genistein affects breast cancer cells treatment depending on the ERα/ERβ ratio. *Journal of Cellular Biochemistry*, *117*(1), 218–229. https://doi.org/10.1002/jcb.25268

Poór, M., Boda, G., Needs, P. W., Kroon, P. A., Lemli, B., & Bencsik, T. (2017). Interaction of quercetin and its metabolites with warfarin: Displacement of warfarin from serum albumin and inhibition of CYP2C9 enzyme. *Biomedicine & Pharmacotherapy*, *88*, 574–581. https://doi.org/10.1016/j.biopha.2017.01.092

Pratheeshkumar, P., Budhraja, A., Son, Y. O., Wang, X., Zhang, Z., Ding, S., Wang, L., Hitron, A., Lee, J. C., Xu, M., Chen, G., Luo, J., & Shi, X. (2012). Quercetin inhibits angiogenesis mediated human prostate tumor growth by targeting VEGFR-2 regulated AKT/mTOR/P70S6K signaling pathways. *PLoS ONE*, *7*(10), e47516. https://doi.org/10.1371/journal.pone.0047516

Preet, A., Ganju, R. K., & Groopman, J. E. (2008). Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. *Oncogene*, *27*(3), 339–346. https://doi.org/10.1038/sj.onc.1210641

Pyun, B. J., Choi, S., Lee, Y., Kim, T. W., Min, J. K., Kim, Y., Kim, B. D., Kim, J. H., Kim, T. Y., Kim, Y. M., & Kwon, Y. G. (2008). Capsiate, a nonpungent capsaicin-like compound, inhibits angiogenesis and vascular permeability via a direct inhibition of Src kinase activity. *Cancer Research*, *68*(1), 227–235. https://doi.org/10.1158/0008-5472.CAN-07-2799

Qi, W. Y., Gao, X. M., Ma, Z. Y., Xia, C. L., & Xu, H. M. (2020). Antiangiogenic activity of terpenoids from *Euphorbia neriifolia* Linn. *Bioorganic Chemistry*, *96*, 103536. https://doi.org/10.1016/j.bioorg.2019.103536

Qin, N., Lu, S., Chen, N., Chen, C., Xie, Q., Wei, X., Ye, F., He, J., Li, Y., Chen, L., Jiang, L., Lu, X., Yuan, Y., Li, J., Jiao, Y., & Huang, R. (2019). Yulangsan polysaccharide inhibits 4T1 breast cancer cell proliferation and induces apoptosis in vitro and in vivo. *International Journal of Biological Macromolecules*, *121*, 971–980. https://doi.org/10.1016/j.ijbiomac.2018.10.082

Rabiau, N., Kossai, M., Braud, M., Chalabi, N., Satih, S., Bignon, Y. J., & Bernard-Gallon, D. J. (2010). Genistein and daidzein act on a panel of genes implicated in cell cycle and angiogenesis by polymerase chain reaction arrays in human prostate cancer cell lines. *Cancer Epidemiology*, *34*(2), 200–206. https://doi.org/10.1016/j.canep.2009.12.018

Radwan, M. M., Chandra, S., Gul, S., & ElSohly, M. A. (2021). Cannabinoids, phenolics, terpenes and alkaloids of cannabis. *Molecules (Basel, Switzerland)*, *26*(9), 2774. https://doi.org/10.3390/molecules26092774

Rahaman, M. M., Hossain, R., Herrera-Bravo, J., Islam, M. T., Atolani, O., Adeyemi, O. S., Owolodun, O. A., Kambizi, L., Daştan, S. D., Calina, D., & Sharifi-Rad, J. (2023). Natural antioxidants from some fruits, seeds, foods, natural products, and associated health benefits: An update. *Food Science & Nutrition*, *11*(4), 1657–1670. https://doi.org/10.1002/fsn3.3217

Rajabi, M., & Mousa, S. A. (2017). The role of angiogenesis in cancer treatment. *Biomedicines*, *5*(2), 34. https://doi.org/10.3390/biomedicines5020034

Ramadan, W. S., Alkarim, S., Moulay, M., Alrefeai, G., Alkudsy, F., Hakeem, K. R., & Iskander, A. (2023). Modulation of the tumor microenvironment by ellagic acid in rat model for hepatocellular carcinoma: A potential target against hepatic cancer stem cells. *Cancers (Basel)*, *15*(19), 4891. https://doi.org/10.3390/cancers15194891

Ramer, R., Fischer, S., Haustein, M., Manda, K., & Hinz, B. (2014). Cannabinoids inhibit angiogenic capacities of endothelial cells via release of tissue inhibitor of matrix metalloproteinases-1 from lung cancer cells. *Biochemical Pharmacology*, *91*(2), 202–216. https://doi.org/10.1016/j.bcp.2014.06.017

Rashidi, M., Mahmoudian, E., Mirzaei, S., Mazloomi, S. N., Bazi, A., Azadeh, H., & Mozaffari, M. (2022). Harmaline downregulates angiogenesis markers and suppresses the growth of 4T1 breast cancer cells in vivo and in vitro. *Chemico-Biological Interactions*, *365*, 110087. https://doi.org/10.1016/j.cbi.2022.110087

Ren, F., Wu, K., Yang, Y., Yang, Y., Wang, Y., & Li, J. (2020). Dandelion polysaccharide exerts anti-angiogenesis effect on hepatocellular carcinoma by regulating VEGF/HIF-1alpha expression. *Frontiers in Pharmacology*, *11*, 460. https://doi.org/10.3389/fphar.2020.00460

Reuben, S. C., Gopalan, A., Petit, D. M., & Bishayee, A. (2012). Modulation of angiogenesis by dietary phytoconstituents in the prevention and intervention of breast cancer. *Molecular Nutrition & Food Research*, *56*(1), 14–29. https://doi.org/10.1002/mnfr.201100619

Ribatti, D., Annese, T., Ruggieri, S., Tamma, R., & Crivellato, E. (2019). Limitations of anti-angiogenic treatment of tumors. *Translational Oncology*, *12*(7), 981–986. https://doi.org/10.1016/j.tranon.2019.04.022

Ricci, J., Kim, M., Chung, W. Y., Park, K. K., & Jung, M. (2011). Discovery of artemisinin-glycolipid hybrids as anti-oral cancer agents. *Chemical & Pharmaceutical Bulletin*, *59*(12), 1471–1475. https://doi.org/10.1248/cpb.59.1471

Roberts, W. G., & Palade, G. E. (1997). Neovasculature induced by vascular endothelial growth factor is fenestrated. *Cancer Research*, *57*(4), 765–772. https://www.ncbi.nlm.nih.gov/pubmed/9044858

Rodrigo, K. A., Rawal, Y., Renner, R. J., Schwartz, S. J., Tian, Q., Larsen, P. E., & Mallery, S. R. (2006). Suppression of the tumorigenic phenotype in human oral squamous cell carcinoma cells by an ethanol extract derived from freeze-dried black raspberries. *Nutrition and Cancer*, *54*(1), 58–68. https://doi.org/10.1207/s15327914nc5401_7

Rose, D. P., & Connolly, J. M. (1999). Antiangiogenicity of docosahexaenoic acid and its role in the suppression of breast cancer cell growth in nude mice. *International Journal of Oncology*, *15*(5), 1011–1015. https://doi.org/10.3892/ijo.15.5.1011

Saadaoui, I., Rasheed, R., Abdulrahman, N., Bounnit, T., Cherif, M., Al Jabri, H., & Mraiche, F. (2020). Algae-derived bioactive compounds with anti-lung cancer potential. *Marine Drugs*, *18*(4), 197. https://doi.org/10.3390/md18040197

Saini, M. K., & Sanyal, S. N. (2014). Targeting angiogenic pathway for chemoprevention of experimental colon cancer using C-phycocyanin as cyclooxygenase-2 inhibitor. *Biochemistry and Cell Biology*, *92*(3), 206–218. https://doi.org/10.1139/bcb-2014-0016

Sajadimajd, S., Momtaz, S., Haratipour, P., El-Senduny, F. F., Panah, A. I., Navabi, J., Soheilikhah, Z., Farzaei, M. H., & Rahimi, R. (2019). Molecular mechanisms underlying cancer preventive and therapeutic potential of algal polysaccharides. *Current Pharmaceutical Design*, *25*(11), 1210–1235. https://doi.org/10.2174/1381612825666190425155126

Salles, E. L., Naeini, S. E., Khodadadi, H., Bhandari, B., Rezaee, S., Threlkeld, E., Rogers, H. M., Costigliola, V., Terry, A. V. Jr., Hess, D. C., Deb, S., Deb, S. P., Yeudall, W. A., Yu, J. C., Wang, L. P., & Baban, B. (2023). Inhalant cannabidiol impedes tumor growth through decreased tumor stemness and impaired angiogenic switch in NCI-H1437-induced human lung cancer model. *Human Cell*, *36*(3), 1204–1210. https://doi.org/10.1007/s13577-023-00869-8

Sannappa Gowda, N. G., Shiragannavar, V. D., Puttahanumantharayappa, L. D., Shivakumar, A. T., Dallavalasa, S., Basavaraju, C. G., Bhat, S. S., Prasad, S. K., Vamadevaiah, R. M., Madhunapantula, S. V., & Santhekadur, P. K. (2023). Quercetin activates vitamin D receptor and ameliorates breast cancer induced hepatic inflammation and fibrosis. *Frontiers in Nutrition*, *10*, 1158633. https://doi.org/10.3389/fnut.2023.1158633

Sansone, C., Pistelli, L., Calabrone, L., Del Mondo, A., Fontana, A., Festa, M., Noonan, D. M., Albini, A., & Brunet, C. (2023). The carotenoid diatoxanthin modulates inflammatory and angiogenesis pathways in vitro in prostate cancer cells. *Antioxidants (Basel)*, *12*(2), 359. https://doi.org/10.3390/antiox12020359

Santi, A., Kugeratski, F. G., & Zanivan, S. (2018). Cancer associated fibroblasts: The architects of stroma remodeling. *Proteomics*, *18*(5–6), e1700167. https://doi.org/10.1002/pmic.201700167

Saragusti, A. C., Ortega, M. G., Cabrera, J. L., Estrin, D. A., Marti, M. A., & Chiabrando, G. A. (2010). Inhibitory effect of quercetin on matrix metalloproteinase 9 activity molecular mechanism and structure–activity relationship of the flavonoid–enzyme interaction. *European Journal of Pharmacology*, *644*(1–3), 138–145. https://doi.org/10.1016/j.ejphar.2010.07.001

Sarıbaş, G. S., Turna Saltoğlu, G., Yalçın Azarkan, S., Akarca Dizakar, Ö., & Yalçınkaya, S. (2023). Effects of irinotecan (CPT-11), ellagic acid and combination of both on HeLa cells in 2D and 3D culture. *Cyprus Journal of Medical Sciences*, *8*(3), 173–183. https://doi.org/10.4274/cjms.2023.2022-49

Schaly, S., Islam, P., Abosalha, A., Boyajian, J. L., Shum-Tim, D., & Prakash, S. (2022). Alginate-chitosan hydrogel formulations sustain baculovirus delivery and VEGFA expression which promotes angiogenesis for wound dressing applications. *Pharmaceuticals (Basel)*, *15*(11), 1382. https://doi.org/10.3390/ph15111382

Sengupta, S., Eavarone, D., Capila, I., Zhao, G., Watson, N., Kiziltepe, T., & Sasisekharan, R. (2005). Temporal targeting of tumour cells and neovasculature with a nanoscale delivery system. *Nature*, *436*(7050), 568–572. https://doi.org/10.1038/nature03794

Sflakidou, E., Leonidis, G., Foroglou, E., Siokatas, C., & Sarli, V. (2022). Recent advances in natural product-based hybrids as anti-cancer agents. *Molecules (Basel, Switzerland)*, *27*(19), 6632. https://doi.org/10.3390/molecules27196632

Shaheen, S., Khalid, S., Aaliya, K., Gul, A., Hafeez, A., Armaghan, M., Almarhoon, Z. M., Calina, D., Khan, K., & Sharifi-Rad, J. (2024). Insights into Nimbolide molecular crosstalk and its anticancer properties. *Medical Oncology*, *41*(6), 158. https://doi.org/10.1007/s12032-024-02379-5

Shakiba, E., Bazi, A., Ghasemi, H., Eshaghi-Gorji, R., Mehdipour, S. A., Nikfar, B., Rashidi, M., & Mirzaei, S. (2023). Hesperidin suppressed metastasis, angiogenesis and tumour growth in Balb/c mice model of breast cancer. *Journal of Cellular and Molecular Medicine*, *27*(18), 2756–2769. https://doi.org/10.1111/jcmm.17902

Shanmugam, M. K., Warrier, S., Kumar, A. P., Sethi, G., & Arfuso, F. (2017). Potential role of natural compounds as anti-angiogenic agents in cancer. *Current Vascular Pharmacology*, *15*(6), 503–519. https://doi.org/10.2174/1570161115666170713094319

Sharma, A., Ghani, A., Sak, K., Tuli, H. S., Sharma, A. K., Setzer, W. N., Sharma, S., & Das, A. K. (2019). Probing into therapeutic anti-cancer potential of apigenin: Recent trends and future directions. *Recent Patents on Inflammation & Allergy Drug Discovery*, *13*(2), 124–133. https://doi.org/10.2174/1872213x13666190816160240

Sheikh, I., Sharma, V., Tuli, H., Aggarwal, D., Sankhyan, A., Vyas, P., Sharma, A., & Bishayee, A. (2020). Cancer chemoprevention by flavonoids, dietary polyphenols and terpenoids. *Biointerface Research in Applied Chemistry*, *11*(1), 8502–8537. https://doi.org/10.33263/briac111.85028537

Shen, W., Liang, B., Yin, J., Li, X., & Cheng, J. (2015). Noscapine increases the sensitivity of drug-resistant ovarian cancer cell line SKOV3/DDP to cisplatin by regulating cell cycle and activating apoptotic pathways. *Cell Biochemistry and Biophysics*, *72*(1), 203–213. https://doi.org/10.1007/s12013-014-0438-y

Sheng, X., Jin, J., He, Z., Huang, Y., Zhou, A., Wang, J., Ren, X., Ye, D., Zhang, X., Qin, S., Zhou, F., Wang, B., & Guo, J. (2020). Pazopanib versus sunitinib in Chinese patients with locally advanced or metastatic renal cell carcinoma: Pooled subgroup analysis from the randomized, COMPARZ studies. *BMC Cancer*, *20*(1), 219. https://doi.org/10.1186/s12885-020-6708-8

Sherapura, A., Siddesh, B. M., Malojirao, V. H., Thirusangu, P., Avin, B. R. V., Kumari, N. S., Ramachandra, Y. L., & Prabhakar, B. T. (2023). Steroidal

alkaloid solanidine impedes hypoxia-driven ATM phosphorylation to switch on anti-angiogenesis in lung adenocarcinoma. *Phytomedicine*, *119*, 154981. https://doi.org/10.1016/j.phymed.2023.154981

Shetti, D., Zhang, B., Fan, C., Mo, C., Lee, B. H., & Wei, K. (2019). Low dose of paclitaxel combined with XAV939 attenuates metastasis, angiogenesis and growth in breast cancer by suppressing Wnt signaling. *Cells*, *8*(8), 892. https://doi.org/10.3390/cells8080892

Shi, H., Li, X. Y., Chen, Y., Zhang, X., Wu, Y., Wang, Z. X., Chen, P. H., Dai, H. Q., Feng, J., Chatterjee, S., Li, Z. J., Huang, X. W., Wei, H. Q., Wang, J., Lu, G. D., & Zhou, J. (2020). Quercetin induces apoptosis via down-regulation of vascular endothelial growth factor/Akt signaling pathway in acute myeloid leukemia cells. *Frontiers in Pharmacology*, *11*, 534171. https://doi.org/10.3389/fphar.2020.534171

Shi, Z., Zhu, J.-X., Guo, Y.-M., Niu, M., Zhang, L., Tu, C., Huang, Y., Li, P.-Y., Zhao, X., Zhang, Z.-T., Bai, Z.-F., Zhang, G.-Q., Lu, Y., Xiao, X.-H., & Wang, J.-B. (2020). Epigallocatechin gallate during dietary restriction—Potential mechanisms of enhanced liver injury. *Frontiers in Pharmacology*, *11*, 609378.

Silva-Reis, R., Silva, A. M. S., Oliveira, P. A., & Cardoso, S. M. (2023). Antitumor effects of *Cannabis sativa* bioactive compounds on colorectal carcinogenesis. *Biomolecules*, *13*(5), 764. https://doi.org/10.3390/biom13050764

Singh, C. K., Kaur, S., George, J., Nihal, M., Pellitteri Hahn, M. C., Scarlett, C. O., & Ahmad, N. (2015). Molecular signatures of sanguinarine in human pancreatic cancer cells: A large scale label-free comparative proteomics approach. *Oncotarget*, *6*(12), 10335–10348. https://doi.org/10.18632/oncotarget.3231

Sohn, S. I., Priya, A., Balasubramaniam, B., Muthuramalingam, P., Sivasankar, C., Selvaraj, A., Valliammai, A., Jothi, R., & Pandian, S. (2021). Biomedical applications and bioavailability of curcumin—An updated overview. *Pharmaceutics*, *13*(12), 2102. https://doi.org/10.3390/pharmaceutics13122102

Song, H., Jung, J. I., Cho, H. J., Her, S., Kwon, S. H., Yu, R., Kang, Y. H., Lee, K. W., & Park, J. H. (2015). Inhibition of tumor progression by oral piceatannol in mouse 4T1 mammary cancer is associated with decreased angiogenesis and macrophage infiltration. *Journal of Nutritional Biochemistry*, *26*(11), 1368–1378. https://doi.org/10.1016/j.jnutbio.2015.07.005

Soumya, S. J., Athira, A. P., Binu, S., & Sudhakaran, P. R. (2016). mTOR as a modulator of metabolite sensing relevant to angiogenesis. In K. Maiese, *Molecules to medicine with mTOR* (pp. 229–243), ISBN 9780128027332. https://doi.org/10.1016/b978-0-12-802733-2.00014-1

Stielow, M., Witczyńska, A., Kubryń, N., Fijałkowski, Ł., Nowaczyk, J., & Nowaczyk, A. (2023). The bioavailability of drugs—The current state of knowledge. *Molecules (Basel, Switzerland)*, *28*(24), 8038. https://doi.org/10.3390/molecules28248038

Su, X., Zhou, D., & Li, N. (2022). Bioactive stilbenes from plants. *Studies in Natural Products Chemistry*, *73*, 265–403. https://doi.org/10.1016/b978-0-323-91097-2.00006-6

Subbaraj, G. K., Elangovan, H., Chandramouli, P., Yasam, S. K., Chandrasekaran, K., Kulanthaivel, L., Pandi, S., & Subramanian, S. (2023). Antiangiogenic potential of troxerutin and chitosan loaded troxerutin on chorioallantoic membrane model. *BioMed Research International*, *2023*, 5956154. https://doi.org/10.1155/2023/5956154

Sudha, T., El-Far, A. H., Mousa, D. S., & Mousa, S. A. (2020). Resveratrol and its nanoformulation attenuate growth and the angiogenesis of xenograft and orthotopic colon cancer models. *Molecules (Basel, Switzerland)*, *25*(6), 1412. https://doi.org/10.3390/molecules25061412

Sung, Y. C., Jin, P. R., Chu, L. A., Hsu, F. F., Wang, M. R., Chang, C. C., Chiou, S. J., Qiu, J. T., Gao, D. Y., Lin, C. C., Chen, Y. S., Hsu, Y. C., Wang, J., Wang, F. N., Yu, P. L., Chiang, A. S., Wu, A. Y., Ko, J. J., Lai, C. P., & Chen, Y. (2019). Delivery of nitric oxide with a nanocarrier promotes tumour vessel normalization and potentiates anti-cancer therapies. *Nature Nanotechnology*, *14*(12), 1160–1169. https://doi.org/10.1038/s41565-019-0570-3

Surh, Y. (1999). Molecular mechanisms of chemopreventive effects of selected dietary and medicinal phenolic substances. *Mutation Research*, *428*(1–2), 305–327. https://doi.org/10.1016/s1383-5742(99)00057-5

Sweeney, C. J., Miller, K. D., Sissons, S. E., Nozaki, S., Heilman, D. K., Shen, J., & Sledge, G. W. (2001). The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. *Cancer Research*, *61*(8), 3369–3372. https://www.ncbi.nlm.nih.gov/pubmed/11309294

Tadros, S. A., Attia, Y. M., Maurice, N. W., Fahim, S. A., Abdelwahed, F. M., Ibrahim, S., & Badary, O. A. (2022). Thymoquinone suppresses angiogenesis in DEN-induced hepatocellular carcinoma by targeting miR-1-3p. *International Journal of Molecular Sciences*, *23*(24), 15904. https://doi.org/10.3390/ijms232415904

Tahergorabi, R., & Hosseini, S. V. (2017). Proteins, peptides, and amino acids. In C. M. Galanakis, *Nutraceutical and functional food components* (pp. 15–38). ISBN 9780128052570. https://doi.org/10.1016/b978-0-12-805257-0.00002-8

Tammela, T., Zarkada, G., Nurmi, H., Jakobsson, L., Heinolainen, K., Tvorogov, D., Zheng, W., Franco, C. A., Murtomaki, A., Aranda, E., Miura, N., Yla-Herttuala, S., Fruttiger, M., Makinen, T., Eichmann, A., Pollard, J. W., Gerhardt, H., & Alitalo, K. (2011). VEGFR-3 controls tip to stalk conversion at vessel fusion sites by reinforcing Notch signalling. *Nature Cell Biology*, *13*(10), 1202–1213. https://doi.org/10.1038/ncb2331

Tan, J., Han, Y., Han, B., Qi, X., Cai, X., Ge, S., & Xue, H. (2022). Extraction and purification of anthocyanins: A review. *Journal of Agriculture and Food Research*, *8*, 100306, ISSN 2666-1543. https://doi.org/10.1016/j.jafr.2022.100306

Tan, W. F., Lin, L. P., Li, M. H., Zhang, Y. X., Tong, Y. G., Xiao, D., & Ding, J. (2003). Quercetin, a dietary-derived flavonoid, possesses antiangiogenic potential. *European Journal of Pharmacology*, *459*(2–3), 255–262. https://doi.org/10.1016/s0014-2999(02)02848-0

Taraboletti, G., Poli, M., Dossi, R., Manenti, L., Borsotti, P., Faircloth, G. T., Broggini, M., D'Incalci, M., Ribatti, D., & Giavazzi, R. (2004). Antiangiogenic activity of aplidine, a new agent of marine origin. *British Journal of Cancer*, *90*(12), 2418–2424. https://doi.org/10.1038/sj.bjc.6601864

Tevar, R., Jho, D. H., Babcock, T., Helton, W. S., & Espat, N. J. (2002). Omega-3 fatty acid supplementation reduces tumor growth and vascular endothelial growth factor expression in a model of progressive non-metastasizing malignancy. *Journal of Parenteral and Enteral Nutrition*, *26*(5), 285–289. https://doi.org/10.1177/0148607102026005285

Tian, L., Goldstein, A., Wang, H., Ching Lo, H., Sun Kim, I., Welte, T., Sheng, K., Dobrolecki, L. E., Zhang, X., Putluri, N., Phung, T. L., Mani, S. A., Stossi, F., Sreekumar, A., Mancini, M. A., Decker, W. K., Zong, C., Lewis, M. T., & Zhang, X. H. (2017). Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. *Nature*, *544*(7649), 250–254. https://doi.org/10.1038/nature21724

Tran, T. T., Vu, L. B., Nguyen, H. Q., Pham, H. B., Do, X. T., Than, U. T. T., Pham, T. T., Do, L. D., Le, K. T., Nguyen, T. P., & Hoang, M. T. (2022). Dual roles of oxostephanine as an Aurora kinase inhibitor and angiogenesis suppressor. *International Journal of Molecular Medicine*, *50*(5), 133. https://doi.org/10.3892/ijmm.2022.5189

Trapp, V., Parmakhtiar, B., Papazian, V., Willmott, L., & Fruehauf, J. P. (2010). Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture. *Angiogenesis*, *13*(4), 305–315. https://doi.org/10.1007/s10456-010-9187-8

Tsakiroglou, P., VandenAkker, N. E., Del Bo, C., Riso, P., & Klimis-Zacas, D. (2019). Role of berry anthocyanins and phenolic acids on cell migration and angiogenesis: An updated overview. *Nutrients*, *11*(5), 1075. https://doi.org/10.3390/nu11051075

Tseng, S. H., Lin, S. M., Chen, J. C., Su, Y. H., Huang, H. Y., Chen, C. K., Lin, P. Y., & Chen, Y. (2004). Resveratrol suppresses the angiogenesis and tumor growth of gliomas in rats. *Clinical Cancer Research*, *10*(6), 2190–2202. https://doi.org/10.1158/1078-0432.ccr-03-0105

Tsui, K. H., Wu, M. Y., Lin, L. T., Wen, Z. H., Li, Y. H., Chu, P. Y., & Li, C. J. (2019). Disruption of mitochondrial homeostasis with artemisinin unravels anti-angiogenesis effects via auto-paracrine mechanisms. *Theranostics*, *9*(22), 6631–6645. https://doi.org/10.7150/thno.33353

Urzì, A. G., Tropea, E., Gattuso, G., Spoto, G., Marsala, G., Calina, D., Libra, M., & Falzone, L. (2023). Ketogenic diet and breast cancer: Recent findings and therapeutic approaches. *Nutrients*, *15*(20), 4357. https://doi.org/10.3390/nu15204357

Ushio-Fukai, M., & Nakamura, Y. (2008). Reactive oxygen species and angiogenesis: NADPH oxidase as target for cancer therapy. *Cancer Letters*, *266*(1), 37–52. https://doi.org/10.1016/j.canlet.2008.02.044

Uttarawichien, T., Kamnerdnond, C., Inwisai, T., Suwannalert, P., Sibmooh, N., & Payuhakrit, W. (2021a). Quercetin inhibits colorectal cancer cells induced-angiogenesis in both colorectal cancer cell and endothelial cell through downregulation of VEGF-A/VEGFR2. *Scientia Pharmaceutica*, *89*(2). https://doi.org/10.3390/scipharm89020023

Uttarawichien, T., Kamnerdnond, C., Inwisai, T., Suwannalert, P., Sibmooh, N., & Payuhakrit, W. (2021b). Quercetin inhibits colorectal cancer cells induced-angiogenesis in both colorectal cancer cell and endothelial cell through downregulation of VEGF-A/VEGFR2. *Scientia Pharmaceutica*, *89*(2), 23. https://www.mdpi.com/2218-0532/89/2/23

Uvez, A., Aydinlik, S., Esener, O. B. B., Erkisa, M., Karakus, D., & Armutak, E. I. (2020). Synergistic interactions between resveratrol and doxorubicin inhibit angiogenesis both in vitro and in vivo. *Polish Journal of Veterinary Sciences*, *23*(4), 571–580. https://doi.org/10.24425/pjvs.2020.135803

Vanella, L., Di Giacomo, C., Acquaviva, R., Barbagallo, I., Li Volti, G., Cardile, V., Abraham, N. G., & Sorrenti, V. (2013). Effects of ellagic acid on angiogenic factors in prostate cancer cells. *Cancers (Basel)*, *5*(2), 726–738. https://doi.org/10.3390/cancers5020726

Varghese, S., Joseph, M. M., Aravind, S. R., Unnikrishnan, B. S., Pillai, K. R., & Sreelekha, T. T. (2019). Immunostimulatory plant polysaccharides impede cancer progression and metastasis by avoiding off-target effects. *International Immunopharmacology*, *73*, 280–292. https://doi.org/10.1016/j.intimp.2019.05.025

Varinska, L., Gal, P., Mojzisova, G., Mirossay, L., & Mojzis, J. (2015). Soy and breast cancer: Focus on angiogenesis. *International Journal of Molecular Sciences*, *16*(5), 11728–11749. https://doi.org/10.3390/ijms160511728

Vergote, I., Scambia, G., O'Malley, D. M., Van Calster, B., Park, S. Y., Del Campo, J. M., Meier, W., Bamias, A., Colombo, N., Wenham, R. M., Covens, A., Marth, C., Raza Mirza, M., Kroep, J. R., Ma, H., Pickett, C. A., Monk, B. J., & TRINOVA-3/ENGOT-ov2/GOG-3001 investigators. (2019). Trebananib or placebo plus carboplatin and paclitaxel as first-line treatment for advanced ovarian cancer (TRINOVA-3/ENGOT-ov2/GOG-3001): A randomised, double-blind, phase 3 trial. *Lancet Oncology*, *20*(6), 862–876. https://doi.org/10.1016/S1470-2045(19)30178-0

Vijayababu, M. R., Arunkumar, A., Kanagaraj, P., Venkataraman, P., Krishnamoorthy, G., & Arunakaran, J. (2006). Quercetin downregulates matrix metalloproteinases 2 and 9 proteins expression in prostate cancer cells (PC-3). *Molecular and Cellular Biochemistry*, *287*(1–2), 109–116. https://doi.org/10.1007/s11010-005-9085-3

Wang, B., Li, D., Cherkasova, V., Gerasymchuk, M., Narendran, A., Kovalchuk, I., & Kovalchuk, O. (2022). Cannabinol inhibits cellular proliferation, invasion, and angiogenesis of neuroblastoma via novel miR-34a/tRiMetF31/PFKFB3 axis. *Cancers (Basel)*, *14*(8). https://doi.org/10.3390/cancers14081908

Wang, F., Cao, Y., Liu, H. Y., Xu, S. F., & Han, R. (2003). Anti-invasion and anti-angiogenesis effect of taxol and camptothecin on melanoma cells. *Journal of Asian Natural Products Research*, *5*(2), 121–129. https://doi.org/10.1080/1028602021000054973

Wang, H., Liu, B., Zhang, C., Peng, G., Liu, M., Li, D., Gu, F., Chen, Q., Dong, J. T., Fu, L., & Zhou, J. (2009). Parkin regulates paclitaxel sensitivity in breast cancer via a microtubule-dependent mechanism. *Journal of Pathology*, *218*(1), 76–85. https://doi.org/10.1002/path.2512

Wang, J., Ma, Y., Yang, J., Jin, L., Gao, Z., Xue, L., Hou, L., Sui, L., Liu, J., & Zou, X. (2019). Fucoxanthin inhibits tumour-related lymphangiogenesis and growth of breast cancer. *Journal of Cellular and Molecular Medicine*, *23*(3), 2219–2229. https://doi.org/10.1111/jcmm.14151

Wang, X., Li, Y., Liu, W., Shen, Y., Lin, Z., Nakajima, A., Xu, J., & Guo, Y. (2023). A polysaccharide from *Inula japonica* showing in vivo antitumor activity by interacting with TLR-4, PD-1, and VEGF. *International Journal of Biological Macromolecules*, *246*, 125555. https://doi.org/10.1016/j.ijbiomac.2023.125555

Wang, Y., Wang, Y., Liu, Y., Liu, Q., Jang, J., & Han, J. (2018). Preparation, characterization, and antioxidant activities of cellulose nanocrystals/genistein nanocomposites. *BioResources*, *14*(1), 336–348. https://doi.org/10.15376/biores.14.1.336-348

Wang, Z., Chen, Y., Yang, L., Yao, D., & Shen, Y. (2023). Combinative effects of beta-elemene and propranolol on the proliferation, migration, and angiogenesis of hemangioma. *PeerJ*, *11*, e15643. https://doi.org/10.7717/peerj.15643

Wang, Z., Wang, Z., Du, C., Zhang, Y., Tao, B., & Xian, H. (2021). beta-elemene affects angiogenesis of infantile hemangioma by regulating angiotensin-converting enzyme 2 and hypoxia-inducible factor-1 alpha. *Journal of Natural Medicines*, *75*(3), 655–663. https://doi.org/10.1007/s11418-021-01516-y

Wautier, J. L., & Wautier, M. P. (2022). Vascular permeability in diseases. *International Journal of Molecular Sciences*, *23*(7). https://doi.org/10.3390/ijms23073645

Welti, J., Loges, S., Dimmeler, S., & Carmeliet, P. (2013). Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer. *Journal of Clinical Investigation*, *123*(8), 3190–3200. https://doi.org/10.1172/JCI70212

Wendong, Y., Jiali, J., Qiaomei, F., Yayun, W., Xianze, X., Zheng, S., & Wei, H. (2024). Biomechanical forces and force-triggered drug delivery in tumor neovascularization. *Biomedicine & Pharmacotherapy*, *171*, 116117. https://doi.org/10.1016/j.biopha.2023.116117

Williams, R. J., Spencer, J. P., & Rice-Evans, C. (2004). Flavonoids: Antioxidants or signalling molecules? *Free Radical Biology and Medicine*, *36*(7), 838–849. https://doi.org/10.1016/j.freeradbiomed.2004.01.001

Wroblewska-Luczka, P., Cabaj, J., Bargiel, J., & Luszczki, J. J. (2023). Anticancer effect of terpenes: Focus on malignant melanoma. *Pharmacological Reports*, *75*(5), 1115–1125. https://doi.org/10.1007/s43440-023-00512-1

Xia, C., Meng, Q., Liu, L. Z., Rojanasakul, Y., Wang, X. R., & Jiang, B. H. (2007). Reactive oxygen species regulate angiogenesis and tumor growth through vascular endothelial growth factor. *Cancer Research*, *67*(22), 10823–10830. https://doi.org/10.1158/0008-5472.CAN-07-0783

Xia, N., Daiber, A., Förstermann, U., & Li, H. (2017). Antioxidant effects of resveratrol in the cardiovascular system. *British Journal of Pharmacology*, *174*(12), 1633–1646. https://doi.org/10.1111/bph.13492

Xiaomeng, W., Ji, J., Xu, M., Rui, X., Zhang, Q., Dong, M., & Li, W. (2023). Structural analysis and effects of exopolysaccharide (LHEPS-3) from *Lactobacillus helveticus* MB2-1 on human hepatoma HepG-2 cells: Inhibition of proliferation, migration and angiogenesis. *Russian Journal of Bioorganic Chemistry*, *49*(3), 616–628. https://doi.org/10.1134/s1068162023030251

Xie, G.-H., Xie, W., Piao, H., & Li, D. (2019). Defensive mechanism in human cholangiocarcinoma cells against hypoxia by cyanidin-3-glucoside treatment. *International Journal of Pharmacology*, *15*(3), 361–369. https://doi.org/10.3923/ijp.2019.361.369

Xu, J. Y., Meng, Q. H., Chong, Y., Jiao, Y., Zhao, L., Rosen, E. M., & Fan, S. (2013). Sanguinarine is a novel VEGF inhibitor involved in the suppression of angiogenesis and cell migration. *Molecular and Clinical Oncology*, *1*(2), 331–336. https://doi.org/10.3892/mco.2012.41

Xue, B., Guo, H., & Tao, Y. (2022). Sophoridine inhibits breast cancer cell migration and angiogenesis by regulating vascular endothelial growth factor receptor 2/extracellular signal-regulated kinase 2 pathways. *Current Topics in Nutraceutical Research*, *20*(3), 588–593. https://doi.org/10.37290/ctnr2641-452X.20:588-593

Xue, M., Ge, Y., Zhang, J., Liu, Y., Wang, Q., Hou, L., & Zheng, Z. (2013). Fucoidan inhibited 4T1 mouse breast cancer cell growth in vivo and in vitro via downregulation of Wnt/beta-catenin signaling. *Nutrition and Cancer*, *65*(3), 460–468. https://doi.org/10.1080/01635581.2013.757628

Xue, Y. T., Li, S., Jiang, X. Y., Xin, M., Li, H. H., Yu, G. L., He, X. X., & Li, C. X. (2023). The reason and mechanism of propylene glycol alginate sodium sulfate (PSS) mediated allergic side effect. *International Journal of Biological Macromolecules*, *241*, 124638. https://doi.org/10.1016/j.ijbiomac.2023.124638

Yan, Y., Li, X., Zhang, C., Lv, L., Gao, B., & Li, M. (2021). Research progress on antibacterial activities and mechanisms of natural alkaloids: A review. *Antibiotics (Basel)*, *10*(3). https://doi.org/10.3390/antibiotics10030318

Yan, Y., Yao, L., Sun, H., Pang, S., Kong, X., Zhao, S., & Xu, S. (2020). Effects of wogonoside on invasion and migration of lung cancer A549 cells and angiogenesis in xenograft tumors of nude mice. *Journal of Thoracic Disease*, *12*(4), 1552–1560. https://doi.org/10.21037/jtd-20-1555

Yang, G. W., Jiang, J. S., & Lu, W. Q. (2015). Ferulic acid exerts anti-angiogenic and anti-tumor activity by targeting fibroblast growth factor receptor 1-mediated angiogenesis. *International Journal of Molecular Sciences*, *16*(10), 24011–24031. https://doi.org/10.3390/ijms161024011

Yang, J., Ren, B., Yang, G., Wang, H., Chen, G., You, L., Zhang, T., & Zhao, Y. (2020). The enhancement of glycolysis regulates pancreatic cancer metastasis. *Cellular and Molecular Life Sciences*, *77*(2), 305–321. https://doi.org/10.1007/s00018-019-03278-z

Yang, L., Zhang, Y., Yang, H., Yu, L., & Rohani, S. (2022). Evaluation of cytotoxicity and anti-angiogenesis induced by crocetin-delivering alginate hydrogel/chitosan nanoparticle carrier system on human ovarian cancer cell line (A2780): An in vitro evaluation. *Journal of Biomedical Nanotechnology*, *18*(7), 1746–1754. https://doi.org/10.1166/jbn.2022.3384

Yao, Y., Zhou, L., Liao, W., Chen, H., Du, Z., Shao, C., Wang, P., & Ding, K. (2019). HH1-1, a novel Galectin-3 inhibitor, exerts anti-pancreatic cancer activity by blocking Galectin-3/EGFR/AKT/FOXO3 signaling pathway. *Carbohydrate Polymers*, *204*, 111–123. https://doi.org/10.1016/j.carbpol.2018.10.008

Yau, T., Park, J. W., Finn, R. S., Cheng, A. L., Mathurin, P., Edeline, J., Kudo, M., Harding, J. J., Merle, P., Rosmorduc, O., Wyrwicz, L., Schott, E., Choo, S. P., Kelley, R. K., Sieghart, W., Assenat, E., Zaucha, R., Furuse, J., Abou-Alfa, G. K., & Sangro, B. (2022). Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): A randomised, multicentre, open-label, phase 3 trial. *Lancet Oncology*, *23*(1), 77–90. https://doi.org/10.1016/S1470-2045(21)00604-5

Yeh, C. L., Pai, M. H., Li, C. C., Tsai, Y. L., & Yeh, S. L. (2010). Effect of arginine on angiogenesis induced by human colon cancer: In vitro and in vivo studies. *Journal of Nutritional Biochemistry*, *21*(6), 538–543. https://doi.org/10.1016/j.jnutbio.2009.03.005

Ying, Y., & Hao, W. (2023). Immunomodulatory function and anti-tumor mechanism of natural polysaccharides: A review. *Frontiers in Immunology*, *14*, 1147641. https://doi.org/10.3389/fimmu.2023.1147641

Yoo, Y. C., Watanabe, S., Watanabe, R., Hata, K., Shimazaki, K., & Azuma, I. (1997). Bovine lactoferrin and lactoferricin, a peptide derived from bovine lactoferrin, inhibit tumor metastasis in mice. *Japanese Journal of Cancer Research*, *88*(2), 184–190. https://doi.org/10.1111/j.1349-7006.1997.tb00364.x

Yu, X. H., Wu, J. B., Fan, H. Y., Dai, L., Xian, H. C., Chen, B. J., Liao, P., Huang, M. C., Pang, X., Zhang, M., Liang, X. H., & Tang, Y. L. (2022). Artemisinin suppressed tumour growth and induced vascular normalisation in oral squamous cell carcinoma via inhibition of macrophage migration inhibitory factor. *Oral Diseases*, *30*(2), 363–375. https://doi.org/10.1111/odi.14418

Yu, Y., Huang, X., Liang, C., & Zhang, P. (2023). Evodiamine impairs HIF1A histone lactylation to inhibit Sema3A-mediated angiogenesis and PD-L1 by inducing ferroptosis in prostate cancer. *European Journal of Pharmacology*, *957*, 176007. https://doi.org/10.1016/j.ejphar.2023.176007

Yuan, L., & Hu, Y. (2023). *Sambucus adnata* polysaccharide SPS-1 inhibits growth of transplanted lung cancer via polarizing tumor associated macrophage from M2 into M1. *Natural Product Communications*, *18*(7). https://doi.org/10.1177/1934578x231182253

Yue, P. Y., Wong, D. Y., Wu, P. K., Leung, P. Y., Mak, N. K., Yeung, H. W., Liu, L., Cai, Z., Jiang, Z. H., Fan, T. P., & Wong, R. N. (2006). The angiosuppressive effects of 20(R)-ginsenoside Rg3. *Biochemical Pharmacology*, *72*(4), 437–445. https://doi.org/10.1016/j.bcp.2006.04.034

Zang, M., Hou, J., Huang, Y., Wang, J., Ding, X., Zhang, B., Wang, Y., Xuan, Y., & Zhou, Y. (2021). Crocetin suppresses angiogenesis and metastasis through inhibiting sonic hedgehog signaling pathway in gastric cancer. *Biochemical and Biophysical Research Communications*, *576*, 86–92. https://doi.org/10.1016/j.bbrc.2021.08.092

Zeng, D., Zhou, P., Jiang, R., Li, X. P., Huang, S. Y., Li, D. Y., Li, G. L., Li, L. S., Zhao, S., Hu, L., Ran, J. H., Chen, D. L., Wang, Y. P., & Li, J. (2021). Evodiamine inhibits vasculogenic mimicry in HCT116 cells by suppressing hypoxia-inducible factor 1-alpha-mediated angiogenesis. *Anti-Cancer Drugs*, *32*(3), 314–322. https://doi.org/10.1097/CAD.0000000000001030

Zeng, W., Lao, S., Guo, Y., Wu, Y., Huang, M., Tomlinson, B., & Zhong, G. (2022). The influence of EGCG on the pharmacokinetics and pharmacodynamics of bisoprolol and a new method for simultaneous determination of EGCG and bisoprolol in rat plasma. *Frontiers in Nutrition*, *9*, 907986. https://doi.org/10.3389/fnut.2022.907986

Zhang, J., Li, Y., Li, Y., Li, Y., Gong, X., Zhou, L., Xu, J., & Guo, Y. (2022). Structure, selenization modification, and antitumor activity of a glucomannan from *Platycodon grandiflorum*. *International Journal of Biological Macromolecules*, *220*, 1345–1355, ISSN 1226-8453. https://doi.org/10.1016/j.ijbiomac.2022.09.029

Zhang, R., Li, L., Li, H., Bai, H., Suo, Y., Cui, J., & Wang, Y. (2024). Ginsenoside 20(S)-Rg3 reduces KIF20A expression and promotes CDC25A proteasomal degradation in epithelial ovarian cancer. *Journal of Ginseng Research*, *48*(1), 40–51. https://doi.org/10.1016/j.jgr.2023.06.008

Zhang, S., Zhang, H., Shi, L., Li, Y., Tuerhong, M., Abudukeremu, M., Cui, J., Li, Y., Jin, D. Q., Xu, J., & Guo, Y. (2021). Structure features, selenylation modification, and improved anti-tumor activity of a polysaccharide from *Eriobotrya japonica*. *Carbohydrate Polymers*, *273*, 118496. https://doi.org/10.1016/j.carbpol.2021.118496

Zhang, Y., & Brekken, R. A. (2022). Direct and indirect regulation of the tumor immune microenvironment by VEGF. *Journal of Leukocyte Biology*, *111*(6), 1269–1286. https://doi.org/10.1002/JLB.5RU0222-082R

Zhou, L., Sui, H., Wang, T., Jia, R., Zhang, Z., Fu, J., Feng, Y., Liu, N., Ji, Q., Wang, Y., Zhang, B., Li, Q., & Li, Y. (2020). Tanshinone IIA reduces secretion of pro-angiogenic factors and inhibits angiogenesis in human colorectal cancer. *Oncology Reports*, *43*(4), 1159–1168. https://doi.org/10.3892/or.2020.7498

Zhu, X. Y., Guo, D. W., Lao, Q. C., Xu, Y. Q., Meng, Z. K., Xia, B., Yang, H., Li, C. Q., & Li, P. (2019). Sensitization and synergistic anti-cancer effects of Furanodiene identified in zebrafish models. *Scientific Reports*, *9*(1), 4541. https://doi.org/10.1038/s41598-019-40866-2

Zhu, Z., Zhao, Y., Li, J., Tao, L., Shi, P., Wei, Z., Sheng, X., Shen, D., Liu, Z., Zhou, L., Tian, C., Fan, F., Shen, C., Zhu, P., Wang, A., Chen, W., Zhao, Q., & Lu, Y. (2016). Cryptotanshinone, a novel tumor angiogenesis inhibitor, destabilizes tumor necrosis factor-α mRNA via decreasing nuclear-cytoplasmic translocation of RNA-binding protein HuR. *Molecular Carcinogenesis*, *55*(10), 1399–1410. https://doi.org/10.1002/mc.22383

Ziegler, J., & Facchini, P. J. (2008). Alkaloid biosynthesis: Metabolism and trafficking. *Annual Review of Plant Biology*, *59*, 735–769. https://doi.org/10.1146/annurev.arplant.59.032607.092730

Ziogas, A. C., Gavalas, N. G., Tsiatas, M., Tsitsilonis, O., Politi, E., Terpos, E., Rodolakis, A., Vlahos, G., Thomakos, N., Haidopoulos, D., Antsaklis, A., Dimopoulos, M. A., & Bamias, A. (2012). VEGF directly suppresses activation of T cells from ovarian cancer patients and healthy individuals via

VEGF receptor Type 2. *International Journal of Cancer*, *130*(4), 857–864. https://doi.org/10.1002/ijc.26094

Zou, L., Liu, X., Li, J., Li, W., Zhang, L., Li, J., & Zhang, J. (2019). Tetramethylpyrazine enhances the antitumor effect of paclitaxel by inhibiting angiogenesis and inducing apoptosis. *Frontiers in Pharmacology*, *10*, 707. https://doi.org/10.3389/fphar.2019.00707

Zuo, H. X., Jin, Y., Wang, Z., Li, M. Y., Zhang, Z. H., Wang, J. Y., Xing, Y., Ri, M. H., Jin, C. H., Xu, G. H., Piao, L. X., Ma, J., & Jin, X. (2020). Curcumol inhibits the expression of programmed cell death-ligand 1 through crosstalk between hypoxia-inducible factor-1alpha and STAT3 (T705) signaling pathways in hepatic cancer. *Journal of Ethnopharmacology*, *257*, 112835. https://doi.org/10.1016/j.jep.2020.112835

Zykova, T. A., Zhu, F., Zhai, X., Ma, W. Y., Ermakova, S. P., Lee, K. W., Bode, A. M., & Dong, Z. (2008). Resveratrol directly targets COX-2 to inhibit carcinogenesis. *Molecular Carcinogenesis*, *47*(10), 797–805. https://doi.org/10.1002/mc.20437

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