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FROM SPICE TO THERAPY: THE ANTIANGIOGENIC POTENTIAL OF EUGENOL

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ABSTRACT

Nyctanthes Antiangiogenesis, the process of inhibiting new blood vessel formation, has become a pivotal strategy in the treatment of cancer and other angiogenesis-dependent diseases. Eugenol, a bioactive compound found in clove oil, has gained attention for its broad pharmacological properties, including anti-inflammatory, antioxidant, and anticancer effects. Recent studies suggest that eugenol exhibits significant antiangiogenic potential by targeting key regulators of angiogenesis, such as Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMPs). This review examines the molecular mechanisms underlying eugenol's antiangiogenic activity, focusing on its ability to inhibit VEGF expression, disrupt endothelial cell migration, and reduce microvessel density in tumor models. Additionally, the therapeutic implications of eugenol as a natural antiangiogenic agent in cancer treatment, alongside its potential for overcoming resistance to conventional antiangiogenic therapies, are discussed. While promising, further research is needed to optimize its efficacy, bioavailability, and clinical application. This review highlights the growing interest in natural compounds like eugenol as complementary or alternative strategies in antiangiogenesis therapy.

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INTRODUCTION

Angiogenesis or neovascularization is the formation of new microvessels from an established vascular network and was first proposed in 1971 by Judah Folkman as a therapeutic target for cancer. Tumors cannot grow beyond the size of 1 mm without developing their own blood supply (Folkman, 2010). One of the key factors responsible for angiogenesis, the Vascular Endothelial Growth Factor (VEGF) was identified (Senger*et al.,* 1983; Leung *et al.,* 1989). The process of angiogenesis is governed by a delicate balance between multiple endogenous pro- angiogenic and anti-angiogenic factors. An imbalance in these factors leads to the development or progression of pathological conditions. The angiogenic process involves interactions among multiple cell types including endothelial cells (EC) and circulating endothelial progenitor cells, pericytes, vascular smooth muscle cells, stromal cells, including stem cells, and parenchymal cells. These interactions occur through secreted factors such as VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and angiopoietins, as well as through extracellular cell matrix (ECM) interactions (Carmeliet *et al*.,2000; Carmeliet, 2005; Folkman, 2006). The interaction between EC and the ECM is critical and influences cellular processes such as EC migration, proliferation, differentiation and apoptosis which are essential in the process of angiogenesis.

Mechanisms of Angiogenesis: Angiogenesis is a multistep process which is tightly regulated by an intimate balance between pro- and anti-angiogenic factors.

The angiogenic factors VEGF, FGF, Tumour growth factor(TGF) and Platlate PDGF stimulate angiogenesis by either acting locally, or they are released into the blood stream and activate angiogenesis through binding to their corresponding receptors on pre-existing endothelial cells and/or perivascular cells (Cao, 2008). Upon ligand binding to the receptors, a cascade of intracellular signal transduction is triggered resulting in activation of the endothelial cell and initiation of the cellular mechanisms required for angiogenesis including basal membrane degradation, endothelial cell proliferation and migration, formation of tube-like structures, and finally vascular maturation by coverage with smooth muscle cells or pericytes to ensure stability (Davis &Senger, 2005).The dynamics of angiogenesis as well as the morphology of the resulting vasculature differs depending on which factor induces the process (Cao*et al*, 2004). In case of the most studied angiogenic factor, VEGF, a mature vessel may be exposed to a gradient of VEGF induced by hypoxia in a nearby tissue such as a tumor. VEGF activates VEGF receptor 2 (VEGFR2) on endothelial cells leading to production of matrix-metalloproteases (MMPs) which disrupt EC-pericyte contacts, degrade the basal membrane and induce a tip-cell behavior in one cell, which is allowed to form cell processes important for cell migration such as filopodia and lammelopodia. The tip cell starts migrating up the angiogenic factor gradient but remain in contact with the underlying and proliferating endothelial cells (stalk cells) and thus retain the connection to the original vessel. At a certain point, the tip cell meets other tip cells, anastomose i.e. fuse and thus form a circulation loop. The endothelial chordslumenize, allowing blood to flow through the vessel and the vessels mature by recruiting perivascular mural cells which are tightly associated with the endothelial cells thus providing stability and trophic factors for

the endothelial cells, leading to their maturation and re-entry into quiescence.

Role of VEGF) in angiogenesis in cancer: VEGF is a glycoprotein and major mediator for new blood vessel formation. It was first discovered in late 1970s as a secretory factor from tumor cells and characterized as a potent vascular permeability factor. It was identified as a critical player in angiogenesis and became a controversial molecule regarding its effects in the disease processes and the emerging paradigms in therapeutic trials to suppress or enhance its action. Solid tumors require adequate supply of nutrients from the blood to survive, grow, and metastasize (Hanahan and Folkman, 1996). The VEGF family currently comprises seven members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor (PGF). All members have a common VEGF homology domain. This core region is composed of a cystine knot motif, with eight invariant cysteine residues involved in intra and intermolecular disulfide bonds at one end of a conserved central four-stranded β-sheet within each monomer, which dimerize in an antiparallel, side-by-side orientation (Neufeld *et al*., 1999; Ortega *et al*., 1999). Endothelial sprouting is a basic mechanism for tumor vascularization (Figure 1). It is a process that is controlled by balance between ″pro-angiogenic and anti-angiogenic″factors. During sprouting, pericytes detach and blood vessels dilate, and the process is under control of VEGF and angiopoietins (Dome *et al*., 2007). The production of VEGF and other growth factors by the tumour results in the formation of new vasculature in and around the tumour, allowing it to grow exponentially. Tumour vasculature formed under the influence of VEGF is structurally and functionally abnormal. Blood vessels are irregularly shaped, tortuous, have dead ends and are not organized into venules, arterioles and capillaries. They are also leaky and hemorrhagic, which leads to high interstitial pressure. These characteristics mean that tumour blood flow is suboptimal, resulting in hypoxia and further VEGF production. This central role of VEGF in the production of tumour vasculature makes it a rational target for anticancer therapy (Carmeliet, 2005).

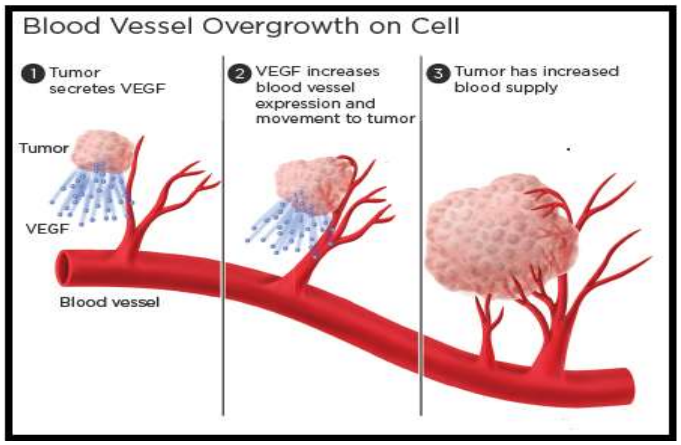

Figure1. Mechanism of tumour angiogenesis

Angiogenesis and Cancer: Angiogenesis plays a critical role in the growth and spread of cancer. Blood supply is necessary for tumors to grow beyond few millimeters in size. Tumors can cause this blood supply to form by giving off chemical signals that stimulate angiogenesis. Tumors can also stimulate nearby normal cells to produce angiogenesis signaling molecules. The resulting new blood vessels provide the growing tumors with oxygen and nutrients, allowing the cancer cells to invade nearby tissue eventually leading to metastases. Scientists are studying natural and synthetic angiogenesis inhibitors, also called anti-angiogenic agents, to prevent or slow down the growth of cancer.

Anti-Angiogenesis Therapy: Inhibition of VEGF pathway using antibodies or chemical inhibitors restricts the growth of blood vessels and inhibits tumor growth in the clinics. Intriguingly, Preclinical studies conducted by two independent laboratories in mouse cancer model had presented results contradicting this expectation (Figure.2). Thus, anti-angiogenesis therapy seemed to be straightforward as expected and necessitates the understanding of angiogenesis in animal models for more efficacious and safer use of anti-angiogenesis therapy to combat cancer. Other substantial problems with anti-angiogenesis therapy include the poor understanding of drug resistance and drug delivery system (Jain, 2005).

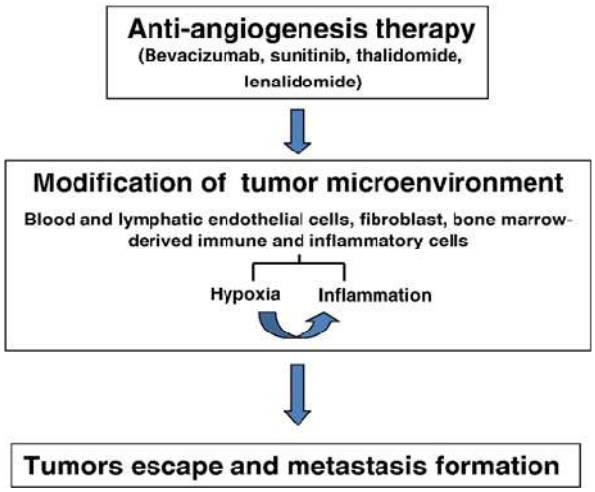

Figure 2. Emerging Quandary of Anti-angiogenesis Therapy.

Tyrosine kinase receptors inhibitors: Tyrosine kinases are enzymes that catalyze the transfer of the γ phosphate group from adenosine triphosphate to target proteins. They play an important role in diverse normal cellular regulatory processes. Tyrosine kinases can be classified as receptor protein kinases and non-receptor protein kinases. The receptor tyrosine kinases are membrane-spanning cell surface proteins that play critical roles in the transduction of extracellular signals to the cytoplasm. Non-receptor tyrosine kinases, on the other hand, relay intracellular signals (Pawson, 2002). There are multiple types of targeted therapies available for the prevention of cancer including monoclonal antibodies, inhibitors of tyrosine kinases, and antisense inhibitors of growth factor receptors. Tyrosine kinases play a critical role in the modulation of growth factor signaling. Activated forms of these enzymes can cause increase in tumor cell proliferation and growth, induce anti-apoptotic effects, and promote angiogenesis and metastasis (Finley, 2003).

Breakpoint cluster region - Abelson BCR-ABL Tyrosine kinase receptors Inhibitors

Imatinib Mesylate (STI571): The BCR-ABL protein is considered an ideal target for imatinib, since the BCR-ABL mutation is present in almost all patients with chronic mylogenous leukemia, Imatinib specifically inhibited or killed proliferating myeloid cell lines containing BCR-ABL but was minimally harmful to normal cells (Druker*et al*., 1996)

Epidermal growth factor receptor tyrosine kinase receptor inhibitors

Gefitinib: The epidermal growth factor receptor (EGFR) signal transduction pathways have been implicated in the regulation of various neoplastic processes, including cell cycle progression, inhibition of apoptosis, tumor cell motility, invasion, and metastasis. EGFR activation also stimulates VEGF, which is the primary inducer of angiogenesis. Gefitinib is a selective EGFR (ErbB1) tyrosine kinase inhibitor (Petit *et al*., 1997).

Erlotinib (OSI-774): Erlotinib hydrochloride is an orally available, potent, reversible, and selective inhibitor of the EGFR (ErbB1) tyrosine kinase (Ranson, 2004).

Lapatinib (GW-572016): Lapatinib is a reversible and specific receptor tyrosine kinase inhibitor of both ErbB1 and ErbB2 and has

been shown to have activity against ErbB1 and ErbB2, as well as Akt-overexpressing human tumor xenograft (Rusnak *et al*., 2001).

Canertinib (CI-1033)

Platelet-Derived Growth Factor Inhibitors

Leflunomide (SU101): Leflunomide is a small molecule inhibitor of Platelet-Derived Growth Factor receptor (PDGFR) mediated phosphorylation and thus inhibits PDGF-mediated cell signaling (Shawver*et al*., 1997).

List of the herbs with antiangiogenic potential as follows (Patil, *et al.*, 2010)

Sr. No.	Scientific name	Local name	Active ingredient
1	*Ocimum sanctum*	Holy basil	Eugenol, carvanol
2	*Terminalia arjuna*	Arjuna bark	Arjunolic acid, tannins
3	*Andrographispaniculats*	Kirayat	Kalmeghin, triterpenoid
4	*Taxas spp.*	Yews	Taxol
5	*Catharanthusroseus*	Vinca	Vincristine, Vinblastine
6	*Podophyllumpeltatum*	May apple	Podophyllotoxin
7	*Curcuma longa*	Turmeric	Curcumin
8	*Magnolia officinalis*	Houpo (Chinese herb)	Magnolol, magnocurarine
9	*Ginkgo biloba*	Fossil tree	Ginkgetin, bilobalide

Eugenol: Eugenol is a phenolic photochemical compound, extracted from certain essential oil. As it was extracted from the buds and leaves of *Eugenia caryophyllata (*clove) for the first time, it was named as Eugenol. Being a major component in the extracts of various medicinal herbs it got much attention by the researchers and opened up a wide area of research in applying it as a medicine to cure various diseases. Eugenol is known to have several pharmacological properties i.e. anaesthetic, antioxidant, antimicrobial, ant-helminthic, anti-inflammatory, anti-carcinogenic and anti-fumigant properties. It has been in use as a traditional remedy for toothache and also for culinary purposes. This versatile molecule is a key ingredient in perfumes, cosmetics and flavorings agents.

Plant sources of Eugenol: Eugenol is extracted from several aromatic plants. Besides the *Eugenia caryophyllata* (cloves) which contains about 80-95 % Eugenol, it is also isolated from *Myristica fragrans* (Nutmeg), *Cinnamomum tamala* (Tajapatta), *Ocimum sanctum* (Krishna Tulsi) and *Pimenta racemesa* (Bay Leaf). The essential oil from the fresh leaves of these plants has shown Eugenol percentage as 0.89, 60.2, 57.94 and 45.6 respectively (Raja *et al.,* 2015; Mahapatra, 2011).

Physical and chemical properties of Eugenol: Eugenol belongs to a class of phenylpropanoids ($C_{10}H_{12}O_2$). The IUPAC name of the compound is 4-Allyl-2-methoxyphenol having molecular mass 164.2g/mol with pKa=10.19 at 25°C. Eugenol and isoeugenol are the two isoforms of it. It is also known as caryophyllic acid, allylguaiacol, 2-methoxy-4-(2-propenyl) phenol, 4-allylcatechol-2-methyl ether. The phenolic group confers the antioxidant property to it. It is partially soluble in water and solubility increases with organic solvents. The colour of the compound ranges from clear to pale yellow. Eugenol is absorbed via small intestine when administeredorally and is rapidly distributed in all organs when administered intraperitoneally (Harborne *et al*., 1993; Shishodia*et al.,* 2003, Raja *et al.,* 2015).

Tests for identification of Eugenol (Mangathayaru, 2013). The identification of Eugenol was done by method developed by Mangthayaru, (2013) which is described below.

- 5 drops of Eugenol are dissolved in 10 ml of water. Then add 3 drops of ferrous chloride solution, a bluish green color appears which indicates the presence of Eugenol.
- When 0.1 g of picric acid, 1 ml of benzene, and 9 ml of petroleum benzene are added to 0.5 ml of Eugenol and heated until crystals dissolve, the solution becomes orange yellow indicating the presence of Eugenol.
- To five drops of Eugenol dissolved in 5 ml of ethanol. Few drops of ferric chloride solution are added. A blue color indicates the presence of Eugenol.

Advantage of possible combination of herbal and conventional cancer chemotherapy: The toxic effect of modern anticancer drugs can be a major limitation to their effective use. Medicinal herbs and their derivative phyto-compounds are being increasingly recognized as useful complementary treatments for cancer. Combination therapy with conventional therapeutics is the most effective treatment strategy in cancer to overcome drug toxicity and drug induced resistance. A large number of clinical studies have reported the beneficial effect of herbal medicine on the survival, immune modulation and quality of life (QOL) of cancer patients. In cervical cancer cells (HeLa), Eugenol showed its synergistic activity with 5-fluorouracil (Hemaiswarya *et al.,* 2013).

Pharmacological outcome of drug interaction: When two or more drugs are used together, the pharmacological response is not necessarily the sum of two agents used individually. Depending on magnitude of pharmacological response produced by the combination of two drugs, drug interaction is broadly divided into four types: addition, potentiation, synergism and antagonism.

Assays for Anti-Angiogenesis: One of the technical challenges in the studies of angiogenesis is selection of the appropriate assay. There are many *in vitro*, *in vivo* and *in ovo* angiogenesis assays. It has been proved from previous research that it is necessary to use a combination of assays for accurate identification of the cellular and molecular events in angiogenesis and to find complete range of effects of a given test compound.

***In Vitro* Assays:** The ability to maintain endothelial cells in culture has enabled the study of endothelial cell proliferation, migration, and function. The bovine aortic endothelial cell assay is an established system. *In vitro* assays are relatively inexpensive and give more rapid results. However, an ability to inhibit endothelial cell proliferation, migration, and tubule formation *in vitro* may not predict *in vivo* response. *In vitro* assays are a rapid method for initial screening of large number of agents. Definitive conclusions cannot be based on *in vitro* assays alone.

Cultivation of Cardiac Myocytes in Agarose Medium: Cardiac myocytes are isolated from the left ventricular myocardium of the mice and placed in culture medium. Heart explants are incubated for seven days. Angiogenic stimulants are added every other day and after seven days endothelial sprouts are photographed and sprout formation is calculated (Myung*et al*., 2007).

The Chick Aortic Arch Assay: This method is the modification method of the rat aortic ring assay. It is rapid method and it takes 1-3 days with serum free medium. The chick aortic arch assay can be performed by incubating chick aortic arch ring in culture medium contain test substance. The aortic arches are isolated from 12-14 chick embryos and cut into 1mm rings and cultured in well plate containing matrigel (Makoto *et al*., 2007).

Rat Blood Vessel Culture Assay: The rat thoracic veins are isolated and fibro-adipose tissue is removed. The veins were washed with Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), (Masami *et al*., 1991). Due to the complex cellular and molecular activities of angiogenic reactions, *in vivo* studies are more informative than *in vitro* studies providing that the biology of the assay and the experimental design are relevant; *in*

vitro studies of ECs are, however, in many instances a necessary complement to *in vivo* experiments.

HUVEC Assay: This assay mimics human angiogenesis in which native human umbilical vein-derived endothelial cells (HUVECs) get activated by pro-angiogenic substances and form tube-like structure that can be measured by phase contrast microscopy.

Cell Cord Formation Assay: In this method the growth factor reduced matrigel is pipetted into a well of a 48-well plate the tubular lengths of the cells are measured using software (Veronica *et al*., 2007).

Tube Formation Assay: The endothelial cells are isolated and cultured in medium in gelatin coated flasks. The cells from passages four to seven are used for the angiogenesis study. Gels are examined and the tube length is determined for each well followed by determination of each group by using software. All experiments were terminated at 48 h (Suya *et al*., 2001).

Gelatin Zymography: This assay can also be called as Matrix Metalloproteinase (MMP) assay. In this the matrix metalloproteinase activities of the myocardial tisssue are measured using sodium dodecyl sulphate (SDS) polyacrylamide gels. Gelatin is used as a substrate because connective tissue degrading enzymes such as gelatinase rapidly cleave it and it is easily incorporated into poly acryl amide gels (Wei *et al*., 2001).

In Vivo Assays: *In vivo* biologic assays are more specific for detecting anti-angiogenic activity. *In vivo* assays provide a more complete physiologic assessment of angiogenesis, but are more time consuming and expensive.

Hind Limb Ischemia Model: This method is mostly used for the evaluation of angiogenic substances. The haemodynamic changes lead to the formation of new blood vessels i.e. while large vessels with low flow tend to augmentation of blood flow which leads to the stimulation of vascular sprouting and maintain the potency of the newly formed collateral vessels thereby providing blood flow to the ischemic tissue ((Tabibiazar and Rockson 2001).

CAM Assay: Originally used by embryologists to study the developmental potential of embryonic tissue grafts, the CAM assay has been adopted to the study of tumor angiogenesis as well as to test pro- and anti-angiogenic factors. Chick embryos with intact chorioallantoic membrane (CAM) are incubated with the test material and are evaluated for blood vessel proliferation by digital imaging (Theodore *et al*., 2004).

Corneal Angiogenesis: The cornea is the only tissue of the body that is both avascular and transparent. These unique anatomical features make the cornea ideal for observation of angiogenesis in mice, rats, and rabbits. Slow-release polymer pellets or sponges containing pro-angiogenic molecules (VEGF-A, FGF-2) or tumor cells are implanted into stromal pockets created surgically. The growth of new vessels from the peripheral limbal vasculature can be monitored daily, allowing rates of angiogenesis to be determined (Barbel *et al*., 2007).

Zebrafish Angiogenesis Assay: Here the angiogenesis occurring in the head and somites of the fish trunk is measured enzymatically or by micro-angiography. Zebrafish provide a system for drug screening that combines the biological complexity of *in vivo* models with the ability for much higher-throughput screening than other available animal models. Major molecular pathways regulating angiogenesis in mammalian systems are conserved in zebrafish (Liang *et al*., 2001).

Matrigel Plug Assay: This model is used for the evaluation of both angiogenic and anti-angiogenic agents. The injection of foreign substances in to the animal leads to the stimulation of the inflammatory cells including macrophages and neutrophils which leads to the stimulation of angiogenesis (Tabibiazar *et al*., 2001).

Sponge Implantation Method: This model was used for the evaluation of angiogenesis and anti- angiogenic agents. Stimulation of inflammation by foreign substance leads to the angiogenesis. In this method the sponge can be prepared by using sterile absorbable gel foam (Mathur *et al*., 2006).

Angiogenesis Inhibitors and Promoters

Angiogenesis Inhibitors

Endostatin: Endostatin is the carboxy terminal fragment of collagen XVII. It is thought to induce apoptosis inendothelial cells and inhibition of their migration to sites of neo-vascularisation, probably by interfering with endothelial cell adhesion. In preclinical models, endostatin has inhibited the growth of a widevariety of human primary and metastatic tumours. Clinical trials suggest that endostatin is well tolerated, but only minor evidence of anti-tumour activity has been observed.

Angiostatin: Another endogenous inhibitor of angiogenesis is angiostatin. Like endostatin, it directly induces apoptosis of endothelial cells by disrupting the normal adhesion contacts between the endothelial cells. Angiostatin also acts by inhibiting VEGF andbFGF (Clarke and Sharma, 2006).

Thrombospondins: Thrombospondin1 (TSP1) was the first protein to be recognized asa naturally occurring inhibitor of angiogenesis. It is a large multifunctional ECM glycoprotein that regulates various biological events, like cell adhesion, angiogenesis, cellproliferation and survival, transforming growth factor β (TGF β) activation, and protease activation. Some studies suggest that TSP1 may possess dual activity (pro-angiogenic and anti-angiogenic) depending on proteases that generate fragments of TSP1. (Kyriakides *et al.,* 2002).

Angiogenesis Promoters

Vascular Endothelial Growth Factor (VEGF): VEGF-A (also known as vascular permeability factor VPF, commonly termed VEGF) is a 34–46 kDa secreted glycoprotein that assembles into a disulphide-linked homodimer. There are atleast eight known human isoforms that are the result of alternative RNA splicing and termed VEGF121, VEGF145, VEGF162, VEGF165, VEGF165B, VEGF183, VEGF189 and VEGF206 according to their length of amino acids. VEGF121 is soluble whereas the larger isoforms bind to the cell surface or to the ECM through heparin or proteoglycane-binding domains. The predominantisoform in humans is VEGF165 often termed VEGF.It binds to VEGF-receptor 1 (VEGFR1), VEGFR2, Neuropilin-1 and Neuropilin-2 on EC.VEGF-B is approximately 44% identical to VEGF, it exists in the two isoforms VEGF-B167 and VEGF-B186.VEGF-C and VEGF-D (also known as c-fos induced growth factor FIGF) form a subgroup within the VEGF family asthey consist of a central VEGF homology domain with N and C-terminal extensions that are cleaved during protein maturation and are not seen in the other VEGFs or placenta inhibitory growth factor (PlGF). PlGF is mainly expressed in the placenta and tumours and forms disulphide-linked homodimers but can also form hetero dimmers with VEGF.The three VEGF-receptors VEGFR1 (=Flt-1 = Fms-like tyrosine kinase1), VEGFR2 (=Flk-1 =KDR= kinase domain region) and VEGFR3 (=Flt-4) are receptors with seven immunoglobulin-like domains in their extra-cellular part anda split tyrosine kinase domain intracellularly. These receptors are mostly expressed on endothelial cells (Bouis *et al.,* 2002).

FGF: It is comprised of 23 different proteins and classified in to six different groups. These ligands are among the earliest angiogenic factors and involved in promoting cell proliferation, migration and differentiation of vascular ECs.

Angiopoietins: Since their first discovery in 1996, Angiopoietins have been a focus of growing interest in angiogenesis-research. In adult tissue Ang1 is constitutively and widely expressed especially in platelets and megakaryocytes as well as in highly vascularised tissues, but not in tissues with low vascularization. Ang2 is only expressed in

the ovary, placenta and uterus, organs with constant blood vessel growth and regression as well as in (chicken) testicular development and regression and in rheumatoid arthritis synovial fibroblasts (Scott *et al.,* 2002). Ang1 inhibits the activating effects of VEGF and tumour necrosis factor (TNF) on EC such as induction of tissue factor expression (TF) Murine Ang3 is a widely expressed, context-dependent antagonist, homologue to human Ang4, which is a TIE2 agonist, predominantly expressed in the lung.

Epidermal Growth Factor (EGF): EGF is secreted by platelets, macrophages and monocytes and in salivary, lacrimal and duodenal glands as well as in the kidney. It has no direct effects on vascular endothelium but is nevertheless involved in tumour proliferation, metastasis, apoptosis, angiogenesis and wound healing (Albo *et al.,* 2004).

CONCLUSION

The journey of eugenol from a common spice-derived compound to a potential therapeutic agent underscores its significant pharmacological versatility, particularly in the realm of antiangiogenesis. By targeting critical pathways such as VEGF, MMPs, and inflammatory mediators, eugenol exhibits promising antiangiogenic effects that could inhibit tumor growth and metastasis. Its natural origin, coupled with its demonstrated ability to interfere with endothelial cell function and reduce microvessel formation, positions eugenol as a potential adjunct or alternative to conventional antiangiogenic therapies, especially in cancer treatment.However, despite its promising in vitro and in vivo results, the therapeutic application of eugenol faces several challenges. These include optimizing its bioavailability, determining effective dosing regimens, and addressing potential side effects. Further research, particularly clinical trials, is necessary to validate its efficacy in humans and to understand its interactions with standard treatment modalities.In conclusion, eugenol holds great promise as a natural antiangiogenic agent, and with continued investigation, it may emerge as a valuable tool in the fight against angiogenesis-driven diseases like cancer. Its integration into modern therapeutic strategies could represent a shift toward more natural, less toxic treatment options.

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