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Recent Advancement on Experimentally Proven Phytopharmaceuticals that Inhibit Vasculature Development, Cancer Cell Invasion and Metastasis

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ABSTRACT

In modern medical science, targeting the tumour vasculature instead of the tumour cells is of great interest for the management of tumour associated complications. In context to that, the review was planned to explore the mechanisms of pathological angiogenesis responsible for cancer cell invasion and metastasis. The experimentally proven phytopharmaceuticals having a significant effect to inhibit vasculature development are represented schematically. The scientific literature from authenticated databases (Scopus, PubMed, etc.) search was conducted with emphasis on the previous fifteen years, combining the keywords as selected. Mechanisms of pathological angiogenesis responsible for cancer cell invasion and metastasis have been explained with possible regulatory protein involvement. A total of 97 experimentally proven plant molecules, studied in this review, including 69 plant species among 40 plant families, are summarized in a schematic way.

Hopefully, this review will facilitate the biomedical scientists in setting up the appropriate research questions around the molecular targets discussed in this review for the management of cancer cell invasion and migration and for further proof-of-concept validation studies for exploring such phytopharmaceuticals.

Introduction

The formation of new blood vessels is a vital multistep process in our body with both advantages and disadvantages, as it is responsible for the normal physiological growth on one hand while on the other it accounts for some diseases [1]. Blood vessels aid in oxygen and essential nutrients delivery to the cells and discard catabolic wastes from them [2]. The formation of new blood vessels from a pre-existing one is known as angiogenesis or neovascularization [3]. In 1971, a hypothesis by Judah Folkman first demonstrated that; "the growth of solid neoplasms is always accompanied by neovascularization" [4]. He also isolated a stimulatory factor, Tumour Angiogenesis Factor (TAF), present only in the tumour cells (exception: placenta) [4]. In the absence of angiogenesis, cancer cells cannot grow beyond 2mm3 and may become necrotic or apoptotic [5]. Angiogenesis initiation is triggered by various chemical or physiological factors, among which "Hypoxia" is the key inceptive factor (physiological) [6]. The initiation of angiogenesis, also referred to as "Angiogenic Switch" is a tumour growth and progression process influenced by the tumour type, its microenvironment, and other stimulatory factors, and can eventuate at any stage of a tumour [7]. There are some angiogenic stimulatory factors or pro-angiogenic factors or TAF or Tumour Angiogenesis Factors (VEGF, FGF, EGF, etc.) that assist angiogenesis and some antiangiogenic factors (Thrombospondin-1, statins, etc.) that have inhibitory effects, a gross amount of which leads to tumour dormancy, even for a few years [7].

However, when the normal proportion of pro-angiogenic and antiangiogenic attributes are imbalanced (basically pro-angiogenics increases largely than anti-angiogenics), angiogenesis triggers, uncontrolled vessel formation starts and the dormant tumour starts proliferating, a phenomenon is known as "Angiogenic Switch" [8]. Among the many angiogenesis affecting factors, vascular endothelial growth factor or VEGF was the first identified (1983) angiogenesis initiator and thrombospondin-1 or TSP-1 was the first identified (1990) angiogenesis inhibitor [8]. White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT) are responsible for angiogenic factor production. WAT maintains vascular growth while BAT is involved with the metabolic processes of tumour growth [9]. Synergistic action of pericytes (perivascular cells that wrap around blood capillaries) and endothelial cells involves some regulators that may be responsible for physiological and pathophysiological conditions like; vasculature development, angiogenesis, and tumour metastasis [10]. Although, the role of pericytes in angiogenic sprouting is not quite clear, pericyte-targeted therapies have become very effective these days, to inhibit uncontrolled tumour growth [10]. In this review, we have summarized and explained pathological angiogenesis, its role in cancer cell invasion and metastasis and presented schematically the important experimentally proven phytopharmaceuticals that have been found to be beneficial in inhibiting vasculature development. The review is expected to facilitate the biomedical scientists in setting up appropriate research questions around molecular targets for the management of cancer cell invasion and migration.

Angiogenesis and Type of Angiogenesis

Angiogenesis has a great impact on normal physiological growth as well as disease conditions. Physiological angiogenesis is associated with normal tissue growth and vasculogenesis, whereas pathological angiogenesis is associated with illness. Almost all pro-angiogenics are related to various angiogenesis types. Especially, vascular endothelial growth factor (VEGF) plays a key role in both normal angiogenesis (by ensuring endothelial cell proliferation, survival, and metastasis) as well as in angiogenic disorders or pathological angiogenesis (by enhancing the release of proinflammatory cytokines) [11]. Extracellular matrix (ECM) and vascular basement membrane (BM) are key mediators in physiological angiogenesis [12,13]. Vascular or circulatory system is the first physiological system that develops in mammalian embryogenesis [14]. Physiological angiogenesis occurs during wound healing, menstrual cycle, embryo implantation, pregnancy, etc. [15]. There are various *in vitro* and in silico models (continuum model, cell-based model, hybrid mathematical model) for wound healing angiogenesis, but these have some limitations which need further improvement [16]. Leutial angiogenesis, stimulated and regulated by Macrophages, Polymorphonuclear neutrophils, Eosinophils, etc., occurs almost regularly in the corpus luteum (CL) and is related to the formation and function of the luteal structure, ovulation, peripubertal and postpartum periods, etc. [17,18].

Embryo implantation is regulated by both physiological and pathological angiogenesis in the endometrium [19]. Female reproductive hormones, e.g., Estrogen, Progesterone, Human Chorionic Gonadotrophin (hCG), etc., regulate various stages of endometrium angiogenesis [20]. The imbalance of angiogenic factors during pregnancy may lead to miscarriage, defective placentation, or other pregnancy-related disorders [20]. Mitochondria are also indirectly linked with the angiogenesis process. Mitochondrial Complex III produces mROS (mitochondrial reactive oxygen species) that stabilizes HIF-1α, which then releases VEGF from cells leading to angiogenesis [21]. Skeletal muscle is also driven by the angiogenesis process [22]. Alteration of pro-angiogenics and anti-angiogenics balance leads to the shifting of physiological angiogenesis to pathological angiogenesis, thus resulting in diseased conditions, like; tumor formation and progression, all types of cancers (breast, liver, lung, ovarian, GIT, melanoma, etc.), diabetic retinopathy, cardiovascular diseases, psoriasis etc. in the body [23-24]. Pathological retinal angiogenesis is related to vascular leakage, bleeding and fibrosis, visual impairment, etc. and occurs in disease conditions like; retinopathy of prematurity (ROP) and age-related macular degeneration (AMD caused by angiogenic factor imbalance, by factors like-retinal hypoxia, ischemia or inflammation) [25]. Ocular neovascular disease, a leading cause of vision impairment and blindness, occurs because of IL-17 regulated VEGF and other inflammatory cytokines [26].

Diabetic retinopathy or DR (caused by vascular damage in the retina) is a pathophysiological condition associated with VEGF overexpression and some proinflammatory cytokines (TNF-α, IL-

1β, etc.) [27]. Therapeutic angiogenesis is an experimental approach that deals with the external delivery of angiogenic growth factors (like; VEGF, HIF-1) for the treatment of ischemic or injured tissues or fibrosis to promote targeted neovascularization or surgical revascularization process [28]. HIF-1 is used to cure endometriosis and blindness, VEGF can be used (*in vivo*) in coronary and peripheral artery disease, ischemic ulcers, etc. [15,28]. Particular biomaterials deliver these angiogenic stimulatory factors to our body in some specific manner; example: PEG hydrogel, PEG-fibrinogen hydrogel, PEGDA hydrogel, Porcine pericardium, ECM, PLG microspheresin-scaffold, etc. [12]. Gene therapy, stem cell therapy, microvesicle/exosome therapy, combinational gene stem cell therapy, engineered exosome therapy, etc., are some well-established scientific approaches to therapeutic angiogenesis [29].

Mode of Vessel Formation and Branching

Circulatory or cardiovascular system maintains body homeostasis along with other physiological process like- supply of blood cells, essential nutrients, oxygen, and elimination of waste materials by creating a blood vessel network all over our body [30]. Blood vessel formation occurs mainly via Vasculogenesis and Angiogenesis, two different processes of vascularization consisting of various molecules and signalling pathways [30,31]. Mainly Embryonic development triggers vasculogenesis, whereas angiogenesis can be triggered by hypoxia and some other factors [31]. Vasculogenesis results in the formation of vascular network in embryonic stage followed by the expansion of those blood vessels by angiogenesis [31]

However, some factors responsible for both vasculogenesis and angiogenesis includes-

a. HIF-1α stimulation by Lactate in endothelial cells (EC) under normoxic conditions leads to hypoxia whereas Lactate mediated vascular endothelial growth factor (VEGF pathway) upregulation results in vasculogenesis and tumour angiogenesis [32,33].

b. Endothelial Ca2+ signalling induces both angiogenesis and vasculogenesis [34].

c. CD27-CD70 T cell co-stimulation in lymphoid organs results in neovascularization in the human body [35].

d. Vessel branching process mainly occurs through two distinct mechanisms.

I. By bud or sprout formation of pre-existing vessels or sprouting angiogenesis and,

II. By forming of pillar or tube-like new vessels from endothelial cells or non-sprouting angiogenesis or splitting angiogenesis or intussusceptive angiogenesis [36,37].

Sprouting angiogenesis (SA), mechanized with the budding process, undergoes three main steps; proliferation or dilation, elongation, stabilization, where elongation further consists of cell migration, basement membrane degradation, lumen formation [38,39]. In such angiogenesis, the endothelial cell (EC) is proliferated and initiates sprouting with the help of VEGF-Angiopoietin factor [38]. Two significant cellular phenotypes, tip cells and stock cells, and some factors like platelet-derived growth factor-β (PDGF-β), matrix metalloproteinases (MMPs) play a vital role in vessel elongation and tube formation, [38,39]. The stock cells work in a proliferative way while tip cells as migratory units in lumen formation to form a vascular network [39]. Angiopoietins and their receptors (Tie-1 and Tie-2) then decrease the pericyte-endothelial cell interactions and stabilize these newly formed vessels [38]. In a recent study, it has been shown that a transcription factor, myocyte enhancer factors-2 (MEF2) significantly regulated SA by upregulating Delta-like ligand-4 (Dll4) factor [40]. Meanwhile, intussusceptive angiogenesis (IA), coordinated by the 'intussusception' process, may be defined as the transluminal tube formation and splitting longitudinally into two vessels from a preexisting single blood vessel [41]. The term 'intussusception' signifies 'growth within itself' [42]. Mainly, eruption and branching of new vessels occur due to cytoplasmic partial pressure [38]. IA undergoes a very complicated series of process

a. Expansion of blood vessels by intussusceptive microvascular growth (IMG) mechanism,

b. Isolation of new vessels by intussusceptive arborization (IAR) mechanism,

c. Augmentation through intussusceptive branching remodelling (IBR) [43]. Due to the fast and unpredictive nature of the mechanism, the vascular network is reconstructed now and then [41].

The general interrelations between SA and IA are shown in Table 1. Although, sprouting angiogenesis is a standard antiangiogenic therapy target for treating malignant and non-malignant human diseases, intussusceptive angiogenesis (IA) is also a significant target in controlling tumour growth for some reasons.

- It is a rapid but low energy consuming branching process with approximately 50% of the total vasculature in certain types of cancers originated through IA. Therefore, it can be an important druggable target.
- IA also assists in tumour regrowth and expands the vascular network rapidly in local or organ specific, even after antiangiogenic therapy.
- Angiogenic switch plays a key role in the development of anti-angiogenic therapy and tumour resistance. Angiogenic switch from SA to IA heavily depends upon some pro-angiogenic factors (NO VEGF signalling, etc.) [38].

Table 1: The basic comparison between two types of branching in angiogenesis.

Specification	Sprouting Angiogenesis	Non-sprouting/ Intussusceptive Angiogenesis
Involved Cell Type	Endothelial cells and two distinct cellular phenotypes - tip and stalk cells	Pericytes, Endothelial cells, Macrophages, Blood cells and Myofibroblast.
Branching Process	Through budding in mid vessels	Through endothelial pillar formation in the vessel lumen
Characteristics of Branching Process	Slow Process	Very fast Process (Branch formed within hour or minutes)
	Energy requirement is high	Minute energy required for the process
	Physiology +++	Physiology ++
	Pathology +	Pathology ++++
Migration of Cells	Cell migration occurs through Outwards	Cell migration occurs through Inwards
Markers	No morphological and cellular markers	No cellular markers but mesh and pillar formation incapillar-ies, veins, and arteries as morphological markers
Blood Flow	Blood flow not influenced by branching	Blood flow influenced by branching
Vasculature Remodelling	No vascular remodelling takes place	Vascular remodelling occurs extensively
Signaling molecules	Angiopoietin, Notch, VEGF, Ephrin Pathways. PDGF-B, MCP-1	Altered expression of same molecules/isoforms

Angiogenic Stimulatory Factors

Various mechanical, chemical or molecular factors trigger the angiogenesis process.

Mechanical Stimulatory Factors

Researchers found clear evidence on the impact of mechanical microenvironment on tumor angiogenesis, however their mechanism processes are still confusing and controversial [44,45].

However, recently it has been identified that,

I. Fluid shear stress of blood capillaries.

II. Increased muscle contraction led to the rise of NO level.

III. Increased Collagen Matrix and Endothelial-Cell-Matrix (ECM) stiffening can introduce mechanical stimulation in tissue angiogenesis [44,45].

Molecular Stimulatory Factors

A number of chemical factors and pathways also have a great impact on angiogenesis. Some of them are summarized here

VEGF: The vascular endothelial growth factor (VEGF) is the key mediator of angiogenesis along with cancer cell proliferation, invasion, and metastasis [46]. VEGF belongs to a heparin-binding glycoprotein family, consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PLGF) and shows affinity towards 3 types of receptors, VEGFR1 (binds with VEGF-A, B and PLGF), VEGFR2 (binds with VEGF-A), and VEGFR3 (binds with VEGF-C and VEGF-D) [47]. Many studies support the presence of VEGFRs in liquid and solid tumours like; NSCLC, melanoma, prostate cancer, leukaemia, breast cancer, etc. which on subsequent stimulation by VEGF regulates tumour cell proliferation [48]. VEGF shows both neurotrophic and neuroprotective effects on glial and neuronal cells; apparently, they actively participate in neuronal vessel development in CNS and PNS [49]. It is also associated with ocular neovascularization [50]. Often, VEGF-a overexpression results in Hepatocellular carcinoma and lung cancer [46,51]. VEGF and SEMA4D synergistically showed an angiogenic effect on ovarian cancer [52]. PIN2/TRF1-interacting telomerase inhibitor-1 or PinX1 can suppress renal cancer angiogenesis through downregulation of VEGF expression in the mir-125a-3p/VEGF signalling pathway [53]. PR1P, a novel therapeutic peptide, binds with VEGF, which on further overexpression promotes fibrosis or revascularization of injured tissue [54].

HIF-1: Hypoxia, a principal physiological state of our body, is caused by the unrestrained replication of cancer cells, the development of nonfunctional vasculature in solid tumoursetc. and noticed when a shortage of adequate supply of oxygen in body tissue fails to meet oxygen demand [55,56]. HIF or hypoxia-inducible factor, which is a heterodimeric transcriptional factor, consists of α and β (also known as aryl hydrocarbon receptor nuclear translocator or ARNT) subunits which are further subdivided into (1) HIF-1α or HIF-1, (2) HIF-2α or HIF-2, (3) HIF-3α or HIF-3 and (1) ARNT1, (2) ARNT2, (3) ARNT3 [55,57]. Among all, the α subunit (especially HIF-1α), is more oxygen-sensitive and the key mediator of a hypoxic response that produces angiogenic growth factors and various cytokines leading to angiogenesis [58]. HIF-1α plays a pivotal roles in cardiac hypertrophy and end-stage heart failure, whereas the development of HIF-2α by myocardial

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hypoxia can play a protective role in cardiac failure [58]. The HIF-1α expression regulates every step involved in tumorigenesis towards cancer like; cell cycle regulation, glucose metabolism, angiogenesis, erythropoiesis, cell proliferation and invasion, etc., and radio resistance neovascularization by releasing the pro-angiogenic cytokine (i.e.-VEGF) although HIF-1-dependent tumour cell apoptosis has inhibitory effect on tumour growth by promoting glucose deprivation [59]. HIF-1α is also involved in pulmonary hypertension, critical limb ischaemia (CLI), retinopathy, diabetic ulcer, ageing, etc [60]. HIF-1α along with its downstream factors regulate metabolic reprogramming and angiogenesis in cutaneous tumours like; Merkel cell carcinoma, melanoma, basal cell carcinoma, and squamous cell carcinoma [61].

TNF-α: Tumour Necrosis Factor (TNF) is an inflammatory cytokine (protein), derived from monocytes, other immunological or parenchymal cells [62,63]. TNF was first reported about 45 years ago, in mid-1975, by Carswell et al.; although TNF was first observed in the 1960s [64]. Carswell et al. reported that an endotoxin tutor necrosis factor (TNF) acts indirectly by causing the host to release a substance, that mimics the tumour necrotic action of endotoxin and is selectively toxic for malignant cells [64]. Gradually TNF became a rapidly growing prototype family or superfamily with more than 20 ligands and over 29 receptors [65]. There is main two types of membrane-bound receptors- TNFR-1 (expressed by almost all mammalian cell types), TNFR-2 (expressed by mainly immune cells and endothelial cells); that activates through a soluble TNF-a ligand stimulus [64,66]. TNF plays a conflicted role in cancer biology by promoting and suppressing tumour, by promoting angiogenesis along with some other biological activity through various signalling pathways [67,68].

TGF-β: The regulatory cytokine family, transforming growth factor-β (TGF-β) plays multiple roles in embryogenesis, adult angiogenesis and cancer [69]. TGF-β exists as 3 isoforms- TGF-β1, TGF-β2, and TGF-β3 and shows dual roles in both cancer and angiogenesis [69]. There are several specific stromal activators (MMPs, Integrins, ROS, ECM protein, TSP-1 or thrombospondin-1, bone morphogenetic protein 1 or BMP1 etc.) and inhibitors (Proteoglycans, Fibrillin's, Fibulins, Fibronectin, etc.) that operate latent TGF-β activation and suppression [70]. Although the exact mechanism of TGF-β's role in angiogenesis is still unclear, but from some preclinical studies it has been observed that tumour angiogenesis stimulates through plasminogen-dependent activation of TGFβRI/ SMAD1/5 [70]. Besides, in the tumour microenvironment, angiogenesis is inhibited when enhanced TGF-β concentration upregulates fibronectin through TGFβRI/ SMAD2/3 signalling pathway [70,71]. Studies in animal models revealed, at early stages of neovascular age-related macular degeneration or nAMD, TGF-β concentration in the aqueous humour decreases and shows protective and antiangiogenic stimulation, while later, in the diseased stage, it shows pro-angiogenic effects, and in human patients, it inhibits tumour development in early stages, whereas in later stages, it supports tumour invasion and metastasis [72-74]. TGF-β1 secreted from radial glia (RG) cells of the brain regulates RG and endothelial cell interaction to form blood vessels resulting in the development of the cerebral cortex [75]. It also regulates melanoma distal metastase, hepatic angiogenesis [76,77]. Leucine-rich α-2 glycoprotein (LRG) and Interleukin-37 (IL-37) promote lung fibrosis and angiogenesis, respectively, via TGF-β signalling [78,79]. Besides, TGF-β represses VEGFA-mediated angiogenesis in colon cancer metastasis, breast cancer bone metastase, but stimulate glioblastoma through VEGFR signalling [80,82]. A study on bovine ovaries proved that TGF-β has an inhibitory effect on both the angiogenesis in female reproductive organs and steroidogenesis (formation of steroids) [83]. Studies revealed transforming growth factor-β1 overexpression can cause airway remodelling and lung fibrosis by enhancing collagen ⍰ and ⍰, in mustard lung [84].

PARP-1: PARP (Poly (ADP-ribose) polymerase), recently known as ARTs or ADP-ribosyl transferases, is a protein family including 17 members that have diverse structures, enzymatic activity, subcellular localization and functions [85-87]. Among all, the first discovered and extensively discussed member is PARP-1 or ART-1, a DNA-dependent nuclear enzyme [86,88,89]. Structurally, it consists of 3 domains- 1) DNA-binding region, 2) auto modification region, and 3) catalytic region or the PARP site [90]. In essence, the catalytic region of PARP-1 is associated with DNA damage repair, but in case of severe damage, it induces cell death by NAD+ and ATP depletion [90,91]. It is already proven that PARP and angiogenesis are correlated and PARP-1 inhibitors can suppress the angiogenesis process [92]. The impact of PARP-1 overexpression in cancer angiogenesis is shown in Table 2 [93-96].

Table 2: Impact of PARP-1 overexpression in cancer angiogenesis.

Factor	Cancer Type	Regulating Process	Ref.
Promotion of Angiogenesis by Overexpression of PARP-1	Colon Cancer	upregulating the NF-κB pathway	[93]
	Epithelial Ovarian Cancer	upregulating VEGF-A	[91]
	Pancreatic Cancer	activating HIF or Hypoxia-inducible factor	[94]
	Metastatic Melanoma	upregulating EMT (endothelial to mesenchymal transition) transformation	[95]
	Breast Cancer (especially ER- BC and Triple Negative BC)	—	[96]

MMP: MMPs or matrix metalloproteinases are zinc-dependent catalytic enzyme groups that have a significant contribution in both physiological as well as pathological processes of the human body [97]. There are mainly 24 human MMPs under 6 subfamilies which are associated with the formation of vasculature, destruction of some extracellular matrix (ECM) proteins, like; collagen, etc. and activation of some inflammatory cytokines as well [98]. MMPs are mainly secreted by platelets, fibroblasts, leukocytes, endothelial cells, and vascular smooth muscle as proenzymes [99,100]. Some findings suggest that MMPs promote angiogenesis by activating some signalling pathways and receptors or by enzyme overexpression; besides, it can inhibit angiogenesis related vascular sprouting by converting large proangiogenic molecules into relatively smaller antiangiogenic proteins [101]. Expression of MMPs is a risk factor of cardiovascular disease (CVD), chronic kidney disease (CKD), and Peripheral Vascular Disease (PVD) [99]. MMPs, are also associate with tumour maturity-proliferation-migration and several types of cancer subtypes [101] (Table 3) [102-122]. There are some natural modulators in our body that randomly bind to any MMP in 1:1 ratio and inhibits MMPS, known as tissue inhibitors of metalloproteinases or TIMPs and few synthetic MMP-inhibitors like; metal ions (Cu2+, Mg2+, Mn2+ etc), doxycycline (only MMPi approved by FDA) acts by reducing MMP secretion.

VASH-2: Vasohibin (VASH) consisting of two subfamilies with - VASH-1 and VASH-2, are recently discovered angiogenesis regulator genes that show antipathic effects on tumour angiogenesis; by inhibiting angiogenesis (VASH-1) and by stimulating angiogenesis (VASH-2), although there are 52.5% similarities between full-length human VASH-1 and VASH-2 genes at the amino acid level [123]. VASH-2 generally on exposure to mononuclear cells of bone marrow starts angiogenesis as a chemical stimulator [124]. Studies revealed that VASH-2 can be used as a biomarker in oesophageal squamous cell carcinoma (ESCC) as the plasma concentration level and tumour expression level of VASH-2 were found to increase at a proportional rate [125]. Epigenetic mechanism involving transcriptional start site (TSS) upregulation and activation of histone modifications occurs -354 to -10 region of VASH-2 gene, which probably leads to VASH-2 overexpression following increased angiogenesis in hepatocellular carcinoma (HCC) [126]. VASH-2 expression is related to angiogenesis in human retinal microvascular endothelial cells or HMVEC [127]. VASH-2 promotes tumour angiogenesis by altering gene expression and metastasis by tubulin de-tyrosination of PDAC or Pancreatic Ductal Adenocarcinoma cells [128]. Two growth factors; fibroblast growth factor-2 (FGF-2) and growth/ differentiation factor-15 (GDF-15) overexpression leads to VASH-2 induced breast cancer cell proliferation [129]. Overexpression of VASH2 indicated as a predictor in oesophageal squamous cell carcinoma (ESCC) and accelerated tumour angiogenesis in some specific types of ovarian cancer by enhancing tumour growth and peritoneal dissemination of tumour cells [130,131].

Experimentally Proven Phytopharmaceutical to Inhibit Vasculature Development

Experimentally proven phytopharmaceuticals inhibiting vasculature development are summarized based on most impacted and cited literature published in the last 15 years; 2005- 2020) as searched from the authenticated databases (Scopus, PubMed, etc), including the keywords like- Pathological Angiogenesis, Cancer Cell Invasion, Metastasis, Cell Migration, Experimentally Proven Phytopharmaceutical, Inhibition of Vasculature Development, Modern Target for Cancer treatment in Table 4. [132-245] A total of 97 plant molecules, studied in this review, including 69 plant species among 40 plant families are summarized in a schematic way. The respective compounds/ extracts are included with their respective sources/ families and the specific protocols/ methodologies used for the experimental proof-of-of-concept studies are tabularized in Table 3 [102-122].

Table 3: MMP subgroups with associated cancer types. [*Abbreviations* - HCC=Hepatocellular Carcinoma, HNSCC= Head and Neck Squamous Cell Carcinoma, TNBC= Triple Negative Breast Cancer, CNV=Corneal Neovascularization, CLL=Chronic Lymphocytic Leukemia, ESCC=Esophageal Squamous Cell Carcinoma, MCC=Markel Cell Carcinoma, GIT = Gastrointestinal Tract].

MMP Subgroups	MMP	Few Associated Cancer Types	Ref.
Collagenases	MMP-1	HCC	[104]
		HNSCC	[100]
	MMP-8	HCC	[104]
		Colorectal Cancer	[105]
		Gastric Cancer	[106]
		Lung Cancer	[107]
	MMP-13	HCC	[104]
		Ovarian Cancer	[108]
		Thyroid Cancer	[109]
	MMP-18	HCC	[104]

Gelatinases	MMP-2	HCC	[104]
		Pancreatic Cancer	[110]
		CNV	[102]
	MMP-9	HCC	[104]
		CNV	[102]
		Breast Cancer (TNBC)	[111]
		CLL (as both Pro-angiogenic & Anti-angiogenic)	[112]
Stromelysins	MMP-3	HCC	[104]
		ESCC	[113]
		Thyroid Cancer	[109]
	MMP-10,	HCC	[104]
	MMP-11	HCC	[104]
		Breast Cancer	[111]
Matrilysins	MMP-7	HCC	[104]
	MMP-26	HCC	[104]
		Glioma	[114]
MMP Membrane-Type (MT)-MMPs	MMP-14, MMP-15	Breast Cancer	[111]
	MMP-16	HCC	[104]
	MMP-17	Breast Cancer	[115]
	MMP-23	Melanoma	[116]
	MMP-24	Breast Cancer	[117]
		Lung Cancer, Gastric Adenocarcinoma	[104]
	MMP-25	Brain Cancer, Colon Cancer, Urothelial Cancer, Prostate Cancers	[104]
Other MMPs	MMP-12	GIT Cancer	[118]
	MMP-19, MMP-20	Ovarian Cancer	[119]
	MMP-21	ESCC	[120]
		MCC	[121]
	MMP-27	Thyroid Cancer	[122]
	MMP-28	HCC	[104]
		MCC	[121]

Table 4: Experimentally Proven Phytopharmaceutical to Inhibit Vasculature Development. Summarized based on most Impacted and Cited Literature published in last 15 years; 2005- 2020).

Sl. No.	Compound/ Extract	Source/ Family	Protocols used	Results	Reference (Year)
1.	6’-Sialylgalactose (6SG) (semisynthetic)	Chemically modified from milk protein	For checking antiangiogenic activity Cell viability assay, Western blot analysis, Tube-forming assay, Migration assay, Immunofluorescence, Retinal angiogenesis assay, Oxygen-induced retinopathy, Matrigel plug assay, Tumor allograft, Immunohistochemistry and morphometric analysis were performed by authors.	a. 6SG effectively suppressed VEGF-A-induced VEGFR-2 phosphorylation and *in vitro* angiogenesis in HUVECs without cytotoxicity. b. Inhibition of VEGFR2-mediated signalling may be the mechanism. c. VEGF-A-induced extracellular-regulated kinase (ERK)/Akt activation and formation of actin stress fiber in human umbilical vein endothelial cells (HUVEC) were also inhibited by the compound.	[132]

2.	Oridonin	*Isodonrubescens;*	Endothelial cell migration, invasion and tube formation assays, Western blot analysis, Molecular docking analysis and Breast tumor xenograft model in nude mice	a. Oridonin significantly reduced the proliferation, invasion, migration, and tube formation of HUVECs.	[133]
		Rabdosia nervosa (Hemsl)	Cell Culture and Proliferation Assay, Tube Formation and Migration Assay, Aortic Ring Assay, Mouse Corneal Micropocket Assay, Xenograft Mouse Tumor Model, Spontaneous Metastasis Model and Hematoxylin& Eosin Staining, Immunohistochemistry, Immunofluorescence, Transendothelial Migration of Tumor Cells, Real-time Quantitative Polymerase Chain Reaction, Immunoblot Assay	a. Oridonin significantly suppressed the proliferation, migration, and capillary-like structure formation of human umbilical vascular endothelial cells *in vitro,* results its tumor angiogenesis inhibitory effect and propose a mechanism. b. Studies provided evidence supporting the central role of Notch in tumor angiogenesis.	[134]
3.	Eupatorin	Commonly found in a variety of fruits, vegetables, and herbs	Scratched/ wound healing assay, Transwell migration and invasion assay in HUVECs, Mouse aorta ring assay and Real-time PCR (qPCR) analysis were carried out as anti-angiogenic confirmation assay.	a. Eupatorin is a potent candidate to induce apoptosis and inhibit the invasion, migration and angiogenesis of MDA-MB-231 and MCF-7 cells through Phospho-Akt pathway inhibition and cell cycle blockade.	[135]
4.	Curcumolide	*Curcuma wenyujin*	Oxygen-induced retinopathy (OIR), Histological analysis, TUNEL assay, Cell viability, Cell proliferation, migration assay, Tube formation assay in HUVECs, Quantitative real-time PCR analysis, Western blotting and Molecular docking	a. Curcumolide significantly decrease VEGF-induced HRMECs proliferation, migration and tube formation in a dose-dependent manner.	[136]
5.	Menkudu Leaves	*Morinda citrifolia* L.	Only *ex –ovo* Chicken Chorioallantoic Membrane Assay (CAM)	a. Phytochemical compounds of Menkudu leaves extracts, can inhibit angiogenesis.	[137]
6.	Solomon amide A (precursor of Solo F–OH)	*Theonella swinhoei*	Tubular-Like Structures Formation on Matrigel, Wound Healing Assay, Cell Invasion Assay, Zymographic Assays for MMP-2 and MMP-9 Detection, Chick Chorioallantoic Membrane (CAM) Assay, FGF-2 Induced Angiogenesis, Zebrafish Yolk Membrane (ZFYM) Assay, Western Blot Analysis, *In Vitro* Measure of VEGFR2 TK Activity	a. Some key steps of the angiogenic process are inhibited by Solo F–OH including the proliferation, migration, and invasion of endothelial cells. b. Diminish their capability to degrade the extracellular matrix (MMP) proteins.	[138]
7.	Fascaplysin	*Fascaplysinopsissp*	Matrigel assay, Immunofluorescence microscopy,	a. Fascaplysin induced autophagy in vascular endothelial cells, which subsequently facilitate the anti-angiogenic action.	[139]
8.	Sulfated Galactofucan	*Sargassum thunbergii*	Anti-angiogenic Activities were performed as described in the corresponding research paper.	a. Low molecular weight sulfatedgalactofucan, in higher fucose content, showed anti-angiogenic and anti-tumor activities as well.	[140]
9.	Strigolactone analog GR-24		CAM Assay, Intersegmental vessels formation assay, Caudal fin regeneration assay, MTT proliferation assay, Control assays of *in vitro* toxicity, Tubular structures formation on Matrigel, vascular disruption Assay, Adhesion Assay, Wound healing assay, Invation assay, ECM degradation assays, immunocytochemistry, Wetern blot, Quantitative real-time PCR (qPCR), Flow cytometry for VE-cadherin and PECAM-1 measure and *In vitro* VEGFR2 TK activity	a. GR-24 blocks angiogenesis by maintaining the quiescent phenotype in endothelial cells. b. The mechanism of anti-angiogenic activity of GR-24 involves the inhibition of VEGFR2 phosphorylation. c. Downstream the reduction in activation of FAK, a key regulator protein important for angiogenesis.	[141]

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10.	*Kochia scoparia* seed extract	*Kochia scoparia* (L.) Schrad (Amaranthaceae)	Wound healing assay, migration assay, Trans-well invasion assay, Sulforhodamine B (SRB) assay, Capillary-like tube formation assay, Rat aortic ring assay, Western blot analysis, phosphorylated VEGFR2 concentration measurement was done to check the antiangiogenic potency.	a. VEGF-induced migration, invasion and capillary-like structure formation of HUVECs were suppressed by the exact (20 mg/mL) significantly. b. Micro vessel sprouting from rat aortic rings also inhibited by the same. c. It down-regulated PI3K/AKT/mTOR levels and phosphorylation of VEGFR-2 in HUVECs.	[142]
11.	Methanolic extract of *Cassia occidentalis*		*In-vivo* chorioallantoic membrane (CAM) assay	a. It possessed significant anti angiogenic activity with an IC50 of 70 ±0.11 µg/ml.	[143]
12.	Methanolic extract of *Callistemon viminalis*		*In-vivo* chorioallantoic membrane (CAM) assay	a. antiangiogenic activity of this extract is found with an IC50 of 44 ± 0.19 µg/ml.	[143]
13.	Methanolic extract of *Cleome viscosa*(Leaves and root)		*In-vivo* chorioallantoic membrane (CAM) assay	a. It supressed angiogenesis ac with an IC50 of 70 ± 0.22 µg/ml and 73.2 ± 0.36 µg/ml for leaves and root extracts respectively.	[143]
14.	Methanolic extract of *Mimosa hamata*		*In-vivo* chorioallantoic membrane (CAM) assay	a. It has significant antiangiogenic activity with an IC50 of 65.8 ±0.25 µg/ml.	[143]
15.	4′-hydroxywogonin		Cell viability assayof HUVEs, VEGF Elisa assay, Immunofluorescece assay, Wound healing assay, Transewell migration assay and Tube formation assay were performed for antiangiogenic assessment.	a. The compound decreased the mRNA and protein expression of vascular endothelial growth factor-A (VEGF-A) concentration-dependently. b. The phosphorylation of phosphatidylinositol 3-kinase (PI3K) and AKT were also inhibited by 4′-hydroxywogonin. Hence, the viability and angiogenesis in CRC were inhibited subsequently.	[144]
16.	Triptolide		Cellular migration and invasion assays, Mouse model of ovarian cancer, ELISA and Immunohistochemical staining used to explore the angiopreventive activity.	a. Inhibited cellular invasion and migration of SKOV3/DDP cells, and the expression of adhesion-related proteins integrin β1 (ITGβ1) was also significantly reduced. b. Suppress apoptosis-inhibiting proteins survivin, matrix metalloproteinase-2 (MMP-2) and MMP-9. c. Significantly inhibited vascular endothelial growth factor (VEGF) production related protein clusters of differentiation-31 (CD31) and CD105.	[145]
		Tripterygium wilfordii	Embryo handling, EAP staining for visual inspection, RNA isolation, semi-quantitative reverse transcription (RT) and polymerase chain reaction (PCR).	a. Among all extracted molecule, triptolide showed the most potent antiangiogenic activity against vessel formation at 1.2 uM.	[146]

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17.	Vialinin A		Cytotoxicity assay, Cell Migration Assay, *In Vitro* Angiogenesis Assay, Measurement of ROS and MDA Generation in HUVECs, Analysis of Inflammatory Cytokines Secreted by HUVECs, Western Blot Analysis, NF-κB Transcription Factor Assay and *In Vivo* Matrigel Plug Assay were the major experiments.	a. Vialinin A prevented VEGF induced HUVEC cell growth in a dose-dependent manner. b. Inhibited VEGF-induced migration and tube formation of HUVECs. c. VEGF-induced generation of reactive oxygen species (ROS) and malondialdehyde (MDA) were also inhibited by it. d. Showed the ability to inhibit VEGF-induced NF-κB nuclear translocation as well as DNA binding activity and subsequent angiogenesis as well.	[147]
18.	Cucurbitacin B	*Pedicellus melo*	Cell viability assay, *In vitro* migration assay, Capillary lie structure formation assay, CAM assay, Assessment of apoptosis by Annexin V-FITC/PI staining, Western blotting	a. HUVEC cell proliferation, migration, tubulogenesis *in vitro* were inhibited. b. angiogenesis in chick embryo chorioallantoic membrane (CAM) assay *in vivo* was blocked by Cucurbitacin B. c. It can induce HUVEC apoptosis and may induce apoptosis of ECs by triggering the mitochondrial apoptotic pathway.	[148]
19.	Cannabinoids	*Cannabis sativa* L.	*In vitro* NO scavenging assay, CAM assay, MMP-1 inhibition assay and Cytotoxicity and VEGF inhibition assay in MCF-7 cell lines were performed to check parameters related to angiogenesis.	a. Among various sample *C. sativa L.* from "Pondo" region (Eastern Cape, South Africa) showed best inhibitory effect on MCF-7 cancer cell growth and angiogenesis by inhibiting NO, MMP-1 and VEGF.	[149]
		Cannabis sativa	Antiangiogenic activities were checked by - Cellular viability analysis, evaluation of sprout formation, Migration assay, Tube formation assay in HUVECs, western blot, siRNA transfections, Fibrin bead assay.	a. JWH-133 decreased migration as well as tube and sprout formation of HUVEC. b. Inhibition of sprout formation in A549 cells co-cultured with HUVEC was also confirmed after cannabinoid treatment. c. Induced expression of tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) and its increased trigger, the intercellular adhesion molecule-1, resulting decrease of HUVEC migration.	[150]
20.	Xanthatin	*Xanthium sibiricum*	CCK-8 assay for cell proliferation, Scratch assay for cell migration, Tube formation test, Establishment and treatment of the alkali burn model, Measurement of corneal neovascularisation, Histological examination, Western blot analysis, Immunofluorescence detection were claimed to be performed.	a. The expression levels of p-VEGFR2, phosphorylated (p-)STAT3, p-PI3K and p-Akt were significantly decreased by Xanthatin. b. It also inhibited corneal neovascularisation in the VEGF-treated HUVECs.	[151]
		Xanthium sibiricum	Cell viability assay, Lactate dehydrogenase toxicity assay, *In vitro* VEGFR2 kinase inhibition assay, Migration assay, Endothelial cell capillary-like tube formation assay, *In vivo* Matrigel plug assay, Immunofluorescence analysis, Western blot analysis, Human breast tumor xenograft mouse model were chosen to check angiogenic parameters.	*a.* *In vitro* and *in vivo* evaluations suggested that xanthatin has the capacity to inhibit angiogenesis and may prove itself as a promising anticancer drug candidate.	[152]
		Xanthium sibiricum	*In vitro* angiogenesis activity by rat aortic ring assay were performed to confirm the antiangiogenic activity.	a. Xanthatin has strong anti-angiogenesis capacity *in vitro*.	[153]

21.	Imperatorin	*Angelica dahurica*	Luciferase reporter assay, Immunofluorescence assay, VEGF ELISA, cell viability assay	a. Imperatorin inhibited HIF-1α protein expression by downregulating the mTOR/p70S6K/4E-BP1 and MAPK pathways. b. Imperatorin can effectively inhibit HIF-1, subsequently angiogenesis and provide new perspectives into the mechanism of its anticancer activity.	[154]
22.	Chemically transformed Wondonin	*Poecillatra wondoensis*	Antiangiogenic activity was estimated through Tube formation assay, Growth of HUVECs by MTT and Diabetic retinopathy by zebrafish model assay.	All findings together suggested, a. the scaffold has the potency to disrupt the structure for development of anti-angiogenesis. b. The drug with novel functions may be used as a probe to elucidate new biological mechanisms related to angiogenic process.	[155]
23.	Baicalein	*Scutellariabaicalensis* Georgi	Tube formation assay, Rat aortic ring assay, CAM assay, Cell viability assay, Immunofluorescence, Wound healing assay, invasion assay of endothelial cells, Gelatin zymography, Molecular modeling and docking analysis, Western blot, qRT-PCR analysis, Immunofluorescence microscopy, Immunoprecipitation, Electrophoretic mobility shift assays (EMSA), Transient transfection and *In vivo* angiogenesis	a. Motility, migration and invasion of HUVECs were significantly inhibited by Baicalein. b. According to the authors, Baicalein exert its anti-angiogenic effect in pathogenic microenvironment via inhibiting the transcriptional activity of AP1.	[156]
24.	Extracts of Anthocyanin	*Hibiscus sabdariffa*	Chick Embryo assay and Molecular Modeling analysis were reported to be done for the anti angiogenic activity.	a. Anthocyanin proved itself as, an angiogenic modulator which can be used to treat uncontrolled angiogenesis related conditions, including age-related macular degeneration.	[157]
25.	3β-acetyl-nor-erythrophlamide (3-ANE)	*Erythrophleumfordii*	Cell proliferation assay, cytotoxicity assay, Immunoprecipitation and western blotting, Wound healing, migration and invasion assays, Cell cycle distribution analysis, Apoptosis assays, Permeability assay, Tube formation assay, Matrigel plug assay, NO fluorometric assay, Xenograft tumor growth assay and immunohistochemistry were carried out to confirm the angiopreventive potency.	a. 3-ANE blocked angiogenesis *in vivo*, also inhibited tumor angiogenesis. b. The human lung adenocarcinoma growth in xenograft tumor in mice model. c. Furthermore, it blocked VEGF-mediated endothelial nitric oxide synthase (eNOS) phosphorylation and NO production along with vascular permeability in HUVECs. The mechanism expected via interfare with the heat-shock protein 90 (HSP90), subsequently VEGF-induced eNOS activity.	[158]
26.	Metabolites of cyperenoic acid by *Cunninghamella elegans*	*Croton crassifolius*	Angiogenic inhibition activity was checked by -Cytotoxicity assay and Anti-angiogenic activity assay.	a. Among all modification hydroxylated two products significantly inhibited VEGF release, subsequently it was thought to have the potential to be used in cancer therapy as a novel angiogenic inhibitor.	[159]
27.	Chemical constituents from *Calvatia nipponica*		HUVEC proliferation *in vitro,* tube formation assays, Vascular endothelial growth factor (VEGF) quantification, estimation of p-p38 and p-ERK in HUVECs were preferred by the researchers.	a. Among all Compounds one showed the most potent angiogenesis inhibition via downregulation of VEGF, p38 and ERK signaling pathways. *b. C. nipponica (a* rare mushroom) would be beneficial in cancer treatment for its anti-angiogenesis blocking property.	[160]

28.	*Zingiber officinale* (ginger) extracts		Fundus photography and vessel diameter, Inflammatory and angiogenic parameter-sassesment, Histopathological studies, Immunohistochemistry, Western blotting, Transmission electron microscopy, estimation of vascular basement membrane thickness were performed as antiangiogenic experiment.	a. It has the potency to reduced expression of NF-κB and the activity of TNF-α and VEGF in the tissue of retina. b. The extract resulted in significant decrease of, the diameter of the retinal vessels, along with vascular basement membrane thickness after oral administration.	[161]
29.	Red Raspberry Phenols		Following studies were carried out to check angiogenic parameters -BrdU proliferation assay, Migration analysis Human microvascular endothelial cells (HMVECs), Capillary-like structures formation assay, western blotting and immunohistochemistry.	a. Red raspberry extracts dose dependently reduced cell viability (GI50= 87, 64±6, 59 mg GAE/mL) and cell proliferation. b. Findings supported; the antiangiogenic potential of red raspberry phenolic extract provide their probable mechanism upon endothelium.	[162]
30.	Scopoletin	*Nicotiana glauca*	*Ex vivo* rats aortic ring assay, MTS assay, *In vivo* matrigel plug assay, *In vivo* assessment of tumor angiogenesis in nude mouse xenograft model, Visualization of tumor vasculature in immunohistochemistry, Molecular docking study	a. Scopoletin showed strong ligand affinity in computer modeling and binding energies toward the following angiogenic factors such as- protein kinase (ERK1), vascular endothelial growth factor A (VEGF-A), and fibroblast growth factor 2 (FGF-2). b. Other studies suggested that the antitumor activity of scopoletin may be due to its strong anti-angiogenic effect, mediated by its ERK1, VEGF-A, and FGF-2 inhibition.	[163]
		Erycibeobtusifolia Benth	Rat aortic ring assay, Cell migration assay, Tube formation assay, Quantification of VEGF levels, RT-PCR assay, Western blotting	a. Scopoletin significantly attenuated FGF-2-induced angiogenesis, due to directly preventing the stimulation action of FGF-2 as well as indirectly decreasing VEGF production. b. It also down-regulated the VEGF expression through NF-κB better than PI-3K/Akt signaling pathway.	[164]
31.	Extracellular Histones	Human recombnant histones	Studies like Flow cytometry studies,Proliferation of ECs, flow cytometry,Proliferation of ECs and Wound healing assay	a. All histones reduced migration, while H2B, H3 and H4 induced cell cycle arrest of endothelial cells and also down regulate the process of tubulogenesis via p38 activation, at non-cytotoxic concentrations and blood vessel formation in the quail chorioallantoic membrane *in vivo* was also reduced by H2B, H3 and H4. b. Their cytotoxic as well as anti-angiogenic effects were suppressed by unfractioned and low-molecular weight heparin and combination of blocking antibodies like TLR2 and TLR4.	[165]
32.	Synthetic Analogue of *Piper longumine*	several species of *Piper s.* (Piperaceae)	Only wound healing assay and Invasion assay by boyden chamber cell assay were performed here.	a. Among all ((*E*)-*N*-acryloyl-3-(3,4,5-trimethoxyphenyl) acrylamide), the analogue designed by molecular simplification, was the most active with an EC50 of 1.5 ± 1 μM. b. It also found to be selectively cytotoxic, with a selectivity index (SI) of 4.4.	[166]

33.	The noni anthraquinone Damnacanthal	*Morinda cordifolia*	*In vivo* angiogenesis assays, docking analysis, *ex vivo* and *in vivo* angiogenesis, tubule-like structures formation, endothelial cell proliferation and survival, migration and remodel extra cellular Matrix assay were performed in this regard.	a. Damnacanthal showed a very potent inhibition of angiogenesis in both *ex vivo* and *in vivo* conditions. b. It inhibited tubulogenesis, proliferation, survival, migration of endothelial cells and also production of extracellular matrix remodelling enzyme.	[167]
34.	Rosmarinic acid		Angiogenesis related studies like -H22 hepatocarcinoma xenograft tumor in mice, serum physiochemical indexes analysis, Pathological observation, ELISA measurements of cytokines in xenografts tumor, Western blot, Effect of RA on NF-kB p65 signaling in xenograft tumor were reported.	a. Rosmarinic acid effectively inhibited tumor growth with fewer toxic effects by down-regulating the secretion of inflammation associated cytokines as well as angiogenesis related cytokines, and suppressing the NF-kB, p65 expression in the xenograft microenvironment.	[168]
		Various plants including ***Lamiaceae*** species	Scientific experiments which were carried out - retinal endothelial cells proliferation assay, Tube formation assay, Western blot analysis, Oxygen-induced retinopathy, Assessment of retinal neovascularization by fluorescein angiography, vascular lumens and Terminal deoxynucleotidyl transferase biotin-dUTP nick endlabeling (TUNEL) assay.	a. Rosmarinic acid has an anti-angiogenic activity to retinal angiogensis in retinopathy of prematurity in a mouse model, which is due to cell cycle arrest with increase of p21WAF1. b. Rosmarinic acid significantly inhibited the proliferation of retinal endothelial cells in a dose-dependently and inhibited *in vitro* tube formation. The anti-proliferative its activity was related to G2/M phase cell cycle arrest on retinal endothelial cells.	[169]
		Many medicinal plants including *Salviaemiltiorrhizae*	*In vitro* angiogenesis assay, Cell proliferation assay, migration assay, Cell adhesion assay, estimation of intracellular ROS, Immunohistochemical assay for VEGF Expression, Radioimmunological assay for IL-8 level and Cell viability and apoptosis analysis of HUVECs (for anti-angiogenic analysis *in vitro*)	a. Rosmarinic acid concentration dependently inhibited various important steps regardingangiogenesis including proliferation, migration, adhesion and tube formation in, *in vitro* HUVEC. b. Also found that, anti-angiogenic potential of RA might be due to its anti-oxidative activity, leading to the inhibition of ROS associated VEGF expression and release of IL-8.	[170]
35.	Combretastatin A-4 in PEG micelle		*In vitro* Cell Viability Assay, Endothelial Cell Tube Formation Assay on HUVECs, Nile Red Internalization in HUVECs,	a. Inhibitory effect of Comb-G3-PEG on tube formation was shown on HUVECs.	[171]
36.	Proanthocyanidins	Fruit peels of *Choerospondiasaxillaris*	Author claims to perform - Cell proliferation assay, Tube formation assay, Western blot analysis, Angiogenesis study of zebrafish embryos.	a. Angiogenesis was suppressed by the extract at 72 h post fertilization of transgenic zebrafish embryo that was also in a concentration dependent fashion.	[172]
		Grape seeds	Cell viability assay, migration assay, Gelatin zymography, Tube formation assay, Chick CAM assay and Western blot analysis were carried out for antiangiogenic potency estimation.	a. Proanthocyanidins inhibited tumor-induced angiogenesis and subsequently blocked colon tumor xenografts development on the chick chorioallantoic membrane; due to their action were related to inhibiting VEGF and Ang-1 expression through scavenging ROS.	[173]

37.	Kaurane diterpenoids	*Wedelia chinensis*	For the estimation of the antiangiogenic potency Quantitative EAP assay, microscopic imaging on zebrafish embryo, Total RNA isolation, reverse transcription and real-time PCR, Lactate dehydrogenase toxicity assay, Tube formation assay, Aortic ring assay, Matrigel plug assay Western blotting	a. Potent anti-angiogenic activity shown by the Petroleum ether (PE) fraction of the plant. b. From the crude extract 12 kaurane diterpenoids isolated showed different effects. Among them 4 compounds could inhibit vessel formation in the zebra fish embryos dose-dependently while the others not and one compound (3α-cinnamoyloxy-9ß-hydroxy-ent-kaura-16-en-19-oic acid or CHKA), established the best effect, by affecting multiple molecular targets related to angiogenesis like- VEGF and angiopoietin in zerbra fish. c. CHKA significantly suppressed a series of VEGF induced proliferation, invasion, and tube formation of endothelial cells crucial for angiogenesis process. d. Also directly inhibited VEGFR-2 tyrosine kinase activity along with downstream signaling pathways in HUVECs.	[174]
38.	Abrus agglutinin (AGG), a plant lectin	*Abrusprecatorius*	Human breast cancer xenografts in athymic nude mice, Immunohistochemical analysis, wound-healing assay, Endothelial cell invasion assay, tube formation assays, CAM assay, transfection and RNA interference, Human angiogenesis protein micro-array and ELISA for IGFBP-2 were performed to check the anti-angiogenic activity.	a. AGG inhibited the pro-angiogenic factor IGFBP-2 expression in an AKT-dependent manner, decreasing angiogenic phenotypes both *in vitro* as well as *in vivo*. Overall results proved, AGG promotes both anti-angiogenic along with apoptotic activities in human breast tumor cells.	[175]
39.	*Juniperus chinensis* extract		Experiments done here are - tube formation assay, migration assay, Matrigel plug assay, CAM assay, *in vivo* subcutaneous tumor model, *In vivo* orthotopic tumor model, Immunohistochemistry analysis and Protein array analysis.	a. CBT-143-S-F6F7, the active component of the extract, showed significant angiogenesis inhibiting activity in various assays, including tube formation and migration in HUVECs. b. In *in vivo* studies, CBT-143-S-F6F7 significantly suppressed subcutaneous Huh7 tumor development in severe combined immunodeficient (SCID) mice. Hence it would prolong the survival of orthotropic Huh7 tumor-bearing SCID mice effectively.	[176]
40.	Odisolane (oxolane derivative)	*Morus alba* L.	For the assessment of antiangiogenic activity studies like Measurements of Cell Viability in Human Umbilical Vein Vascular Endothelial Cells (HUVECs), Measurements of Tube Formation in HUVECs, Western Blot Analysis were performed	a. Odisolane significantly inhibited the tube formation in HUVECs and subsequently angiogenesis, which was expected due todecreased VEGF, p-Akt, and p-ERK protein expression. b. Also, it might be beneficial in anti-angiogenesis therapy for cancer treatment.	[177]
41.	Widdrol	*Juniperus chinensis*	Flow cytometric analysis of cell cycle, Western blot analysis, Tube formation assay, Wound-healing assay and *In vivo* tumor xenograft study were done here.	a. By inhibiting vessel sprouting and growth widdrol may act as a potential anti-angiogenic agent, which may have implications for angio-prevention.	[178]

42.	Quercetin and derivatives	Fruits and vegetables such as onions, apples and grapes	Few antiangiogenic studies like - Migration Assay, Tube Formation Study, Western Blot Analysis were performed.	a. Quercetin inhibited VEGF-induced migration and tube formation of RF/6A cells were also significantly in a dose-dependent manner. b. Quercetin also inhibited VEGF-induced VEGFR-2 downstream signal pathways of RF/6A leading to abrogation of angiogenesis.	[179]
			Scratch assay, Western blotting, Molecular docking for VEGFR2 and VEGF, Membrane perturbation (probed by DSC) were the major experiments in this regard.	a. Among other compounds methoxy-quercetin was found to be most potent antiangiogenic agent with 86% inhibiting capacity (due to an interference with the VEGF/VEGFR2 pathway by inhibiting the phosphorilation of VEGFR2).	[180]
			Cell proliferation assay, vascular changes in zebrafish embryos by microscopy, capillary-like tube formation in Endothelial cell assay, Quantitative real-time PCR, Western blotting analysis were carried out as antiangiogenic protocols.	a. Quercetin disrupted the development of intersegmental vessels, dorsal aorta as well as post erior cardinal vein in transgenic zebrafish embryos. b. In HUVECs, cell viability, the expression of vascular endothelial growth factor receptor2 along with tube formation were inhibited by quercetin dose-dependently. c. Additionally**, quercetin** involved in suppression of extracellular signal-regulated kinase signalling pathway *in vivo* and *in vitro*.	[181]
			Wound healing assay, cell migration, Tube formation and Proliferation of RF/6A cells were performed.	a. Quercetin significantly inhibited, endothelial cell proliferation in a dose-dependent manner. b. It also inhibited the migration and tube formation of RA/6A cells significantly, in a dose-dependent manner.	[182]
		Many fruits, vegetable, olive oil, red wine and tea	Growth inhibition assay, Cell migration assay, Tube formation assay, CAM assay, Reverse transcription-polymerase chain reaction (RTPCR) Assay, Determination of gelatinolytic activity of matrix metalloproteinase 2	a. Quercetin dose-dependently inhibited several important steps of angiogenesis which includes proliferation, migration, and tube formation of human microvascular dermal endothelial cells. b. It also showed down regulation of expression and activity of matrix metalloproteinase 2.	[183]

			To check antiangiogenic activity Reverse transcription, PCR and real-time PCR, Western blot analysis, Intravital assessment of tumor vascularization with SDF imaging and Immunohistochemistry assay	*a.* *In vivo* side stream dark field video microscopy confirmed that NAX014 (berberine derivative) significantly decrease vessel density in mammary tumors in mice model as compared to the control group.	[184]
			Determination of Cell Viability by MTT Assay, Boyden Chamber Cell Invasion and Motility Assays, Wound-Healing Migration Assay, Cell Matrix Adhesion Assay, Determination of MMPs and u-PA by Zymography, Measurement of MMP-2 and u-PA Promoter Activity, Nuclear Factor-kB Binding Assay, Immunofluorescence Staining, Western blot, Snail-1 Small Interfering RNA, Chicken Chorioallantoic Membrane Assay, Zebra fish Angiogenesis Model, Reverse-Transcription Polymerase Chain Reaction, Matrigel Tube Formation Assay, Tumor Growth and Lung Metastasis, Immunohistochemistry Analysis were studied for antiangiogenic potency.	a. Findings suggested that berberine has potency to reduce metastasis and angiogenesis of cervical cancer cells.	[185]
43.	Berberine and derivatives		Protocols used are – ELISA for IL-1β, IL-6, TNF-α, GM-CSF, and IL-2 measure, Tumor-specific capillary formation, estimation of serum nitrite, Endothelial cell viability by MTT assay, production of nitrite and TNF-*α* *in vitro*, Endothelial cell proliferation by 3H-thymidine incorporation, ECs migration by wound healingand ECs invasion through transwell chamber, ECs morphogenesis by tube formation assay, Microvessel outgrowth by rat aortic ring assay, Quantification of VEGF, iNOS, COX-2, and HIF mRNA by RT-PCR.	a. Berberine possessed anti-angiogenic activity which mainly mediated through the inhibition of various pro-angiogenic factors like HIF, VEGF, COX-2, NO, NF-κB, and pro-inflammatory cytokines.	[186]
		Roots, rhizomes and stem barks of many plants, like *Berberis* *vulgaris* (barberry), *Berberis aristata* (tree turmeric), *Berberis* *aquifolium* (Oregon grape), and *Coptis chinensis* (Chinese goldthread)	HUVEC proliferation, HUVECs migration, Tube formation assay, quantification of VEGF level, RT-PCR analysis	a. Berberine inhibited the ability of HCC to stimulate HUVEC's proliferation, migration and tube formation of endothelial cells. b. It suggests that berberine has the potency to influence the cross-talk between the vascular endothelial cells and HCC cells.	[187]
		Corydalis yanhusuo	Antiangiogenesis related asssays are Proliferation, Cell migration, Cell invasion, tube formation of HUVEC cells Western blotting, Gelatin zymography, RNA isolation and real-time PCR analysis	a. The plant extract and its active compound berberine significantly inhibit the VEGF-induced upregulation of matrix metalloproteinase 2 (MMP2) at mRNA as well as protein levels. b. It also showed to be involved VEGF-triggered ERK1/2 pathways.	[188]
44.	Cucurbitacin I (JSI-124)	Plants of the family Cucurbitaceae	For antiangiogenic activity following assay were done - Transfection, Cell Viability and Proliferation Assay, Cell adhesion assay, Cell migration assay, Tube formation assay, Western blot, Chromatin Immunoprecipitation and ELISA.	a. JSI-124 inhibited tumor angiogenesis *in vitro* of the human BC cell line by reducing STAT3 phosphorylation. b. It might reduce the transcription and secretion of VEGF, leading to VEGF autocrine loop inhibition in the tumor microenvironment.	[189]

45.	Luteolin and derivatives		Anti-angiogenesis activity checked through - Wound healing by Scratch assay, Western blotting, Membrane perturbation (probed by DSC), Molecular docking for VEGFR2 AND VEGF	a. All results showed promise for Luteolin and derivatives derivatives as antiangiogenic agents.	[190]
			Phosphatidylinositol 3'-Kinase and Lipid Kinase activity Assay, Immunoprecipitation, Kinase Assay, and Evaluation of the Phosphorylation Status of VEGFR-2, Evaluation of Akt, ERK1/2, p70 S6 Kinase, and p38 Phosphorylation, Assays of Apoptosis, Evaluation of Proliferation, Indirect Immunofluorescence, Rabbit Corneal Neovascularization Assay, A-431 Murine Xenograft Model – all experimements were done to check antiangiogenic poteny.	a. Luteolin inhibited VEGF-induced proliferation of HUVECs along with their survival with an IC50 of about 5μmol/L. b. It also inhibited VEGF-induced phosphatidylinositol 3-kinase (PI3K) activity in HUVECs.	[191]
46.	Penduliflaworosin (Diterpinoid)	*Croton crassifolius*	Endogenous alkaline phosphatase (EAP) assay in Wild-type zebrafish *in vivo* model	a. This plant was screened for anti-angiogenic activity using a zebrafish *in vivo* model, where four of the known compounds were active, among them penduliflaworosin possessed best activity compared to the positive control.	[192]
47.	Extract of *Calliandra* *portoricensis* (CP)		Chick chorioallantoic membrane angiogenesis assay used to check antiangiogenesis.	a. Network of vessels in CAM significantly reduced by extract of *Calliandraportoricensis*, suggesting its antiangiogenic potential.	[193]
48.	Lectin		Studies like CAM assay, Cell migration assay, Molecular docking to explored to anti-angiogenesis.	a. Lectin has the capability to inhibit angiogenesis in *in vitro* models, but the potency has been found to be less than Luteolin.	[190]
49.	Lupeol		Among all only CAM assay, Cell migration assay, Molecular docking were performed to quantify the angiogenic potency.	a. Lupeol has the capability to inhibit angiogenesis in *in vitro* models (but the potency found less than Luteolin).	[190]
50.	Cyperenoic acid	*Croton* *crassifolius*	Quantitative EAP assay, Total RNA isolation, reverse transcription and real-time polymerase chain reaction (RT-PCR) were performed to estimste the antiangiogenic activity.	a. Cyperenoic acid has the capacity to inhibit angiogenesis which is shown through the zebrafish embryo model. b. The anti-angiogenic property without cytotoxicity provides a promise for its traditional use in cancer treatment.	[194]
51.	Cassaine (diterpene alkaloids)	*Erythrophleum fordii*	Tube formation assay and Proliferation of ECs by MTT were performed.	a. Among all compound 3 was found to have the most potent inhibitory effect on the capillary-like structure formation of HUVECs.	[195]
52.	Cucurbitacin-I		Proliferation of HUVECs, Lactate dehydrogenase (LDH) toxicity assay, Wound healing assay, Invasion assay by transwellchamber, Capillary tube formation assay, Rat aortic ring assay, Matrigel plug assay, Western blot	a. Cucurbitacin-I inhibited HUVEC proliferation, invasion, migration and tubule formation, as well as angiogenic activity by rat aorta explants. b. It also inhibited phosphorylation of VEGFR-2 along with FGFR-1. c. Studies corroborate that, cucurbitacin-I can inhibit various attributes of angiogenesis, which contribute to its antitumor effects.	[196]

53.	Syringic acid	cereals such as barley, maize, millet, oat, rice, rye, sorghum, and wheat and in plants like *Raphanus sativus* L.	Zebrafish maintenance and collection of embryos, Morphological observation, RBC staining, Total RNA extraction, reverse transcription, and real-time PCR, Western blot analysis	a. Findings suggest that syringic acid may have anti-angiogenic activity by downregulating VEGF mediated pathway thereby having potential therapeutic benefit and promises to be a weapon against cancer.	[197]
54.	Extract from Pleurotus tuber-regium (PTR)	Tiger milk mushroom	Lactate Dehydrogenase (LDH) Toxicity Assay, Wound-Healing Assay, Transwell Culture Insert Assay, Endothelial Tube Formation Assay, Measurement of Reactive Oxygen Species, RT-PCR Study for mRNA Expression, Quantitative Endogenous Alkaline Phosphatase Assay on Zebrafish Embryo, Microscopic Imaging.	a. Ethanolic extract (EE) showed strong antioxidant activity and could inhibit VEGF- HUVEC migration and tube formation dose dependently. b. It also inhibited the subintestinal vessel plexus (SIVs) formation in zebrafish embryos *in vivo*. c. Results suggested that EE of PTR could have the potential to inhibit angiogenesis effectively.	[198]
55.	Extracts of Portuguese propolis	*A. mellifera*	Cell viability and proliferation assays, Wound healing assay, Chicken Chorioallantoic Membrane (CAM) assay, Western blotting,	a. Ethanolic extract of the drug decreased cell viability of different tumour cells with significantly less cytotoxic against non-tumoural cells. b. It also decreased MDA- proliferation and migration of MB-231 and DU145 cell, with cell cycle changes as well as increased cell death.	[199] (2014)
56.	Extract of Annona atemoya (AA)		Cell viability, Cell migration assay, Tue formation assay, *In vivo* angiogenesis assay, luciferase reporter assay for Hypoxia-inducible factor (HIF), Immunoassay, Real-time polymerase chain reaction, Western blotting and Tumor-induced angiogenesis were performed to check anti-angiogenesis.	a. Angiogenic properties of HUVECs *in vitro* along with angiogenic factor-induced blood vessel formation *in vivo* were significantly inhibited by the ethanolic extract of the drug. b. It also down-regulated VEGF and HIF-1alpha/2alpha expression at the mRNA and protein levels, respectively, in cancer cells under hypoxic conditions.	[200]
57.	1,2,3,4,6-penta-O-galloyl-D-glucopyranose (PGG)	*Astronium graveolens* Jacq.	Antiangiogenic assay and ELISA assay were reported as the performed study.	a. The compound inhibited the interaction between placental growth factor (PlGF), a VEGF family member, as well as its receptor Flt-1 by more than 50% at 1 mg/mL concentration.	[201]
58.	Conjugated Docosahexaenoic Acid (CDHA)		Tue formation, Migration of BAEC in a wound-healing model, Fluorescence dye staining analysis, DNA Fragment assay, *In vivo* study of angiogenesis inhibition by CDHA were carried out.	a. The vessel formation in mice, triggered by tumor cells was suppressed by orally given the compound-CDHA. b. Findings further suggested, for minimizing tumor angiogenesis CDHA has potential use as a therapeutic dietary supplement.	[202]
59.	Mangosteen pericarp ethanolic extract	*Garcinia mangostana* Linn	H_2O_2 Masurement by Colorimetric Hydrogen peroxide kit, Measurement of HIF-1α, NF-κB and iNOS by immunoflurescense, Angiogenesis vasa vasorum measurement.	a. Ethanolic extract of Mangosteen pericarp had a significant effect (*P*=0.05) in decreasing vasa vasorum angiogenesis due to H2O2, HIF-1α, NF-κB, and iNOS inhibition in hypercholesterol-diet-given to rats.	[203]

60.	Raddeanin A (RA)	*Anemone raddeana*	Cell viability assay, Endothelial cell motility assay, Endothelial cell wound healing assay, Endothelial cell transwell migration assay, Endothelial cell tube formation assay, Chick embryo CAM assay, Zebrafish angiogenesis study, Anticancer therapy of RA in subcutaneous HCT-15 xenograft in mice, Western blot assay, Molecular docking	a. Raddeanin A significantly inhibited proliferation, motility, migration, and tube formation in human umbilical vein endothelial cell (HUVEC). b. It also dramatically decreased angiogenesis in chick embryo chorioallantoic membrane (CAM), rescrusted the trunk angiogenesis in zebrafish, as well as suppressed angiogenesis and human HCT-15 colorectal cancer growth in mice xenograft.	[204]
61.	Flavonoids from *Melia azedarach*	*Melia azedarach* L. (Meliaceae)	CAM assay	a. leaf extract of drug reported to have strong anti-angiogenic activities in *in vitro* CAM assay.	[205]
62.	Low molecular weight hyaluronic acid		Chicken chorioallantoic membrane assay	a. Low molecular weight hyaluronic acid (LMWHA) as well as hyaluronic acid (HA) suppressed angiogenesis in chicken embryos. b. LMWHA-1 showed higher anti-angiogenesis activity than LMWHA-2 and HA. c. Results suggested that LMWHA would have potential natural immunomodulatory effect along with a potential activity against anti-angiogenesis.	[206]
63.	(S)-curvularin	*Penicillium sp.*	Reporter gene assays, Electrophoretic mobility shift assay (EMSA), Immunoprecipitation and western blot analysis, Real-time quantitative PCR with light cycler system, Assay for vasculogenic mimicry, Proteome profiler, Chromatin Immunoprecipitation (ChIP) assay	a. (S)-curvularin isolated from the fungus strongly decreased the formation of capillary-like tubules in MDA-MB-231 cells on Matrigel.	[207]
64.	Dehydrocurvularin	*Penicillium sp.*	Reporter gene assays, Electrophoretic mobility shift assay (EMSA), Immunoprecipitation and western blot analysis, Real-time quantitative PCR with light cycler system, Assay for vasculogenic mimicry, Proteome profiler, Chromatin Immunoprecipitation (ChIP) assay,	a. This fungal lactone exhibited potency to reduce the capillary-like structure formation in MDA-MB-231 cells on Matrigel.	[207]
65.	Oxacyclododecindione	*Penicillium sp.*	The fungal lactones strongly decreased the formation of capillary-like tubules of MDA-MB-231 cells on Matrigel.	a. Capillary-like tubules formation in MDA-MB-231 cells on Matrigel was inhibited significantly by Oxacyclododecindione and subsequently the whole angiogenesis process.	[207]
66.	Galiellalactone	*Penicillium sp.*	Reporter gene assays, Electrophoretic mobility shift assay (EMSA), Immunoprecipitation and western blot analysis, Real-time quantitative PCR with light cycler system, Assay for vasculogenic mimicry, Proteome profiler, Chromatin Immunoprecipitation (ChIP) assay,	a. Galiellalactonestrongly inhibited angiogenesis by preventing the Matrigel tube formation *in vitro.*	[207]

67.	Sanguinarine	*Sanguinaria canadensis*	Tube formation assay, Assay of VEGF secretion, Migration assay, Northan blot analysis, Assay of luciferase reporter activity,	a. Sanguinarine markedly repressed the VEGF-induced tube formation in human microvascular endothelial cells (HMVECs) also the migration of human A549 lung cancer cells. b. Sanguinarine decreased both secretion as well as expression of VEGF in HMVECs and A549 lung cancer cells in a dose- and timedependently.	[208]
		Chelidonium majus, Macleaya cordata, and *Sanguinaria canadensis* L	Angiogenesis Assay (Matrigel assay)	a. Sanguinarine reduced the tumor burden in B16 melanoma 4A5 in C57BL/6 mice model, and also showed the same effect in A375 human melanoma in athymic nude mice. b. Sanguinarine also showed a shrinking of angiogenic activity in mice.	[209]
		Sanguinaria canadensis	Assays for migration, sprouting, apoptosis, and DNA synthesis, *In vivo* blood vessel formation, Biochemical analyses	a. Sanguinarine markedly suppressed VEGF-induced endothelial cell migration, sprouting, and survival *in vitro* in a dose-dependent manner at nanomolar concentrations. b. Sanguinarine potently suppressed blood vessel formation *in vivo* in mouse Matrigel plugs and the chorioallantoic membrane of chick embryos.	[210]
68.	Tocotrienol Derivatives	*Garcinia amplexicaulis*	Cell Viability Assay, *In vitro* Capillary Network Formation assay, Adhesion Assay on HUVECs and Migration Assay on HUVECs were performed to check anti angiogenic activity.	a. Isolated two compound, **δ-**amplexichromanol and γ-amplexichromanol, were evaluated on VEGF-induced angiogenesis using a Matrigel assay. b. Both the compounds inhibited angiogenesis of VEGF-induced human primary endothelial cells *in vitro.* c. δ-amplexichromanol also blocked adhesion and migration processes.	[211]
69.	Caged Polyprenylated Xanthones	*Garcinia hanburyi*	Proliferation of the HUVECs, Antiangiogenic Activity Assay on Blood Vessel Formation in Zebrafish Embryos, HUVEC Wound Migration Assay	a. Among 11caged polyprenylated xanthones Xanthone 7 exhibited antiangiogenic activity without any toxicity at a concentrations range of 8 μM-16 μM. b. xanthones 1, 3, 7 and 9 strongly inhibited the migration of HUVEC at alow concentration of 0.5 μM in HUVEC cell migration assay *in vitro*. c. It also suggested that xanthone 7 would be a novel angiogenesis inhibitor.	[212]
70.	Arenobufagin	Toad venom of *Bufo bufo gargarizans*	Cell counting kit (CCK)-8 assay, migration assay, Invasion assay, Tube formation assay of HUVECs, Aortic ring assay, Matrigel plug assay, Western blotting, Molecular modelling, Co-immunoprecipitation (Co-IP) were carried out to confirm the antiangiogenic activity.	a. Arenobufagin is a specific inhibitor of VEGF-mediated angiogenesis. b. Arenobufagin interacted with the ATP-binding sites of VEGFR-2 by docking suggested by computer simulations. c. It also inhibited VEGF-induced VEGFR-2 auto-phosphorylation as well as suppressed the activity of VEGFR-2-mediated signaling cascades.	[213]

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71.	Matairesinol	*Cedrus* *deodara* (Roxb.)	Cell growth and viability assay, mROS levels measurement, *In vitro* capillary tube formation assay, *In vitro* chemo invasion assay, CAM assay, Measurement of VEGF by enzyme-linked immunosorbent assay, Western blot analysis	a. Matairesinol functioned as a novel angiogenesis inhibitor by interfering in mROS signalling.	[214]
72.	Bavachinin	Dried seeds of *Psoralea corylifolia*	Tube formation and proliferation assays, *In vitro* migration assay and Immunohistochemical (IHC) staining were carried out for angiogenic parameters.	a. Bavachinin decreased genes expression which are associated with angiogenesis and energy metabolism that regulated by HIF-1 like vascular endothelial growth factors (VEGF), Glut1 and Hexokinase2. b. It also inhibited tube formation in human umbilical vein endothelial cells and *in vitro* migration of KB cells. c. Bavachinin significantly reduced tumor volume as well as CD31 expression in nude mice with KB xenografts after weekly thrice treatment.	[215]
73.	Tuber extracts of *Vernonia* *guineensis* Benth.		Antiangiogenic assay methods were performed as described by the authors.	*a. Vernonia guineensis* Benth. extracts as well as isolated compounds were found to be effective in anti-angiogenic treatment.	[216]
74.	Ellagic acid		Cell counting assay, BrdU incorporation assay, Lactate dehydrogenase assay, Wound-healing assay, Invasive assay, Tube formation assay, Kinase activity detection, Western blotting, Gelatin zymography, Measurement of reactive oxygen species, Chick aortic ring models, CAM assay, Xenograft models and immunohistochemistry detections and Molecular docking	a. Ellagic acid significantly inhibited a series of VEGF induced angiogenesis including proliferation, migration, and tube formation of endothelial cells. b. VEGFR-2 tyrosine kinase activity as well as its downstream signaling pathways including MAPK and PI3K/Akt in endothelial cells were also inhibited by Ellagic acid.	[217]
75.	Essential oil of Nutmeg	*Myristica fragrans*	Rat aortic ring assay	a. The antiangiogenic activity of nutmeg oil showed significant antiangiogenic activity with IC50 of 77.64 ug/mL.	[218]
76.	Essential oil of Mengkudu	*Morinda citrifolia*	Rat aortic ring assay	a. The antiangiogenic activity mengkudu oil showed significant antiangiogenic activity with IC50 of 109.30 ug/mL.	[218]
77.	Fisetin		Cell growth and death assays, FACS analysis for cell cycle distribution, Reverse transcriptase and PCR, immunoblot analysis, angiogenesis assay on matrigel and wound healing assay, *In vivo* angiogenesis assay were the impotent experiments associated angiogenesis.	a. Fisetin inhibited various attributes of angiogenesis, supporting its antitumor effects. b. Fisetin warrants further investigated for its angiopreventive activity toward cancer control.	[219]

78.	Rhein	*Cassia Alata*L. (Fabaceae)	Proliferation assay of endothelial cell, Endothelial cell migration and invasion assay, tube formation assay, estimation of VEGF165, EGF, and HIF-1a levels in MCF-7 or MDA-MB-435s were performed for antiangiogenesis.	a. Rhein inhibited vascular endothelial growth factor (VEGF165)-stimulated tube formation, proliferation and migration of HUVECs under both normoxic and hypoxic conditions. b. Also, Rhein inhibited *in vitro* angiogenesis through suppression of the activation of phosphatidylinositol 3-kinase (PI3K), phosphorylated-AKT (p-AKT) and phosphorylated extracellular signal-regulated kinase (p-ERK).	[220]
		Rhizomarhei	For the determination of antiangiogenic activity these experiments were done-Total RNA isolation, reverse transcription, semi-quantitative polymerase chain reaction (PCR), MTT assay, Methyl-3H]-thymidine incorporation assay, *In vitro* migration and *In vitro* network formation assay.	a. Rhein almost completely blocked intersegmental blood vessels formation at both 48 and 72 hpf at 20μM. b. It also inhibited subintestinal vessel plexus formation at 72 hpf at same concentration. c. Rhein disrupted multiple molecular targets related to angiogenesis like - angpt2 and tie2 in particular and also inhibited endothelial cell migration.	[221]
79.	Koetjapic acid(KA)	*Sandoricum Koetjaoe* Merr	Cell Proliferation Assay, Rat Aortic Ring Assay, Migration Assay, CAM Assay and Tube Formation Assay were performed.	a. Koetjapic acid inhibited major angiogenesis process steps, endothelial cell migration and differentiation as well as VEGF expression.	[222]
80.	Ageladine A and Analogues		MMP Inhibition Assays and Angiogenesis Assay were the major experiments done for angiogenic parameters etc. Studies are carried out.	a. One compound among the analogues showed significant kinase activity along with little MMP inhibitory activity. b. It was also found to be very effective in an anti-angiogenic screen.	[223]
81.	Betulinic Acid (BA)	Bark of white birch *Betula pubescens*	To determine the antiangiogenic activity Cytotoxicity assay, Western blot analysis, HIF-1a transcription activity assay, Immunocytochemistry, Electrophoretic mobility shift assay (EMSA), tube formation assay, (ELISA) for VEGF, Chromatin immunoprecipitation (ChiP) assay and siRNA trasnfection	a. Betulinic Acid showed anti-angiogenic activity by disturbing the binding of HIF-1a and STAT3 to the VEGF promoter in PC-3 cells in hypoxic condition.	[224]
		Dry bark of *Betula pendula* Roth (birch tree)	CAM Assay, Morphological and Immunohistochemical investigations, Evaluation of the Angiogenesis Process were performed	a. Betulinic acid does possess anti-angiogenic activity in a dose dependent manner, and the nanoemulsion formulation maintained this effect.	[225]
		Bark of white birch *Betula pubescens*	Cytotoxicity assay of endothelial cells and Tube-like structure (TLS) formation assay in same cell line were performed.	a. Betulinic acid significantly imperted cytotoxicity to endothelial cell line ECV304 with an IC50 value of 1.26 ±0.44 lg/mL in a 5-day MTT assay. b. New derivatives of BA have been synthesized having IC50 less than 0.4 lg/mL.Specificity for the endothelial cell against human tumor cell lines DU145, L132, A549, and PA-1 were also determined.	[226]

82.	Nitidine Chloride	*Zanthoxylum nitidum*	Cell viability assay, migration assay, capillary-like tube formation assay in ECs, Matrigel plug assay, Mouse corneal micropocket assay, Immunofluorescence assay Live/dead staining assay, Annexin V/propidium iodide staining assay, , Western blot analysis, RNA isolation and reverse transcriptase PCR, Electrophoretic mobility shift assay, Chromatin immunoprecipitation assay, Gastric tumor xenograft mouse model, Histology and immunohistochemistry	a. Nitidine chloride suppressed VEGF induced endothelial cell proliferation, migration, and tubular structure formation *in vitro* dose dependently. b. It also dramatically reduced VEGF-triggered angiogenesis in mouse cornea and Matrigel plugs *in vivo*.	[227]
83.	Carnosol and carnosic acid	*Rosmarinus officinalis*	Cell growth assay, Apoptosis assays, Tube formation on Matrigel by endothelial cells, Endothelial cell migration assay, Gelatinolytic assay, *In vivo* chorioallantoic membrane assay, *In vitro* VEGFR2 kinase inhibition assay,	a. Angiogenic activities of endothelial cells like differentiation, proliferation, migration and proteolytic capability were reduced by both the mentiond diterpines, which was substantial to make them a good candidate for antiangiogenic therapy.	[228]
84.	GA-13315, a gibberellin derivative		Quantification of tumor micro vessels after xenograft of A549 cellson ALB/c mice Cell migration assay Tube formation assay Detection of VEGF by biotin streptovidin method	a. GA-13315 inhibited chemotactic motility and capillary-like tube formation of human endothelial cells which was induced by recombinant human epithelial growth factor. b. GA-13315 decreased the factor VIII+ microvessel density and the expression of VEGF in A549 tumors, establishing its antiangiogenic potency *in vivo.*	[229]
85.	Celastrol	*Trypterygiumwilfordii* Hook F. (Thunder of God Vine)	Human prostate tumor xenograft mouse model, Histology and immunohistochemistry, Wound-healing migration assay, Transwell migration assay, Capillary-like tube formation assay, Cell viability assay, Rat aortic ring assay, Matrigel plug assay Western immunoblot analysis	a. Celastrol (2 mg/kg/d) significantly reduced the volume and the weight of solid tumorswith decreased tumor angiogenesis. b. This agent also inhibited proliferation, migration, invasion, and capillary tubule formation in HUVECs induced by VEGF, in a dose-dependently manner.	[230]
		Tripterygium wilfordii	Inhibition of cell growth, Cell migration assay, Angiogenesis assay, *In vivo* Matrigel plug assay, Chick chorioallantoic membrane (CAM) model of Angiogenesis, Antitumor experiments, Determination of MVD, Immunohistochemistry,	a. Celastrol inhibited the proliferation of vascular endothelial cells with an IC50 value of 1.33 μg/ml. b. Celastrol, at the concentration of 0.2 μg/ml, significantly inhibited cell migration and tube formation. c. Celastrol inhibited angiogenesis in a dose-dependent manner both *in vitro* and *in vivo.*	[231]
		Tripterygium wilfordii (Thunder God Vines)	RNA isolation, cDNA synthesis and quantitative realtime RT-PCR procedure, Anti-tumor experiments, Determination of MVD, Immunohistochemistry,	a. Celastrol have potential to be used as an anti-angiogenesis drug through its role in suppressing VEGF receptors expression that might consequently reduce the signal transduction between VEGF and VEGFR.	[232]

86.	Ursolic Acid	Chinese herb, *Souyang*	Tumor-Specific Capillary Formation, Rat Aortic Ring Assay, Serum VEGF, TIMP-1, IL-2 and Proinflammatory Cytokine Levels During Angiogenesis, Serum Nitrite Levels During Angiogenesis, MTT Assay, Endothelial Cell Proliferation, Endothelial Cell Migration/Motility, Endothelial Cell Invasion, Gelatin Zymography, Expression of VEGF in B16F-10 Melanoma Cells, Expression of iNOS and GAPDH	a. Ursolic acid inhibited capillary formation in C57BL/6 mice induced by highly metastatic B16F-10 melanoma cells. b. It reduced the expression of VEGF, NO, and proinflammatory cytokines significantly reduced in treated animals compared with those in control animals. c. Ursolic acid also significantly inhibited endothelial cell migration and invasion along with the expression of Matrix metalloproteinases MMP-2 and MMP-9.	[233]
			In vivo chorioallantoic membrane assay, Cell growth assay, Endothelial cell migration assay, Endothelial cell invasion assay, Endothelial cell differentiation assay, Zymographies	a. Ursolic acid is able to inhibit importent steps of angiogenesis including endothelial cell proliferation, migration, and differentiation of endothelial cells. b. stimulated other key steps of angiogenesis, like- extracellular matrix degradation by MMP-2 and urokinase.	[234]
87.	Cucurbitacin E	*Cucubita pepo cv Dayangua*	Migration and capillary-like structure formation (tubulogenesis) assay, CAM assay, Mouse corneal micropocket assay, Xenograft tumor growth assay and immunohistochemistry, Proliferation assay and cell apoptosis analysis, Western immunoblotting, Chromatin immunoprecipitation assay	a. Cucurbitacin E inhibited VEGFR2-mediated Jak–STAT3 and mitogen-activated protein kinases signaling pathways and subsequent angiogenesis process. Results suggested it a potential candidate in the treatment of angiogenesis-related disease.	[235]
88.	**β**-escinoraescin	Seeds of *Aesculus hippocastanum* (horse chestnut)	Western blotting, Immunocytochemistry for STAT3 localization, STAT3 luciferase reporter assay,	**a.** **β**-escinblocked of STAT3 activation, which have a potential in suppression of proliferation and chemosensitization in HCC. Results showed its antiangiogenic potency *in vitro.*	[236]
89.	Sesamin	*Sesamum indicum*	Electrophoretic mobility shift assay, Western blot analysis, IKK assay, Immunocytochemical analysis for NF-κB p65 localization, NF-**κ**B–dependent reporter gene expression assay, Cell proliferation assay, Live/Dead assay,	a. Sesaminincreased expression of TNF-**α**-induced apoptosis, which assocated with suppression of gene products linked to cell survival like- Bcl-2 and survivin, proliferation like- cyclin D, inflammation like- cyclooxygenase-2, invasion like- matrixmetalloproteinase-9 and intercellular adhesion molecule 1, and angiogenesis like; VEGF. Hence the compound proved itself as a potent antiangiogenic agent.	[237]
90.	Terpestacin	*Embellisiachlamydo spora*	*In Vivo* Breast Cancer Xenograft Model Study, Immunohistochemistry, VEGF-Enzyme-linked Immunosorbent Assay, Molecular Cloning, Expression, and Purification of Human UQCRB, Surface Plasmon Resonance (SPR) Analysis, Docking Simulation, Transcriptional Profiling, Measurement of Mitochondrial Membrane Potential, Measurement of Mitochondrial Oxygen Consumption, Western Blot Analysis, Measurement of ROS, Overexpression and RNA Interference Studies of UQCRB, *In Vitro* Invasion and Angiogenesis Assays,	a. Terpestacin inhibited hypoxia-induced reactive oxygen species generation by binding to the 13.4-kDa subunit (UQCRB) of mitochondrial Complex III. b. Finally, such inhibition blocks hypoxia-inducible factor activation as well as tumor angiogenesis *in vivo*, without inhibiting mitochondrial respiration.	[238]

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91.	Pterogynidine alkaloid (Pt)	*Alchornea glandulosa*	MTT assay, BrdU Proliferation Assay, Tunel assay, Invasion assay, Matrigel assay – Tube Formation Index, NF-κB activity	a. Pterogynidine alkaloid decreased the proliferation and invasion capacity of endothelial cells and an effective increase in apoptosis as assessed by bromodeoxyuridine (BrdU) significantly. b. It also decreased the number of capillary-like structures formation in HUVEC were cultured on growth factor reduced-Matrigel. c. Additionally, incubation of HUVEC with the compound resulted in reduced NF-κB activity.	[239]
92.	Leucosesterterpenone	*Leucosceptrumcanum*	Cell proliferation studies, Chemotaxis assay, Endothelial cell migration in wound healing, Cell differentiation and invasion assays in Matrigel, Binding assay, Western blot, Chick chorioallantoic assay	a. Leucosesterterpenone inhibited proliferation, migration in a wounding assay, chemotaxis and tube formation in endothelial cells induced by FGF-2.	[240]
93.	Leucosterlactone	*Leucosceptrumcanum*	Cell proliferation studies, Chemotaxis assay, Endothelial cell migration by wound healing assay, differentiation and invasion of endothelial cell in Matrigel, Binding assay, Western blot, Chick chorioallantoic assay were the major experiments.	b. Leucosterlactone shown the significant antiangiogenic activity in an *in vivo* model in CAM assay. But unfortunately, it remains inactive in most of the *in vitro* assay.	[240]
94.	Deguelin		To check various angiogenic parameter following experiments were done - *In vivo* tumor model and immunohistochemical staining, Chick aortic arch assay and chorioallantoic membrane assay, Matrigel plug assay, Invasion assay, Tube formation and proliferation assays, Immunoblot assays, RT-PCR assay, Luciferase assays, Metabolic labeling	a. Oral administration of Deguelin inhibits tumor growth and blocks tumor angiogenesis in mice. b. Deguelin significantly decreased HIF-1a protein expression and its target genes like VEGF, in cancer cell lines, including H1299 lung cancer cells, and vascular endothelial cells in both condition normoxic and hypoxic.	[241]
95.	Curcumin (Cur)	*Curcuma longa*	Antiangiogenic potecy was checked by following assays like- *In vitro* study of anti-proliferation assay, Intravital fluorescence videomicroscopy study, capillary vascularity measurement,	a. Curcumin exhibited significant decrease in the Capillary Vascularity ($P < 0.005$). b. The anti-angiogenic effects of Curcumin were dose-dependent manner. It also showed 44.96% of capillary vascularity inhibition from the 21 d.	[242]
		Curcuma longa	Experiments performed - *In vivo* Antitumor Activity Curcumin in Human Colorectal Tumor Xenografts in Nude Mice Models, Histologic Sections, Immunohistochemistry for Angiogenesis	a. Liposomal Curcumin treatment showed an anti-angiogenic effect, including suppression of CD31 (an endothelial marker) as well as vascular endothelial growth factor, and interleukin-8 expression by immunohistochemistry.	[243]
		Curcuma longa	Western blotting, Reverse transcription-polymerase chain reaction, Transient transfection and luciferase assay, Tube formation assay, Wound healing for migration assay and Chemoinvasion assay	a. Curcumin significantly decreased hypoxia-induced HIF-1 protein levels and suppressed the transcriptional activity of HIF-1 under hypoxia in HepG2 hepatocellular carcinoma cells, leading to a decrease in the expression of vascular endothelial growth factor (VEGF) factor. b. Curcumin also inhibits hypoxia-stimulated angiogenesis in *in vitro* conditions and down-regulated HIF-1 and VEGF expression in vascular endothelial cells, which would abrogate the angiogenesis process.	[244]

96.	Tetrahydrocurcumin (THC)	*Curcuma longa*	Intravital fluorescence videomicroscopy study, Measurement of capillary vascularity and *In vitro* study of anti-proliferation assay.	a. Capillary vascularity was significantly decrease by Tetrahydrocurcumin and it showed anti-angiogenic activity in a dose-dependent manner. b. It was also observed, that Tetrahydrocurcumin was more effective than curcumin when the other parameters remain same as the capillary vascularity inhibition values were 52.86% and 44.96% ($P < 0.05$) after 21-day treatment.	[242]
97.	Hyperforin	*Hypericum perforatum*	*In vivo* CAM assay, ECs growth assay, ECs viability assay, Tube formation by endothelial cells on Matrigel, Zymographies, MMP-9 activity assay, Endothelial cell migration assay and Endothelial cell invasion assay	a. Hyperforin inhibited the growth of endothelial cells in culture. b. Capillary tube formation on Matrigel was blocked completely by Hyperforin at the low concentration. c. It also exhibited an inhibitory effect on the endothelial cell's invasion.	[245]

Expert Opinion on the Recent Perspectives on Cancer Management

It has been observed that the growth and progression of cancerous tumours beyond a certain size require pathogenic angiogenesis, and therefore angiogenesis inhibition can prove to be an effective strategy in cancer management [246,247]. Typically, the focus on cancer management by angiogenesis inhibition in the recent past has been to develop inhibitors against its stimulant molecules like VEGFR-2, protease inhibitors, etc. [248, 249]. This further with angiogenesis imaging procedures aiding in tumour vasculature characterisation, identification of various biomarkers with the potential to diagnose cancer and even identify patients likely to benefit as well as those with the possibility to develop resistance and/or adverse events from antiangiogenic treatment makes it a promising therapy [250,251]. There is an abundance of experimental phytopharmaceuticals inhibiting angiogenesis however, limited clinical effectivity and high toxicity call for further research in such area [252]. The review presents the physiology of angiogenesis, its stimulants at the molecular level which are basically molecular targets for drug development, mechanisms of angiogenesis, contribution to cancer progression, and a summary of numerous plant compounds/ extracts inhibiting vasculature development along with their families. While the schematic representation of compounds/ extracts having potential anti-vasculature activity together with methods for extraction and development will aid scientists in the timely selection of phytopharmaceuticals for further experimentation, the summarisation of the respective phytochemicals with the plant source/ family would help to trace the origin and provide further scope to identify new plants having potential vasculature development inhibitory activity. Overall, this review will assist in exploring phytopharmaceuticals targeted towards cancer treatment specifically inhibiting vasculature development.

Conclusion

Targeting the tumour vasculature instead of the tumour cells directly is of great interest for tumour management. With regards to this, the review scientifically explained the pathological angiogenesis mechanism responsible for cancer cell invasion and metastasis, and in a similar line, the experimentally proven phytopharmaceuticals having a significant effect inhibiting vasculature development have been represented schematically. Hopefully, this review will facilitate the biomedical scientists in setting up the appropriate research questions around the molecular targets explained here for the management of cancer cell invasion and migration. Therefore, further proof-of-concept validation studies for exploring such phytopharmaceuticals can be possible.

Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

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