RESEARCH PAPER

Dietary Natural Compounds as Anti-Angiogenic Agents in the Prevention and Adjuvant Management of Cancer:

A Comprehensive Mechanistic and Translational Review

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Abstract

Background: New blood vessels that sprout from existing ones (tumour angiogenesis) are indispensable if a dormant neoplastic focus is to become an expanding, invasive tumour capable of metastasis. Drugs that interrupt signalling through vascular endothelial growth factor (VEGF) are now standard in cancer care, but their benefit is often limited by intrinsic or acquired resistance, bypass activation of other pro-angiogenic routes, and toxicity that restricts dosing. Objective: To appraise the mechanistic and translational evidence for diet-derived and nutraceutical compounds as adjunctive or preventive anti-angiogenic agents in cancer. Methods: We carried out a structured narrative synthesis of laboratory, animal and human studies retrieved from Web of Science, Scopus and PubMed, concentrating on polyphenols, carotenoids, organosulfur compounds, isothiocyanates derived from glucosinolates, omega-3 polyunsaturated fatty acids, alkaloids and other phytochemicals. Results: Despite their chemical diversity, these compounds repeatedly converge on a small set of targets: VEGF/VEGFR2 signalling, hypoxia-inducible factor-1alpha (HIF-1alpha), the NF-kappaB (nuclear factor-kappa B), PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) and STAT3 (signal transducer and activator of transcription 3) cascades, matrix metalloproteinase expression, and endothelial cell survival and cycle progression. Preclinical studies consistently show lower microvessel density and smaller tumours. Early-phase studies of green tea catechins, curcumin and resveratrol indicate acceptable safety and shifts in relevant biomarkers, but data on hard clinical endpoints are scarce. Most candidates are limited by low aqueous solubility and extensive first-pass metabolism; nanoformulations (for example liposomes, micelles, and polymer- or lipid-based nanoparticles) measurably improve systemic exposure and delivery to tumours. Conclusion: Anti-angiogenic phytochemicals from the diet form a mechanistically varied and generally well-tolerated supplement to standard oncology care. Before routine clinical use, larger controlled trials, harmonised dosing and bioavailability-enhanced formulations will be required.

Keywords: Angiogenesis; Vascular endothelial growth factor; Dietary polyphenols; Cancer chemoprevention; Nutraceuticals; Tumour microenvironment

How to cite this article: Abdul Ahad Negaban1 Souhardya Roy Chowdhury2 Subhadip Kundu3 Raisa Islam4 Mandal Suprabha Pritiranjan5 Lopamudra Saha6 Prapti Chakraborty7*. Dietary Natural Compounds as Anti-Angiogenic Agents in the Prevention and Adjuvant Management of Cancer:. Int J Drug Deliv Technol. 2026;16(90s):2025-2041. DOI: 10.25258/ijddt.16.90s.203.

1. Introduction

Cancer remains a leading cause of death and disability worldwide. According to the Global Cancer Observatory (GLOBOCAN), about 20.0 million people were newly diagnosed with cancer and 9.7 million died of it in 2022, with lung and female breast cancers together accounting for roughly a quarter of new diagnoses [1,2]. The disease is responsible for nearly one in six deaths globally and ranks among the principal causes of premature death (ages 30–69) in most countries surveyed [1]. Beyond mortality and morbidity, cancer carries economic and social costs that differ by tumour type, region and sex; for instance, cancer deaths among mothers left close to one million children without a mother in 2020, with about half of this loss attributable to breast and cervical cancers [1]. Despite considerable therapeutic progress over the past three decades, five-year survival for many solid tumours is still unsatisfactory, which keeps interest in new treatment and prevention strategies high [3].

Angiogenesis is a biologically central yet pharmacologically tractable process that sustains the growth of solid tumours. Folkman proposed in 1971 that tumours larger than a few cubic millimetres cannot expand unless they recruit their own blood

supply, and this idea has since proved among the most productive in cancer research [4]. Hanahan and Weinberg later listed the induction of angiogenesis among the defining hallmarks of cancer, alongside sustained proliferative signalling, evasion of growth suppressors, resistance to cell death, unlimited replicative potential, and invasion and metastasis [5,6]. The "angiogenic switch", in which a dormant, avascular micro-lesion becomes a vascularised, expanding mass, is now known to occur early in tumorigenesis, frequently during dysplasia, and reflects a shift in the balance between pro-angiogenic factors (VEGF, FGF, PDGF) and natural inhibitors such as thrombospondin-1, endostatin and angiostatin [7,8].

Pharmacological targeting of tumour angiogenesis has produced an established drug class, led by the anti-VEGF monoclonal antibody bevacizumab and a set of small-molecule receptor tyrosine kinase inhibitors that includes sunitinib, sorafenib and pazopanib [9]. Their use in practice, however, has exposed important disadvantages: intrinsic or acquired resistance through compensatory angiogenic routes, tumours that grow without forming new vessels, and adverse effects such as hypertension, proteinuria, impaired wound healing and severe skin toxicity, the last reported in up to 90% of treated patients [10,11,12]. These constraints, together with the low toxicity generally associated with plant-derived compounds, have renewed interest in using such compounds to modulate pro-angiogenic signalling as adjuncts to existing cancer therapy, rather than as stand-alone alternatives [13,14].

Evidence on the bioactivity of dietary phytochemicals, among them polyphenols, carotenoids, organosulfur compounds, isothiocyanates, omega-3 fatty acids and related alkaloids, is growing quickly. It indicates that these molecules can interfere at many points of the angiogenic cascade, from transcription of the VEGF gene to endothelial tube morphogenesis [15,16]. Epidemiological data point the same way: large prospective cohorts consistently link diets rich in fruit, vegetables, legumes and marine omega-3 fatty acids, as in the Mediterranean dietary pattern, with a lower incidence of several solid tumours [17,18,19]. Here we offer an updated, mechanism-oriented overview of the anti-angiogenic actions of food-derived natural compounds, place the findings in the context of tumour angiogenesis biology, outline nanotechnology-based strategies for improving bioavailability, and critically assess how well preclinical results have carried over into early-phase clinical trials.

2. Literature Search and Synthesis Methods

This narrative review drew on peer-reviewed publications retrieved from PubMed/MEDLINE, Scopus and the Web of Science Core Collection, supplemented by hand searching of the reference lists of key reviews and supplementary materials. Search strings paired individual compound names with 'angiogenesis' or 'VEGF' and with cancer-related terms such as 'tumour', 'carcinoma' and 'chemoprevention'. English-language articles reporting in vitro, in vivo or clinical data on the anti-angiogenic mechanisms of dietary compounds were given priority, as were papers describing the molecular biology of tumour angiogenesis and cohort studies relating dietary patterns to cancer risk. Non-peer-reviewed sources, publications in other languages, and studies lacking mechanistic or outcome data on angiogenesis were excluded. Because the field is broad and study designs vary widely (cell-based assays, xenograft models, cohort studies and early-phase trials), a narrative approach was judged more suitable than a formal systematic review or meta-analysis, as is customary for wide-ranging mechanistic reviews of this kind.

3. Molecular Biology of Tumour Angiogenesis

3.1 Physiological versus Pathological Angiogenesis

Angiogenesis is a tightly regulated, multistep process: the basement membrane around endothelial cells of existing capillaries is degraded, the cells migrate along a chemotactic gradient, and they then proliferate and reorganise into patent, perfused tubes [14]. Under normal conditions the process is brief and self-limiting, occurring in embryonic development, the female reproductive cycle and wound repair, after which the vasculature returns to quiescence [6]. In solid tumours, and in diseases such as diabetic retinopathy, psoriasis and rheumatoid arthritis, angiogenesis stays persistently active and yields vessels with abnormal structure and function, including irregular calibre, leakiness and loss of pericyte coverage [20,21]. Such a disorganised vascular network impedes drug delivery [21], raises interstitial pressure, and creates hypoxic niches that further drive angiogenic signalling and favour the selection of more aggressive, treatment-resistant clones [21].

3.2 Key Signalling Pathways Governing Tumour Angiogenesis

VEGF/VEGFR signalling governs both physiological and pathological angiogenesis. Hypoxia, oncogene activation and inflammatory cytokines converge on hypoxia-inducible factor-1alpha (HIF-1alpha), which drives transcription of vascular endothelial growth factor-A (VEGF-A) in tumour and stromal cells [22,23]. Secreted VEGF-A engages VEGFR2 and triggers receptor dimerisation and autophosphorylation. Downstream lie the PI3K/Akt/mTOR, RAS/RAF/MEK/ERK (MAPK) and phospholipase C-gamma/protein kinase C pathways, which regulate endothelial proliferation, migration, survival and vascular permeability [23,24].

Other pro-angiogenic inputs include the fibroblast growth factor (FGF/FGFR), platelet-derived growth factor (PDGF/PDGFR), Delta-like ligand 4/Notch (Dll4/Notch) and angiopoietin/Tie2 systems. These pathways partly overlap and can compensate for one another, and they are increasingly implicated in resistance to VEGF-directed therapy [21,25]. Matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, remodel the extracellular matrix so that endothelial sprouts can invade, and they release matrix-bound VEGF, thereby coupling proteolysis to the angiogenic switch [8]. Table 1 summarises the main molecular drivers of tumour angiogenesis and their roles.

Table 1. Principal molecular drivers of tumour angiogenesis.

Factor / Pathway	Principal Source / Trigger	Receptor(s)	Key Downstream Effectors	Functional Role
VEGF-A / VEGFR2	Hypoxia (HIF-1α), oncogene activation, inflammatory cytokines	VEGFR2 (KDR/Flk-1)	PI3K/Akt/mTOR; RAS/RAF/MEK/ERK; PLCγ/PKC	Drives endothelial proliferation, migration, survival and vascular permeability
FGF / FGFR	Tumour and stromal cells	FGFR 1-4	RAS/MAPK; PI3K/Akt	Promotes endothelial sprouting; can compensate for VEGF blockade
PDGF / PDGFR	Endothelial and tumour cells	PDGFR-α/β	MAPK; PI3K/Akt	Recruits pericytes; supports vessel maturation and stability
Dll4 / Notch	Tip-cell endothelium	Notch 1/4	Notch intracellular domain (NICD)-dependent transcription	Determines tip versus stalk cell fate; controls sprout branching
Angiopoietin-2 / Tie2	Activated endothelium	Tie2	PI3K/Akt	Destabilises vessels; pro- or anti-angiogenic depending on context
MMP-2 / MMP-9	Endothelial cells, macrophages	None (proteases)	ECM degradation; release of matrix-bound VEGF	Remodel the basement membrane and permit sprout invasion
HIF-1α	Intratumoural hypoxia	None (transcription factor)	Induces VEGF, GLUT1 and MMP genes	Master transcriptional regulator of the angiog

Factor / Pathway	Principal Source / Trigger	Receptor(s)	Key Downstream Effectors	Functional Role
				enic switch

3.3 Endogenous Regulation and the Angiogenic Switch

In healthy tissue, pro-angiogenic signals are held in check by endogenous inhibitors such as thrombospondin-1, endostatin, angiostatin and tissue inhibitors of metalloproteinases (TIMPs). Loss of these inhibitors, combined with activation of oncogenes (RAS, MYC) and inactivation of tumour suppressors (p53, VHL), tips the balance towards a pro-angiogenic state, the 'angiogenic switch' [7,26]. The switch coincides with clinically silent premalignant tissue changes, so angiogenesis is now regarded not merely as a late consequence of tumour growth but as an early, rate-limiting step in malignant transformation. This view supports the use of anti-angiogenic agents for chemoprevention as well as for treatment [6,27].

4. Shortcomings of Current Anti-Angiogenic Drug Therapy

In 2004 the U.S. Food and Drug Administration (FDA) approved bevacizumab for metastatic colorectal cancer, making it the first clinically validated anti-angiogenic biologic; its indications were later extended, in combination with cytotoxic chemotherapy, to non-small-cell lung, renal cell, ovarian and cervical cancers [9,28]. Alongside the VEGF-trap aflibercept and the anti-VEGFR2 antibody ramucirumab, multi-targeted tyrosine kinase inhibitors (TKIs), namely sunitinib, sorafenib, pazopanib, axitinib and cabozantinib, have broadened the anti-angiogenic arsenal to renal cell, hepatocellular and gastric malignancies [9,29]. Nonetheless, several inherent limitations restrict what can be achieved by targeting VEGF pharmacologically. The approved agents and their principal drawbacks are listed in Table 2.

First, resistance is widespread, whether intrinsic or acquired during prolonged treatment. It involves compensatory upregulation of alternative pro-angiogenic ligands (FGF2, PDGF, angiopoietin-2), recruitment of bone marrow-derived vasculogenic cells, and VEGF-independent modes of tumour vascularisation such as vessel co-option and vasculogenic mimicry [10,12,21]. Second, high doses of sunitinib and sorafenib have paradoxically promoted invasion and metastasis in preclinical models, an effect linked to treatment-induced hypoxia and/or epithelial–mesenchymal transition [12]. Third, toxicity is clinically significant: hypertension, proteinuria, thromboembolism, impaired wound healing, gastrointestinal perforation and typical skin reactions (hand–foot skin reaction, subungual splinter haemorrhages) affect a considerable proportion of patients and can necessitate dose reduction or discontinuation [11]. Finally, the cost of biologic and small-molecule anti-angiogenic therapy burdens many health systems and puts equitable access out of reach [14]. Together, these shortcomings justify further study of dietary compounds, which are inexpensive, of low toxicity, and potentially able to alter angiogenic signalling, whether as chemopreventive agents in high-risk individuals or as co-adjuvants that might permit lower doses of conventional anti-angiogenic drugs.

Table 2. FDA-approved anti-angiogenic drugs and their principal clinical limitations.

Drug (Class)	Molecular Target	Representative Approved Indications	Principal Limitations
Bevacizumab (humanised mAb)	VEGF-A ligand	Metastatic colorectal cancer, NSCLC, renal cell, ovarian and cervical cancer	High cost; hypertension, proteinuria, GI perforation, delayed wound healing [9]
Sunitinib (multi-target TKI)	VEGFR 1-3, PDGFR, c-KIT	Renal cell carcinoma, GIST, pancreatic neuroendocrine tumours	Acquired resistance, fatigue, cardiotoxicity, hand–foot skin reaction [11]
Sorafenib (multi-target TKI)	VEGFR 2/3, RAF, PDGFR	Hepatocellular, renal cell and thyroid carcinoma	Hepatotoxicity; skin toxicity reported in about 90% of patients [11]
Pazopanib (multi-target TKI)	VEGFR 1-3, PDGFR, c-KIT	Renal cell carcinoma, soft-tissue sarcoma	Hepatotoxicity, hypertension, diarrhoea [29]

Drug (Class)	Molecular Target	Representative Approved Indications	Principal Limitations
Aflibercept (VEGF-trap fusion protein)	VEGF-A, VEGF-B, PlGF	Metastatic colorectal cancer (with chemotherapy)	Haemorrhage, thromboembolism, high cost [9]
Ramucirumab (anti-VEGFR2 mAb)	VEGFR2	Gastric, colorectal, NSCLC, hepatocellular carcinoma	Hypertension, bleeding risk; resistance develops with long-term use [9]

5. Anti-Angiogenic Dietary Polyphenols

Polyphenols form the largest group of anti-angiogenic dietary phytochemicals and have been studied most intensively. More than 8,000 chemically distinct polyphenols have been characterised in foods; they are usually grouped into flavonoids (flavones, flavonols, flavanones, isoflavones, anthocyanins and catechins), stilbenes, curcuminoids, phenolic acids and lignans [15,30]. Several cohort studies link higher polyphenol intake with a lower risk of some solid cancers, notably colorectal, ovarian and hormone-dependent cancers [31,32,33].

5.1 Flavonoids: Quercetin, Kaempferol, Luteolin, Apigenin, Myricetin, and Naringenin

Flavonoids exert anti-angiogenic effects chiefly by blocking autophosphorylation of the VEGFR2 tyrosine kinase and the pathways downstream of it, namely PI3K/Akt/mTOR and MAPK. They are abundant in tea, apples, onions, berries and leafy vegetables. In prostate and breast cancer systems, quercetin suppresses VEGFR2-dependent angiogenesis and downstream Akt activation, and it can also resensitise drug-resistant cancer cells to VEGFR2-targeted therapy [36]. Structure–activity work with methoxy and thio derivatives of quercetin and luteolin confirmed their anti-angiogenic activity in endothelial scratch-migration assays; the concentrations needed for direct cytotoxicity towards breast cancer cells were considerably higher, suggesting a window for selective anti-angiogenic action [37]. Kaempferol enhances endothelial nitric oxide synthase (eNOS) activity while inhibiting VEGFR2 phosphorylation and lowering the activity of downstream PI3K/Akt, MEK and ERK in VEGF-stimulated endothelial cells [38,39]. Apigenin, which is plentiful in parsley, destabilises HIF-1alpha protein and, in non-small-cell lung carcinoma (NSCLC) xenografts, was associated with lower microvessel density and pericyte coverage of the tumour vasculature [40,41]; a separate mechanism involves inhibition of Cdc42-dependent microvesicle biogenesis, which reduces release of microvesicle-bound VEGF from hepatocellular carcinoma (HCC) cells [42]. Myricetin suppresses HIF-1alpha, VEGF, p70S6K and Akt signalling, and naringenin blocks VEGFR2 tyrosine phosphorylation and downstream FAK/paxillin signalling; both reportedly lower levels of the orphan nuclear receptor ERR-alpha, a positive regulator of VEGF transcription [43,44].

5.2 Catechins: Epigallocatechin-3-Gallate (EGCG)

Epigallocatechin-3-gallate (EGCG), the main catechin of green tea, is arguably the best characterised dietary anti-angiogenic compound at the mechanistic level. In human umbilical vein endothelial cells (HUVECs), at concentrations attainable in vivo (0.5–10 micromolar), EGCG prevents assembly of the VEGFR2 signalling complex after VEGF binding and consequently dampens PI3-kinase activity, NF-kappaB nuclear translocation and secretion of the pro-angiogenic cytokine interleukin-8 [45]. In hepatocellular carcinoma cell lines challenged with hypoxia and serum, EGCG also blocks HIF-1alpha accumulation and VEGF expression, and chemically stabilised semisynthetic EGCG derivatives retain this activity by inhibiting both the MAPK/ERK1/2 and PI3K/Akt/HIF-1alpha/VEGF axes [46]. Translational reviews report consistent anti-angiogenic, anti-proliferative and pro-apoptotic effects of EGCG in lung, oesophageal, breast and reproductive-tract cancer models, and note that oral doses realistically reachable with concentrated green tea extracts are well tolerated [47,48,49].

5.3 Curcuminoids: Curcumin

Curcumin, the principal curcuminoid of turmeric (*Curcuma longa*), is the most extensively studied dietary anti-angiogenic compound and has shown anti-angiogenic activity in nearly all major solid tumour models. Mechanistically, it blocks nuclear translocation of NF-kappaB and its binding to DNA, lowering transcription of VEGF, IL-8 and cyclooxygenase-2 (COX-2) in ovarian cancer (OC) cells and xenografts, in line with reduced microvessel density and proliferating cell nuclear antigen expression [50,51]. It also downregulates HIF-1alpha and VEGF, thereby curbing hypoxia-induced angiogenesis; it inhibits tube formation by microvascular endothelial cells through reduced COX-2 and MAPK signalling; and in colorectal carcinoma models it blocks transcription of HIF-1alpha, COX-2, phosphorylated STAT3 and VEGF-A, with curcumin analogues proving more potent than the parent

compound [52,53,54]. Figure 1 depicts these effects schematically.

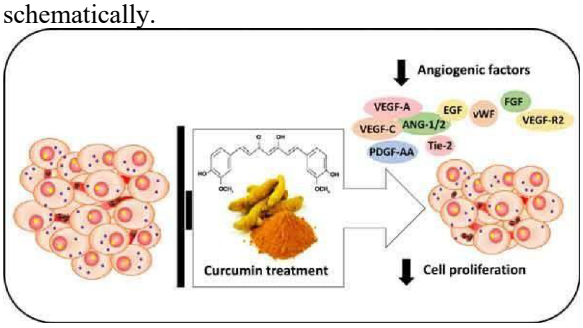


Figure 1. Schematic of the anti-angiogenic effects of curcumin.

In a randomised pilot trial of adjuvant curcumin in patients with multiple myeloma, adding curcumin to standard melphalan–prednisone therapy was accompanied by lower circulating VEGF, interleukin-6 and tumour necrosis factor-alpha and by higher overall remission rates [55]. Earlier phase I–II studies reported that no dose-limiting toxicity occurred with oral curcumin at doses as high as 8 g/day, and curcumin combined with quercetin lowered the number of aberrant crypt foci by about 40% in a phase IIa colorectal chemoprevention trial and reduced colonic adenomas in patients with familial adenomatous polyposis [56]. The main obstacle to translation is the poor aqueous solubility of curcumin and its rapid hepatic glucuronidation and sulfation, which nanoformulation approaches aim to overcome (Section 13) [57]. The structures of curcumin and related compounds from spices are shown in Figure 2.

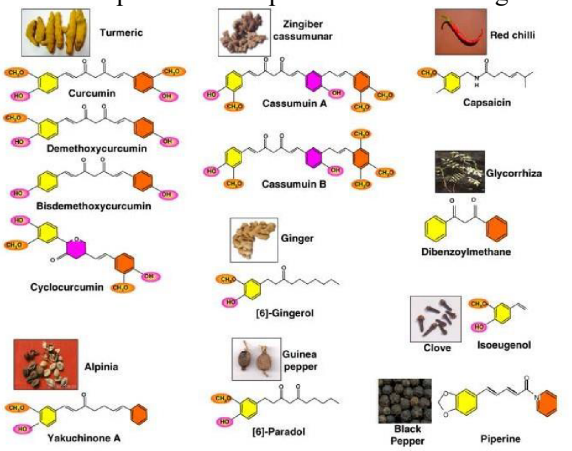


Figure 2. Chemical structures of curcuminoids and structurally related spice-derived compounds.

5.4 Stilbenes: Resveratrol and Piceatannol

Resveratrol, found mainly in grape skin, berries and red wine, curbs angiogenesis through a distinctive dual action: it reduces tumour-cell secretion of VEGF while raising thrombospondin-1, an endogenous angiogenesis inhibitor, within the tumour–endothelial microenvironment [58]. It also limits extracellular matrix breakdown, a prerequisite for endothelial sprouting, by suppressing MMP-2 and MMP-9, and it lowers the activity of VEGFR2, Akt, eNOS and ERK in endothelial cells; in colon xenograft models it acts synergistically with the biflavone ginkgetin. Besides directly affecting VEGF signalling, resveratrol has antineoplastic effects that do not depend on this pathway, for example induction of senescence and cell-cycle arrest through sirtuin-1 (SIRT1) activation in gastric cancer cells [61]. In metabolic terms, a double-blind crossover study in healthy obese men found that 30 days of low-dose resveratrol (150 mg/day) produced effects resembling caloric restriction together with better lipid parameters; these findings are relevant because metabolic disturbance, inflammation and pathological angiogenesis share common mechanisms [62]. The resveratrol analogue piceatannol blocks the binding of VEGF to VEGFR2 and thereby suppresses VEGF-induced generation of reactive oxygen species (ROS) and endothelial proliferation without direct cytotoxicity, which marks it as a selective anti-angiogenic candidate [63].

5.5 Isoflavones: Genistein, Daidzein, and Equol

Isoflavones from soy were among the first dietary compounds recognised as anti-angiogenic. Urine from people eating a traditional Japanese soy-based diet contained substantially more isoflavones, especially genistein, than urine from people on a Western diet, and it strongly inhibited endothelial proliferation stimulated by basic FGF [64]. Genistein suppresses VEGF- and bFGF-induced endothelial proliferation, migration and tube-like structure formation, reduces bFGF-induced endothelial production of plasminogen activator and its inhibitor, and inhibits the receptor tyrosine kinases for VEGF, EGF and PDGF [65,66]. In prostate cancer models genistein inhibits the overactive STAT3, Akt and ERK pathways, which lowers VEGF expression and promotes apoptosis through p53 upregulation and caspase-3/7 activation [67]. Individuals with an ‘equol-producer’ gut microbiome phenotype, more common in Asian than Western populations, convert daidzein to equol, which binds selectively to oestrogen receptor-β and reproduces the anti-angiogenic and anti-proliferative effects of genistein at similar or lower concentrations [68]. Population studies consistently report an inverse association between dietary soy isoflavone intake and both the incidence and the progression of hormone-dependent cancers such as breast and prostate cancer [69,70].

5.6 Ellagitannins and Ellagic Acid

Ellagic acid, the hydrolysis product of ellagitannins abundant in pomegranates, raspberries, strawberries and walnuts, inhibits VEGFR2 tyrosine kinase activity by hydrogen bonding within the receptor’s ATP-binding pocket, a binding mode supported by in silico docking. It also blocks endothelial proliferation,

migration and tube formation in vitro and neovascularisation in the chick chorioallantoic membrane assay [71]. In addition, ellagic acid significantly inhibited tumour growth and phosphorylated VEGFR2 expression, and comparable anti-invasive and anti-angiogenic effects were seen in bladder cancer models, where it limited VEGF-A-driven invasion through the extracellular matrix [72,73].

6. Carotenoids: Lycopene and beta-Carotene

At physiologically relevant concentrations (≥1.15 micromolar), lycopene displays anti-angiogenic activity in human umbilical vein endothelial cells, with or without exogenous tumour necrosis factor (TNF) alpha, and in rat aortic ring assays [74]. An immunomodulatory route has also been proposed: peripheral blood mononuclear cells cultured with lycopene secrete factors that inhibit endothelial tube formation and reduce VEGF-induced activation of matrix metalloproteinase-2 [75,76]. Consistent with this, large prospective cohort data link higher dietary lycopene intake to protection against lethal, highly angiogenic prostate cancer, and in the TRAMP transgenic model of prostate carcinogenesis dietary lycopene supplementation decreased tumour angiogenesis and plasma VEGF [77,78]. Clinical evidence is nonetheless inconclusive: some observational studies show no protective effect on prostate cancer incidence, and interventional data in humans are limited, so adequately powered randomised trials are needed before firm clinical recommendations can be made [79,80].

7. Organosulfur Compounds from Allium Vegetables

Garlic (*Allium sativum*) and related species supply several organosulfur compounds (allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, S-allylcysteine and ajoene) that have strong anti-angiogenic activity in addition to their direct cytotoxic and pro-apoptotic effects on tumour cells [81,82]. Alliin inhibited endothelial tube formation under VEGF and FGF-2 stimulation, with increased nitric oxide and p53 expression, and vascularisation was inhibited by more than 90% in the chick chorioallantoic membrane assay [83,84]. Diallyl trisulfide and allicin both impair capillary tube formation by endothelial cells by disrupting VEGF secretion and lowering VEGFR2 expression; in colon cancer cells they also reduced VEGF, urokinase plasminogen activator receptor and heparanase mRNA, which should curb invasion and metastasis [85]. In neuroblastoma xenografts, adding allicin to cyclophosphamide lowered VEGF mRNA and protein levels and raised infiltration by natural killer cells and by CD4+ and CD8+ T cells, in keeping with anti-angiogenic and immunomodulatory actions, respectively [86]. Encapsulating allicin in a nanoparticle carrier is reported to enhance its anti-angiogenic activity relative to the free compound, which is a promising direction [82].

8. Glucosinolate-Derived Isothiocyanates and Indoles

Broccoli, cabbage, cauliflower, Brussels sprouts, kale and other cruciferous vegetables contain glucosinolates. Chewing, chopping or cooking brings these into contact with the enzyme myrosinase, which converts them into bioactive isothiocyanates (mainly sulforaphane, phenethyl isothiocyanate [PEITC] and benzyl isothiocyanate [BITC]) and into the indole compound indole-3-carbinol (I3C), whose acid-induced condensation product is 3,3'-diindolylmethane (DIM) [87,88]. All of these interact with the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element axis and with NF-kappaB signalling, thereby affecting angiogenesis, apoptosis and cell-cycle control across many tumour types [89]. Sulforaphane modulates multiple pathways that govern angiogenesis, apoptosis and metastasis in cancer cells, and population studies connect a high intake of cruciferous vegetables with lower risks of bladder, breast, colon, lung and prostate cancers [87,90]. Indole-3-carbinol also has anti-oestrogenic activity of relevance to hormone-dependent cancers, together with broad anti-proliferative and pro-apoptotic effects. Animal studies, however, give contrasting results depending on when and how it is administered, and some indicate tumour promotion instead of suppression, which calls for caution about timing and dose in humans [91,92].

9. Omega-3 Polyunsaturated Fatty Acids

Marine omega-3 polyunsaturated fatty acids (PUFAs), principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduce tumour angiogenesis through several overlapping mechanisms. They lower tumour-cell production of pro-angiogenic mediators that activate endothelium, dampen chronic low-grade inflammation, modulate the Akt/mTOR pathway that controls endothelial proliferation, and alter endothelial adhesion and migration by changing integrin and matrix metalloproteinase expression [93,94]. Omega-3 fatty acids are regarded as adjunctive rather than primary treatment, and clinical trials in breast cancer prevention and survivorship have given promising but inconclusive results; some have found favourable changes in inflammatory and angiogenic biomarkers without a matching change in hard clinical endpoints [95,96].

10. Additional Spice- and Root-Derived Anti-Angiogenic Compounds

10.1 Cinnamon and Cinnamaldehyde

Cinnamon bark extract and its main bioactive constituent, cinnamaldehyde, inhibit VEGFR2 kinase activity and downstream signalling, thereby suppressing endothelial cell (EC) proliferation and migration in vitro; in vivo they restrain tumour growth through a combination of anti-angiogenic and CD8+ T-cell-mediated immunomodulatory effects [97,98]. Cinnamon also contains procyanidins that may inhibit NF-kappaB and activator protein-1 (AP-1) transcriptional activity; this places its anti-inflammatory action within a mechanism that bears on anti-angiogenic activity [99].

10.2 Ginger and Gingerols

Basic FGF and VEGF, both key to blood vessel formation, stimulate endothelial proliferation in vitro and neovascularisation in vivo in the rat aortic ring assay, and ginger (*Zingiber officinale*) [100] and its main pungent constituent, 6-gingerol [101], can block this stimulation. In ovarian cancer cell models, ginger extract inhibits NF-kappaB activation and the subsequent secretion of the pro-angiogenic mediators interleukin-8 and VEGF, while 6-gingerol suppresses NF-kappaB activation and secretion of these mediators and also induces G2/M arrest in colorectal cancer cells [101,102]. Ginger extract has also shown anti-inflammatory, antioxidant and anti-angiogenic activity in a hepatocarcinogenesis model, in which it lowered tumour necrosis factor alpha (TNF-alpha) and nuclear factor-kappaB (NF-kappaB) expression and tumour burden [103].

10.3 Garlic-Lemon Combinations and Synergistic Extracts

Combined aqueous extracts of garlic and lemon curbed breast tumour growth in mice by inducing apoptosis, inhibiting angiogenesis and modulating immune function, without hepatic or renal toxicity; this suggests that additive or synergistic anti-angiogenic effects may be attainable with ordinary dietary combinations [104].

10.4 Capsaicin

Capsaicin, the main pungent alkaloid of *Capsicum* species, acts on the transient receptor potential vanilloid 1 (TRPV1) channel, with effects on tumour progression that depend on context. Notably, co-administration of 6-gingerol reversed the tumour-promoting action of capsaicin in an experimental lung carcinogenesis model by increasing TRPV1 expression, underscoring the value of testing dietary phytochemicals in combination rather than singly [105,106].

11. Alkaloids and Biphenolic Compounds

11.1 Berberine

Berberine is an isoquinoline alkaloid found in *Berberis* and *Coptis* species. In glioblastoma xenografts it blocks angiogenesis by acting directly on VEGFR2 and on phosphorylation of the downstream kinase ERK (extracellular signal-regulated kinase), which reduces endothelial migration and tube formation, tumour haemoglobin content and the density of CD31-positive microvessels [107]. In pancreatic cancer cells, pharmacologically relevant concentrations inhibit DNA synthesis and proliferation by suppressing mTORC1 and ERK signalling via AMPK-dependent and AMPK-independent routes; metformin, an antidiabetic biguanide, acts similarly, pointing to a common metabolic weakness [108]. Systems pharmacology studies find that berberine hits several oncogenic nodes (proliferation, invasion, metastasis, angiogenesis), and berberine chloride has been tested in a clinical trial of colorectal cancer chemoprevention in people with ulcerative colitis in remission [109,110].

11.2 Honokiol and Silibinin

Honokiol, a biphenolic compound obtained from *Magnolia* species, was discovered by screening natural product extracts on transformed endothelial cell lines. It inhibits endothelial cells preferentially over fibroblasts, and its strong in vivo activity against angiosarcoma xenografts has been attributed to lower VEGF and VEGFR expression plus increased responsiveness to pro-apoptotic TRAIL signalling [111,112,113]. Silibinin, a flavonolignan of milk thistle (*Silybum marianum*), boosts the effect of nintedanib, a tyrosine kinase inhibitor with anti-angiogenic action, in non-small-cell lung cancer because it overcomes the intrinsic resistance mediated by STAT3; a retrospective clinical cohort found that patients receiving both agents remained on treatment significantly longer before failure [114].

11.3 Anthocyanins

Anthocyanins, the pigments that give berries, grapes and pigmented vegetables their red, purple and blue colours, show anti-angiogenic and anti-metastatic activity in breast cancer models by downregulating matrix metalloproteinases and modulating several receptor-mediated signalling pathways, in addition to their known anti-inflammatory and pro-apoptotic effects [115].

12. A Unifying Mechanistic Perspective

Although the compounds differ greatly in structure, they act on a small number of molecular targets, so they can be sorted into a single mechanistic scheme (Table 3). Five themes recur. First, VEGF-A transcription or secretion is suppressed directly, often by blocking HIF-1alpha stabilisation or NF-kappaB-driven transcription. Second, VEGFR2 ligand binding or autophosphorylation is impaired, which interrupts signal transmission through PI3K/Akt and MAPK/ERK. Third, MMP-2 and MMP-9 are inhibited, which restricts the matrix degradation required for sprout invasion. Fourth, endothelial cells are driven selectively into apoptosis or cell-cycle

arrest, frequently via cyclin-dependent kinases, p53 or sirtuins. Fifth, general anti-inflammatory activity reduces the pro-angiogenic cytokines (interleukin-6, interleukin-8 and tumour necrosis factor-alpha) released by stromal and immune cells within the tumour [15,16,14]. Because many compounds hit several of these targets at once, they may be harder for tumours to bypass than agents directed at VEGF alone.

Table 3. Mechanistic classification of dietary anti-angiogenic compounds.

Mechanistic Class	Representative Compounds	Primary Molecular Target(s)
Reduced VEGF-A transcription or secretion (through HIF-1α or NF-κB inhibition)	Curcumin, EGCG, apigenin, myricetin, ginger/gingerols, resveratrol	HIF-1α protein stability; NF-κB nuclear translocation; VEGF promoter activity [52,46,40]
Blockade of VEGFR2 ligand binding or autophosphorylation	Ellagic acid, piceatannol, kaempferol, quercetin, berberine	VEGFR2 extracellular and kinase domains; downstream PI3K/Akt and MAPK/ERK [71,63,107]
Inhibition of MMP-2/9 activity	Resveratrol, anthocyanins, genistein, allicin/diallyl trisulfide	MMP-2/9 enzymatic activity; ECM proteolysis [59,115,65]
Induction of endothelial apoptosis or cell-cycle arrest	Resveratrol (SIRT1-dependent), honokiol, genistein	SIRT1; caspase-3/7; cyclin-CDK complexes [61,112,67]
Suppression of pro-angiogenic inflammatory cytokines	Ginger, cinnamon, omega-3 PUFAs, garlic organosulfur compounds	NF-κB-driven production of IL-6, IL-8 and TNF-α [101,99,94]

13. Bioavailability Limitations and Nanotechnology-Based Delivery Solutions

Poor oral bioavailability is a nearly universal obstacle to the clinical translation of this class of compounds. It stems from low aqueous solubility, extensive intestinal and hepatic first-pass metabolism (glucuronidation, sulfation), rapid systemic clearance and, for some compounds, chemical instability at physiological pH or on exposure to light [57,116]. Curcumin illustrates the problem: despite strong anti-angiogenic activity in preclinical models, its oral bioavailability in humans is estimated at below 1% because of poor absorption and rapid conjugation [117]. To circumvent these problems, numerous nanoparticle platforms have been developed, among them liposomes, polymeric nanoparticles (particularly chitosan-based), solid lipid nanoparticles, nanostructured lipid carriers, micelles, dendrimers and emulsomes. They improve aqueous solubility, shield labile compounds from degradation, extend circulation time and allow passive accumulation in tumours through the enhanced permeability and retention effect [57,118]. In breast cancer xenograft models, chitosan-encapsulated curcumin markedly outperformed free curcumin in antitumour efficacy, with better tumour targeting and retention [119]. Single nanoparticles co-loaded with curcumin and resveratrol, including peptide-conjugated formulations directed at tumours, showed synergistic antitumour effects in hepatocellular carcinoma models at lower doses [120]. Nanostructured lipid carriers have likewise greatly improved the intestinal permeability and oral bioavailability of resveratrol in intestinal epithelial monolayer models without compromising cell safety [118]. Representative nanoformulation strategies and their reported gains in bioavailability or efficacy are collected in Table 4.

Table 4. Representative nanoformulation strategies for bioavailability enhancement of dietary anti-angiogenic compounds.

Compound	Nanocarrier System	Reported Benefit	Reference
Curcumin	Chitosan nanoparticles	Better tumour targeting and retention; greater antitumour efficacy in breast cancer xenografts	[119]
Curcumin	Emulsome (solid-core lipid)	Aqueous solubility/bioavailability raised	[121]

Compound	Nanocarrier System	Reported Benefit	Reference
	nanocarrier	up to ~10,000-fold	
Curcumin + Resveratrol	Peptide-conjugated, self-assembled co-loaded nanoparticles	Synergistic antitumour effect at lower doses in hepatocellular carcinoma	[120]
Resveratrol	Solid lipid nanoparticles / nanostructured lipid carriers	Better intestinal permeability; protection against photodegradation	[118]
Curcumin + Resveratrol	Nanosized formulation combined with modulated electro-hyperthermia	Stronger host immunity and antitumour effect in colorectal cancer models	[122]
Allicin	Polymeric nanoparticle encapsulation	Stronger anti-angiogenic activity than free allicin	[82]

14. Evidence from Preclinical and Early Clinical Studies

Evidence that dietary compounds inhibit angiogenesis is overwhelmingly preclinical. It rests on endothelial cell assays (proliferation, migration, Matrigel tube formation), ex vivo aortic ring and chorioallantoic membrane preparations, and mouse xenograft or genetically engineered tumour models [123,124]. Human data are fewer but increasing, above all for green tea catechins, curcumin and resveratrol, where early-phase trials report acceptable safety and changes in biomarkers that match the mechanisms identified in the laboratory (Table 5). In phase I–II studies, curcumin was tolerated at daily doses of up to 8 g and showed hints of efficacy in preventing colorectal adenomas and, alongside standard chemotherapy, in multiple myeloma [56,55]. Resveratrol supplementation in groups with metabolic risk improved inflammatory and lipid markers that link angiogenesis, inflammation and metabolic disease [62]. Finished and ongoing trials of berberine and of isothiocyanates from cruciferous vegetables in colorectal chemoprevention point the same way, yet adequately powered trials with angiogenesis-specific endpoints (circulating VEGF, microvessel density in sequential biopsies, dynamic contrast-enhanced imaging) remain scarce and should be prioritised [110,90].

Table 5. Selected preclinical and clinical translational evidence for dietary anti-angiogenic compounds.

Compound	Study Type	Population / Model	Key Reported Outcome
Curcumin	Phase I–II dose escalation	Cancer patients (various)	Well tolerated up to 8 g/day; no dose-limiting toxicity [56]
Curcumin + Quercetin	Phase IIa chemoprevention	Familial adenomatous polyposis	About 40% fewer aberrant crypt foci; fewer adenomas [56]
Curcumin (adjuvant)	Randomised pilot trial	Multiple myeloma patients	Lower VEGF, IL-6 and TNF-α; better overall remission with melphalan–prednisone [55]
Resveratrol	Randomised double-blind crossover	Healthy obese men	Effects resembling caloric restriction; better lipid profile; lower inflammatory markers [62]

Compound	Study Type	Population / Model	Key Reported Outcome
Silibinin + Nintedanib	Retrospective clinical cohort	Advanced NSCLC	Longer time to treatment failure than with nintedanib alone [114]
Berberine chloride	Registered clinical trial	Ulcerative colitis in remission	Under evaluation for colorectal cancer chemoprevention [110]

15. Combination and Synergistic Approaches

Combining dietary anti-angiogenic compounds with one another, or with standard chemotherapy and anti-angiogenic drugs, is increasingly supported by data showing that synergy allows each agent to be used at a lower dose, which could ease both resistance and toxicity [125,126]. Illustrative cases are resveratrol with ginkgetin, which jointly suppressed VEGF-driven angiogenesis in colorectal xenografts; silibinin, which restored the sensitivity of lung cancer to nintedanib; nanoparticle co-formulation, which boosted the activity of allicin; and 6-gingerol, which counteracted the context-dependent tumour-promoting effect of capsaicin [60,114,82,105]. In three-dimensional models of the colorectal tumour microenvironment, curcumin also amplified the cytotoxic and anti-angiogenic action of 5-fluorouracil. Such findings favour using these dietary compounds as chemosensitisers inside multimodal regimens, and not as replacements for established cancer care [54].

16. Epidemiological Evidence and Dietary Patterns

Studies of whole dietary patterns add a population-level perspective to compound-specific pharmacology and indicate that phytochemicals able to modulate angiogenesis may help prevent cancer. The Mediterranean diet, which emphasises fruit, vegetables, pulses, whole grains, olive oil and fish and limits red and processed meat, was associated with lower total cancer incidence in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, and later meta-analyses of observational studies reached similar conclusions [17,18]. Protective associations specific to particular cancers have been described for breast, bladder, gastric, oesophageal and thyroid tumours [127,128,129,130]. Polyphenol intake estimated in EPIC was inversely related to epithelial ovarian cancer risk, and cereal-derived polyphenols were linked to a lower risk of colorectal cancer in the Melbourne Collaborative Cohort Study [31,32]. Reanalysis of data from the PREDIMED randomised trial showed that people with higher total polyphenol intake had lower all-cause mortality, in a cohort selected for high cardiovascular and metabolic risk; because inflammation and angiogenesis underlie both cardiometabolic disease and cancer, that population overlaps substantially with people at high cancer risk [33]. Overall, these epidemiological observations support, at population level, the mechanistic and preclinical findings discussed above, and they suggest that diet as a whole may be a more actionable target for intervention than any one isolated compound.

17. Limitations and Future Directions

Several limitations moderate enthusiasm for the immediate clinical translation of dietary anti-angiogenic compounds. First, most mechanistic data come from in vitro and rodent xenograft studies that used supraphysiological concentrations, which may not be reachable through diet or even routine oral supplementation, so extrapolation to human efficacy must be cautious [117]. Second, poor bioavailability (Section 13) is still only partly resolved: the promising nano formulation strategies are mostly in preclinical or early clinical development [57]. Third, clinical trials so far have typically been small and short and have favoured safety and pharmacokinetic endpoints over hard oncological outcomes such as progression-free or overall survival, which weakens causal inference about anti-angiogenic efficacy in humans [56]. Fourth, some compounds show biphasic or context-dependent behaviour, as illustrated by the differing effects of indole-3-carbinol when given before or after a carcinogen and by the dual tumour-promoting and tumour-suppressing activity of capsaicin via TRPV1; compound- and context-specific dosing guidance is therefore needed instead of generalised chemo preventive advice [91,105]. Finally, pharmacokinetic interactions between concentrated phytochemical supplements and concurrent chemotherapy or anti-angiogenic drugs, particularly through shared cytochrome P450 and UDP-glucuronosyltransferase pathways, need systematic study before combinations can be recommended outside controlled trials [125]. Future priorities include adequately powered randomised trials using bioavailability-enhanced formulations, standardised angiogenesis-specific biomarkers and imaging endpoints, pharmacokinetic–pharmacodynamic modelling to define achievable and safe doses, and mechanistic studies to establish the best sequencing and combination with established anti-angiogenic drugs.

18. Conclusion

Because tumour growth depends on new blood vessels, angiogenesis is a validated and druggable target; yet VEGF-pathway inhibitors reach a ceiling imposed by resistance, side effects and expense. Phytochemicals from the diet, a chemically heterogeneous collection that includes flavonoids, catechins, curcuminoids, stilbenes, isoflavones, carotenoids, organosulfur compounds, isothiocyanates derived from glucosinolates, omega-3 fatty acids and a few alkaloids, nonetheless act on overlapping nodes: VEGF/VEGFR2 signalling, HIF-1alpha stability, NF-kappaB- and STAT3-dependent transcription, matrix metalloproteinase activity and endothelial survival. This makes them a mechanistically coherent, generally low-toxicity complement to conventional anti-angiogenic drugs. Laboratory findings are abundant and consistent across compound classes and tumour types, whereas early clinical results, still modest in size and in the maturity of their endpoints, are encouraging, particularly for green tea catechins, curcumin and resveratrol. To realise this potential, future work must deliver larger, properly powered randomised trials of nano formulations with improved bioavailability, strict angiogenesis-focused biomarker endpoints, and careful study of how pharmacology depends on compound, dose and context. Dietary anti-angiogenic compounds should therefore be viewed as a biologically plausible element of integrative, multimodal cancer prevention and supportive treatment, not as a replacement for established oncological therapy.

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

During the preparation of this work, the author(s) used **Claude (Anthropic)** in order to assist with language editing, grammatical refinement, and improvement of scientific writing. Following the use of this tool, the author(s) carefully reviewed and edited the content as necessary and take full responsibility for the accuracy, originality, integrity, and final content of the published article.

Declaration of Competing Interests

The authors have no competing financial interests or personal relationships to declare that could have influenced the work presented in this paper.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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