Modes of Anti-angiogenesis in Chemical Perspectives

Shan Arif[a, b], Muhammad Imran[a, b], Muhammad Adnan Iqbal[a, b]

Abstract

Angiogenesis is a process which involves formation of new blood vessels and it involves the growth, migration and differentiation of endothelial cells that cause line inside the walls of blood vessels. This process is controlled by chemical signals in body and these signals such as vascular endothelial growth factor (VEGF), combine with receptors on the surface of normal endothelial cells and increase the growth and survival of new blood vessels. Some drugs are used to diminish the combining of VEGF with the receptors from sending the growth signals in new blood vessels. This process is called anti-angiogenesis and also called cancer growth blockers. In the current study, role of synthesized chemical pharmacores like ***Humulus lupulus, Hypericum perforatum, Panax ginseng, Coptis chinensis*** and ***Rheum palmatum*** as anti-angiogenesis has been compiled. The structure activity relationship in inhibiting the angiogenesis has also been discussed.

Keywords: Anti-angiogenesis, Genistein, Epigallocatechin Gallate/ EGCG, Angiostatin.

Abbreviations: VEGF - vascular endothelial growth factor

1.0 Introduction

Growing of new blood vessels from the pre-existing ones is called angiogenesis. This happens when there is a deviation in the oxygen or the nutrient supply to the veins. This may occur by physiological or pathological pathways (Carmeliet, 2005). Angiogenesis can be great or terrible. When it is good it is responsible for procedures like wound healing or direction of menstrual cycle. But when it is awful, it's outcome is tumor, kind or dangerous (Folkman 1971). Angiogenesis is controlled either by local or fundamentals chemical signals, coordinating with the endothelial cells (Mousa and Davis, 2017). Angiogenic support is extremely basic for the growth and metastasis at both local and systematic levels. Adopting the unusual angiogenesis is one of the significant worries of humanity in all. Cancer diagnosis, control and its treatment has been a great challenge for the scientists across the globe. Various ways are embraced to handle the cancer. Generally, it is being done by designing anti-angiogenesis agents innovatively, by identifying and turning off the action of endogenous factors involved in abnormal growth of blood vessels, by exploring the natural sources to hinder angiogenesis or by lessening the quick isolating endothelial cells spreading cancer. The angiogenic inhibitors are generally classified as follows;

a. *Endothelial cell growth inhibitors:* This class of inhibitors works basically by instigating apoptosis and consequently restarting the endothelial cell development. The best example is endostatin (Decker, 1998).

b. *Angiogenesis-signaling blockers:* These are the inhibitors, essentiall for fundamental fibroblast growth factors (bFGF) and VEGF. The best example is Avastin (Folkman, 2002).

c. *The receptor blockers:* They repress ECM eradication and synonymously to inhibitors of MMPs. These work by restarting the receptor activities of numerous development factors (Guba *et al.*, 2002).

2.0 Angiotherapy and its Mechanism

Angiotherapy is similar to the abnormal vessels. It is getting a consideration from various strata of specialists due to its curosity, sustainability, non-invasiveness and out of the box approach. Before discussing the common angiotherapic system it will be smarter to feature a portion of its instruments.

The reason of angiotherapy is to hinder basic stages of

Significance | ***This study can accelerate***

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angiogenesis. This can prompt lessened vessel porousness and blood perfusion, and vascular shrinkage which diminishes the likelihood of a tumor getting oxygen and nutrients (Condeelis and Pollard, 2006). Theoretically, anti-angiogenic therapy may return tumor blood vessels into the ordinary state, and enhance the quality and conveyance of cytotoxic therapeutic agents (D' Souza, 2014). Hence, anti-angiogenic agents work by decreasing the permeability of blood vessels in tumors, and the scattering of interstitial liquids. This leads to a decrease in interstitial pressure and eventually reduces tumor hypoxia (Maeda *et al.*, 2009). If anti-angiogenic therapy is utilized along with cytotoxic agents, the impact of these agents increase, while tumor vessels are at same time standardized (Damgé *et al.*, 1990).

Angiogenesis can be regulated by stimulator substances like chemokines, development elements and extraordinary angiogenic enzymes, some endothelial receptors, and adhesion molecules; and also by some inhibitors like angiostatin and endostatin (Siddiqui *et al.*, 2009). An imbalance between inhibitors and inducers levels can lead to host's of health related issues like cancer, arthritis, heart and brain ischemias (John *et al.*, 2015). During angiogenesis a series of physiological events line each other in a very precise way. These include the scattering of the extracellular matrix; the migration, adhesion and expansion of endothelial cells; and tube formation (Maeda *et al.*, 2009). For these reasons, the inhibitors of the pathological angiogenesis have promising potential in curing the angiogenesis diseases that establish the new class of therapeutic operators in the field of "angiotherapy". Studies have demonstrated that various nutraceutical agents, including those got from natural products, exhibit poor bioavailability when consumed orally (van Walsem *et al.*, 2015). So far, large portion of new potential therapeutics have demonstrated poor pharmacokinetics and biopharmaceutical properties. Therefore, upgraded tranquilize conveyance frameworks are justifies to permit the circulation of therapeutically active drug molecules to the site of action, while limiting the exposure of solid organs and tissues to these molecules as much could reasonably be expected. By the application of Nanotechnology we may accomplish a proficient medication conveyance at the site of need with a maximum effectiveness and a minimum fuss. The safety profile of these drugs is likewise exceptional (El-Nahas *et al.*, 2017). Phospholipids are believed to be valuable transporter molecules for drug delivery. They serve as vehicles for the drug molecules which should have been directed in controlled discharge forms (Xu *et al.*, 2013). This method of planning will limit the toxicity and an improved solubility (Shin *et al.*, 2007). Phytosome is a complex of the drugs that have amphillic properties. It has the ability to bind the phospholipids (Zhang *et al.*, 2013). However, in this review article our focus is fundamentally on the various inhibitors, natural and manmade, with their chemical perspective in angiotherapy.

3.0 Phytochemicals and Medicinal Herbs in Anti-Angiogenesis

Different sorts of cancers are being treated by utilizing the traditional plant sources. The main reason is their almost no symptoms as compared to chemotherapy by synthetic compounds and economy of production (Cragg and Newman, 2005). A genuinely huge number of phytochemicals are found in plants. For example, phenolic diterpenes, flavonoids, polyphenolic acids and tannins (Dawidowicz *et al.*, 2006). Plant Polyphenolics, especially, have drawn the attention because of their potential use as therapeutic agents to target cancer, heart diseases and angiogenesis (Yoysungnoen *et al.*, 2008). Polyphenolics are typically wealthy in antioxidants (Münzel *et al.*, 2010), and contribute in anti-proliferation, anti-carcinogenic and anti-neovascularization processes. Even few phenolics and flavonoids are accounted to diminish the production of reactive oxygen species (ROS) in biological frameworks. ROS create oxidative pressure and contribute in pathologies related with cancer and extreme vascularization. The cancer that develops due to ROS is malignant due to mutations in gene expression and DNA (Kampa *et al.*, 2007). A few *in vivo* and *in vitro* reports have demonstrated the ability of flavonoids to hinder the cancer growth (Batra and Sharma, 2013). In initial stages of cancer flavonoids hinder metabolic activation of carcinogens. In later phases, they induce apoptosis, inhibit cancer cell proliferation and tumor metastasis (Clere *et al.*, 2011).

The presence of phenolic compounds in redox frameworks acts in a multifaceted manner. They may either act as hydrogen donators, diminishing agents, a metal chelating agents or in some cases as singlet oxygen quenchers (Gordon, 1990). Phenolic compounds also help to kill the free radicals generated in the metabolic pathways (Gordon, 1990). Conclusion from these investigations obviously demonstrates a connections between flavonoids, phenolics and their anti-angiogenic, anti-proliferatory and anti-oxidant activities (Stoclet *et al.*, 2004). Diagrammatic classification of polyphenols (flavonoids) has been shown in Figure 3.1.

3.1 Epigallocatechin Gallate/ EGCG

Epigallocatechin gallate (EGCG) is a type of catechin. Its distinctive fixations are found in different varieties of tea. The fruits like apple, plums etc. have trace amount of EGCG in them (Bhagwat *et al.*, 2014; Rashidi *et al.*, 2017). Its structure has been shown in Figure 3.2. Anticancer activity of EGCG is related with the inhibition of invasion by hindering the movement of urokinase (Fujiki *et al.*, 2018; Suganuma *et al.*, 2016) or the matrix metalloproteinases (MMPs) (Garbisa *et al.*, 2001), or by the expulsion of oxygen radicals (Zhang *et al.*, 2000), all of which play key roles in cancer invasion and metastasis. Analysis proposed that green tea consumption by mice has significantly hinder angiogenesis. Few measures of corneal neovascularization like

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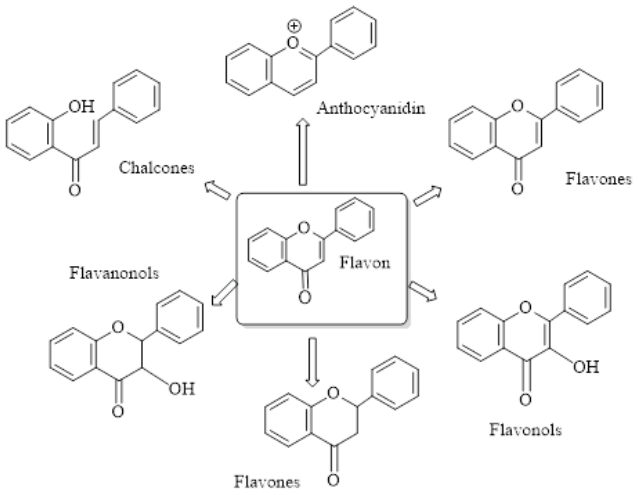

Figure 3.1 | Different groups of flavonoids.

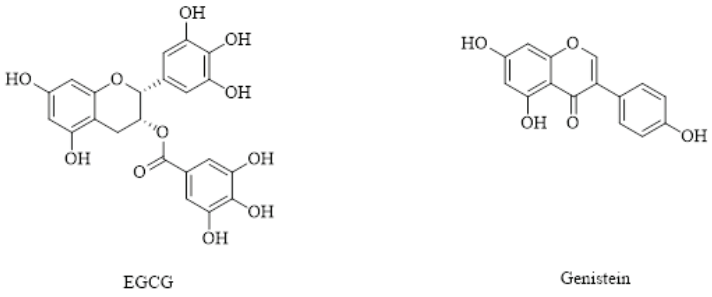

Figure 3.2 | Chemical structures of EGCG and Genistein.

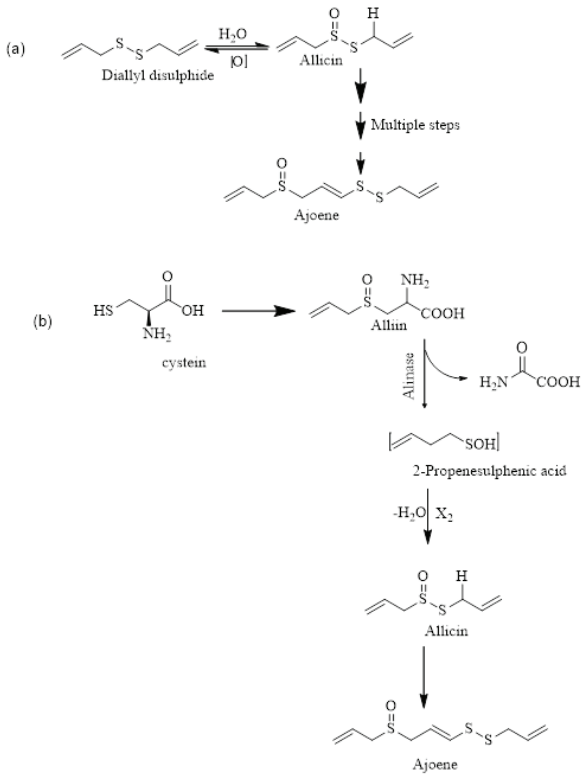

Figure 3.3 | (a) Diallyl disulphide pathway for Ajoene formation and (b) Cystein pathway for Ajoene formation.

blood vessel length, area of neovascularization exhibit that oral consumption of green tea by mice inhibited angiogenesis. EGCG inhibited bovine capillary endothelial cell proliferation that had been animated with fibroblast development factor. Importantly, this growth hindrance was limited to endothelial cells; nonendothelial cells, including murine T241 fibrosarcoma tumour cells, murine fibroblast cells, and rat smooth muscle cells were insensitive to EGCG treatment at the concentrations used (Cao and Cao, 1999; Rashidi *et al.*, 2017).

3.2 Genistein

Genistein is a soy isoflavone and is considered to apply strong antitumor effect partially through its anti-angiogenesis property. However, the precise molecular mechanism is yet obscure. Previous investigations have demonstrated that genistein down-regulates expression of pro-angiogenic factors by mean of inhibiting protein tyrosine kinase (PTK) activity both in breast cancer cells and in xenograft tumors. Anti-angiogenic effect caused by flavonoids is caused by control of VEGF and by inhibiting NFB, PI3-K/Akt, ERK 1/2 signaling pathways. It has been accounted that both genistein analogs quercetin and luteolin suppress VEGF induced phosphorylation of VEGF receptor 2 and their downstream protein kinases AKT, mTOR, and ribosomal protein S6 kinase in HUVEC (Pratheeshkumar *et al.*, 2013). Genistein has additionally been accounted to repress angiogenesis *in vitro* and *in vivo* (Farina *et al.*, 2006; Granese *et al.*, 2015). Genistein at micromolar concentrations has been reported to modify the statement of 256 genes related to HUVEC's proliferation (Mojzis *et al.*, 2008). Its structure is shown in figure 3.2.

3.3 Garlic (Allium sativum) and Anti-angiogenesis

Sulfur-rich *Allium* are regularly good dietary source of selenium (Se), which is frequently inadequate in the human diet and is essential for antioxidative, protective enzymes (González-Morales *et al.*, 2017), Anticancer role of allicin found in garlic was first discovered by Cavallito in 1944 (Block, 2010). Allicin in garlic disintegrtes into ajoene and diallyl disulfide in a series of steps, as shown below. All these compounds were found to have exceptional anti-cancer activities (Sela *et al.*, 2008). Some of these pathways are illustrated in figure 3.3 (a) and (b) (Block *et al.*, 2017). Florinated compounds of allicin and ajoene were synthesized by a number of ways in figure 3.4 (a) and (b).

Besides these chemicals, there are certain plant sources like *Humulus lupulus*, *Hypericum perforatum*, *Panax ginseng*, *Coptis chinensis* and *Rheum palmatum* are evident to have anti-cancer properties (Varinska *et al.*, 2010). How there is still so much debatable, their actual role anti-cancer chemicals cannot be acknowledged except if approved by authenctic scienticfic principles (Dulak, 2005).

Naturally found Inhibitors of Angiogenesis

A number of naturally occurring inhibitors have been explored and investigated, among the most widely recognized are angiostatin, interferons, endostatin, a few interleukins and retinoic acid.

Angiostatin

Angiostatin is produced by the cleavage of amino terminal fragment of plasminogen and acts as an endogenous inhibitors of angiogenesis. It is composed of three to five kringle domains (See Sturcture 3.5). Its major effects incorporate the hindrance of EC migration or their proliferation. An X-ray crystallographic picture of angiostatin shows that one of its kringle structures, K1-3, has exceptional proclivity with proteins and makes it a valuable inhibitor (Abad *et al.*, 2002).

Retinoic acid (RA)

Retinoic acid (RA) is the parent compound and four types of generations of retinoids got from it. Retinoids impact an expansive range of procedures connected with vessel formation, separation and so on. (Altucci and Gronemeyer, 2001). RA is yet another potential inhibitor of angiogenesis. RA showed very amazingly potential when employed on rats with thyroid cancer. It reduced the cell expansion and the secretion of VEGF. Similarly, the volumes of tumours were also reduced in the animals, receiving treatment with RA (Hoffmann *et al.*, 2007). First and second era retinoids include retinol and etretinate individually and demonstrate a marked ability to bind with the receptors shown in figure 3.6.

Studies suggest that retinoids are valuable in the treatment of cancers related to thyroid, prostate or colon. A similar study carried out by Spitzwig in 2003 has demontrated the adequacy of RA by the stimulation of sodium iodide symporter of thyroid carcinoma. (Spitzweg *et al.*, 2003). Unfortunately, currently it is elusive any plant based compounds used in angiotherapy.

4.0 Common Synthetic Angiogenic Inhibitors

4.1 Thalidomide

It is use for the treatment of disease and cancers (Uhl *et al.*, 2006). A novel use of Thalidomide to restrain angiogenic vascularization in rodents (D'Amato *et al.*, 1994). Birth defects caused because of Thalidomide were investigated (Vargesson, 2009). Thalidomide has many side-effects due to metabolic activity and one of these products is CPS49, a fluorinated analogues of thalidomide (synthesis shown in figure 4.1). CPS49 when applied to the upper half of a developing chicken embryo, the blood vessels started to break down very rapidly (Therapontos *et al.*, 2009).

Thalidomide and its analogues influence different tissues and process like angiogenesis by interfering their cytoskeleton. The ability of thalidomide to bind specific endothelial cells is still enigmatic (Kusumbe *et al.*, 2014). Although thalidomide has experienced an abnormal shift in status from the epitome of favouritism to the abyss of rejection and recapturing the lost magnificence. Its conceivable use in the angiotherapy can be visualized in near future because of some hopeful findings.

Lenalidomide

Another analogue of thalidomide, lenalidomide (shown in figure 4.2 (a)) has demonstrated its immunomodulatory potential for nemerous myeloma. Oral administration of lenalidomide impedes the growth factor linked angiogenesis and endothelial cell migration. The conceivable acivity of this medication is may be through akt phosphorylation pathway. Bevcizumab or Avastin (shown in figure 4.2 (b)) has an instigated impact on VEGF induced proliferation on human umbilical vein endothelial cells and neovascularization of corneal cells. The reaction was independent of concentrations of a vastin used (Han *et al.*, 2009).

Sunitinib

Sunitinib is a tyrosine kinase inhibitor utilized in renal carcinoma and gastrointestinal tumours. Mendelsohn and Karas revealed that oral organizaion of sunitinib to athymic bare mice inhibited the growth of many human tumor xenografts. It was reported that a single oral dose (40 mg/kg) inhibited (i) VEGFR2 phosphorylation in mice *in vivo* bearing the A375 melanoma or (ii) PDGFRb phosphorylation in mice bearing the SF767T glioma. This schedule successfully blocked receptor phosphorylation for more than 12 but less than 24 h. Despite the absence of continuous restrain of receptor phosphorylation, this regimen effectively decreased mean vascular thickness (a measure of anti-angiogenesis) and controlled tumor growth. The authors concluded that maintaining plasma sunitinib forces above 125 nM (50 ng/mL) for 12 h on a once daily oral spoke to an initial therapeutic goal in human clinical trials (Mendelsohn and Karas, 1999). Structure is shown in figure 4.3.

Possible Hazards of Anti-angiogenesis Inhibitors

Therapeutic treatment utilizing these inhibitors may cause postponed wound healing and even hypertension. Tissues may create resistance either innately or by acquisition. Furthermore, a shortage of valid and predictive biomarkers has still numerous inquiries to be addressed acceptably (Chen and Cleck, 2009).

Angiotherapy Using Protein Inhibitors

Metalloproteinases

They are also called matrixins and are endopeptidases containing zinc (Verma and Hansch, 2007). These compounds degrade extracellular matrix proteins. It is believed that that they also shape the cell conduct like cell expansion, migration, separation, apoptosis and angiogenesis (Van Lint and Libert, 2007). The zinc binding part of the enzyme is basic for its activity, the part named as P_1 is real determinant of its activity, the part named as α provides the enzyme its major pharmacokinetic properties, the sites showing points P_2 and P_3 are accessible for extensive variety of substituents, all these groups are upheld on a succinate type of backbone (structure shown n figure 4.4). Formation of new vessels is an exceptional and complex process. A typical antigenic process involves the stimulation of walls of endothelial cells of an officially existing capillary. After this human metalloproteinases (hMPs) make space for the attack of new cells by dissolving and breaking the extracellular framework in proteinaceous shape. This follows the mitotic procedure generating new endothelial cells. These cells are

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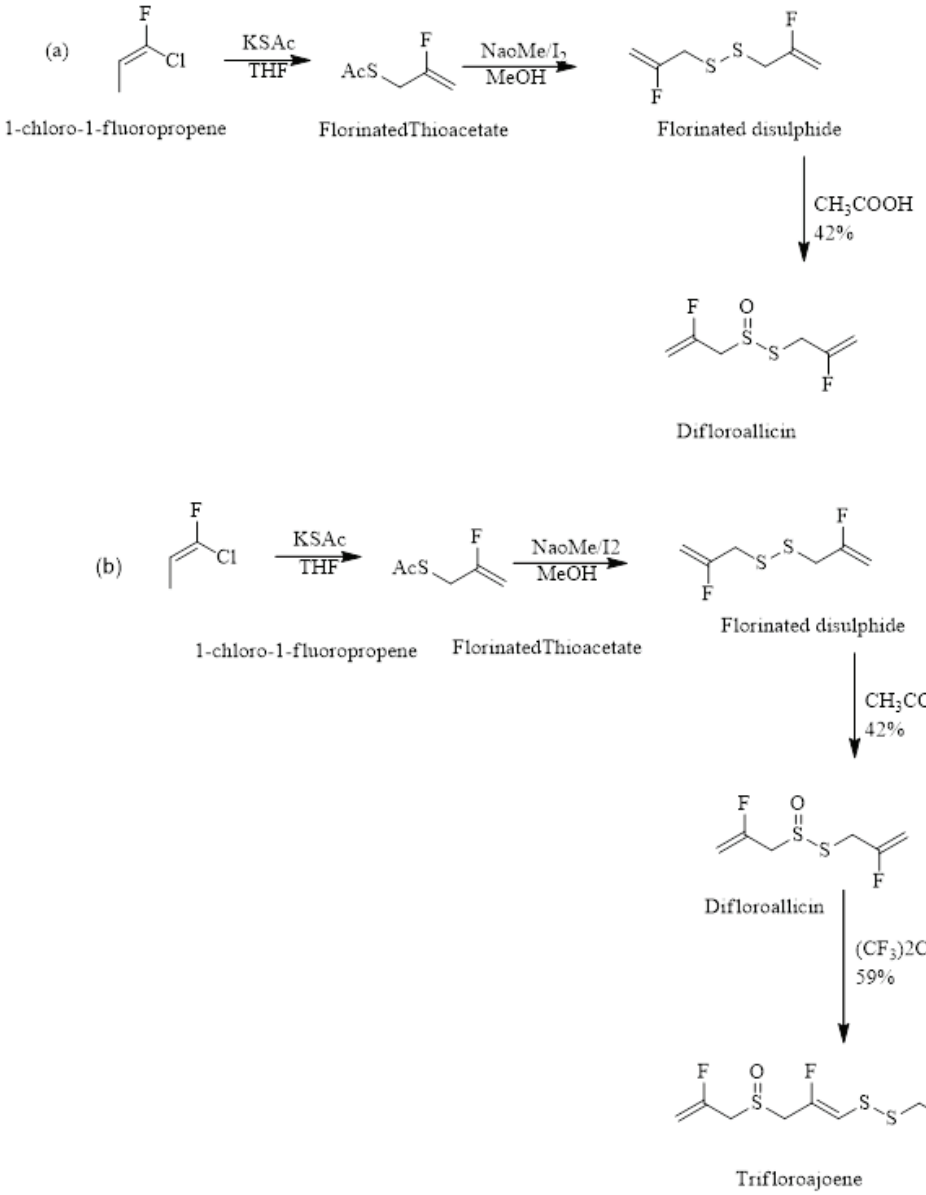

Figure 3.4 | (a) Synthesis of florinated allicin and (b) Synthesis of trifloroajoene.

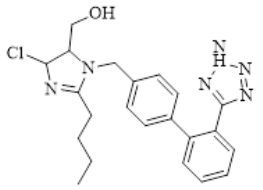

Figure 3.5 | Structure of Angiostatin.

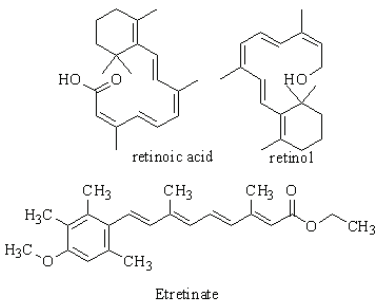

Figure 3.6 | Shows the ability of retinoids to binds with receptor.

the result of this rearranged process responsible for vessel formation. In this way a system of vessels is established which helps and supports in cancer growth (Pavlakovic *et al.*, 2001).

Angiogenin

Another potential inhibitor of dangerous angniogenesis is Ribonuclease 5 or Angiogenin. Recent investigations has demonstrated a reasonable relationship between Angiogenin and tumour growth (Li and Hu, 2012). When it is translocated to the cell nucleus, the result is the upregualtion of the rRNA associated with the procedure of transcription whereas the thump down strains way to the downregulation of rRNA (Gao and Xu, 2008). Angiogenin is thought to influence the human cell line or Hela by interfering in its ability to multiply and this manner is considered to be a potential therapeutic remedial in future (Tsuji *et al.*, 2005). The figure 4.5 is showing the upregualtion of a DNA strand into RNA within the sight of ribonuclesase.

Estrogens

There are three major types of estrogens as estrone (figure 4.6 (a)), estradiol (b), and estriol (c). Estrogens work by managing the cell events by activating their specific family. These receptors are called estrogen receptors (ERs). These ERs regulate a host genes engaged in the vascularization. This is apparent from the presence of enzyme aromatase in the recently growing blood vessels and Endothelial cells (ECs) (Mendelsohn and Karas, 1999). In a study including the mice insufficient in ERs were produced and then their angiogenic functionality was monitored, it was

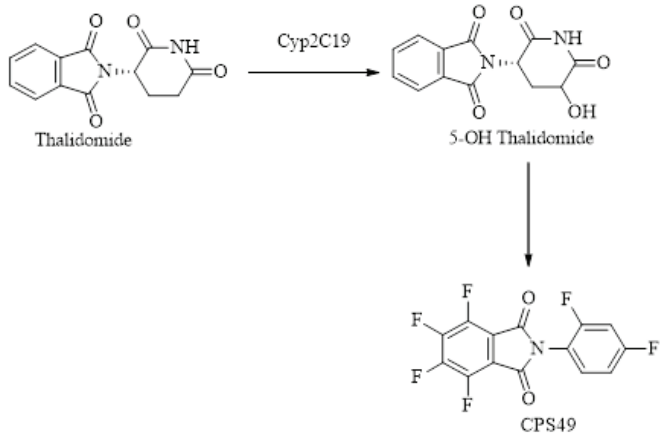

Figure 4.1 | **Breakdown of thalidomide**

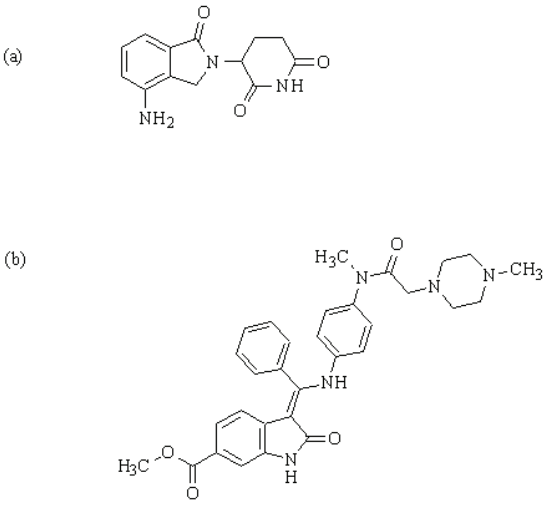

Figure 4.2 | **(a) Chemical structure of Lenalidomide and (b) Chemical structure of Bevacizumab/Avastin.**

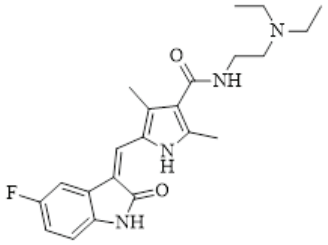

Figure 4.3 | **Chemical structure of Sunitinib.**

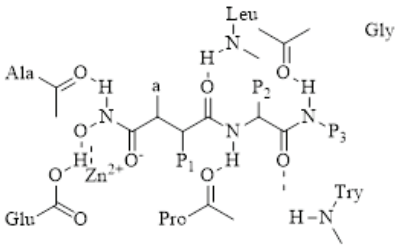

Figure 4.4 | **Structure of a human metalloproteinase**

observed that these mice had host genes and many types of vasculature abnormalities (Zhu *et al.*, 2002). This demonstrates the importance of estrogens in expression of many genes that participate in the new blood vessel formation processes (Tamura *et al.*, 2002).

Interleukins

Interleukins are a wide variety of proteins that are associated with the motioning inside and over the cells. These are produced by leukocytes (Sims *et al.*, 1988). Out of a few human interleukins being studied are being considered for various jobs, Interleukin 8 (IL-8) is the most critical one with context to inflammatory and angiogenic functions. It is discharged by the antigens and releases the signals essentials for vasculature formation. The chemotectic activity of interleukin 8 causes the vasoconstriction at the site of aggravation and back off the blood flow at the purpose of contamination. IL-8 is thought to give rise to colorectal disease by acting as an autocrine and perhaps separating the metalloprotein molecules (Itoh *et al.*, 2005).

Basic Fibroblast Growth Factor (bFGF)

Basement membranes (BM) contain basic Fibroblast Growth Factor (bFGF) which is hypothesized to encourage the process of wound healing and fresh blood vessel formation or angiogenesis (Pavlakovic *et al.*, 2001). An examination was done to talk about the role of bFGF on endothelial progenitor cells (EPCs). It was observed that bFGF has increased the angiongenesis. Application of bFGF as a therapeutic target for cartilage associated to cancer or chondrosarcoma (Therapontos *et al.*, 2009).

Vascular Endothelial Growth Factor (VEGF)

Vascular Endothelial Growth Factor (VEGF) is among the most important contributors of angiogenesis and tumorigenesis (Bergers and Benjamin, 2003). It can actuate or all over again angiogenesis. The type of cells in which it indicates activity range from muscle cells to neurons, however, its key role is on the endothelial cells (shown in figure 4.7). The functions performed by Vascular Endothelial Growth Factor (VEGF) incorporate the expression of genes, permeability of vessels, cell expansion, migration and their survival (Adair and Montani 2010). All this is done when VEGF bind to their receptors, although the pathway in each case might be unique. Studies on laboratory rats uncover that the VEGF concentration was higher in the embryonic stages and any variation from the norm in them resulted in adverse results (Ji *et al.*, 2013). A portion of the pathways received by VEGF in their

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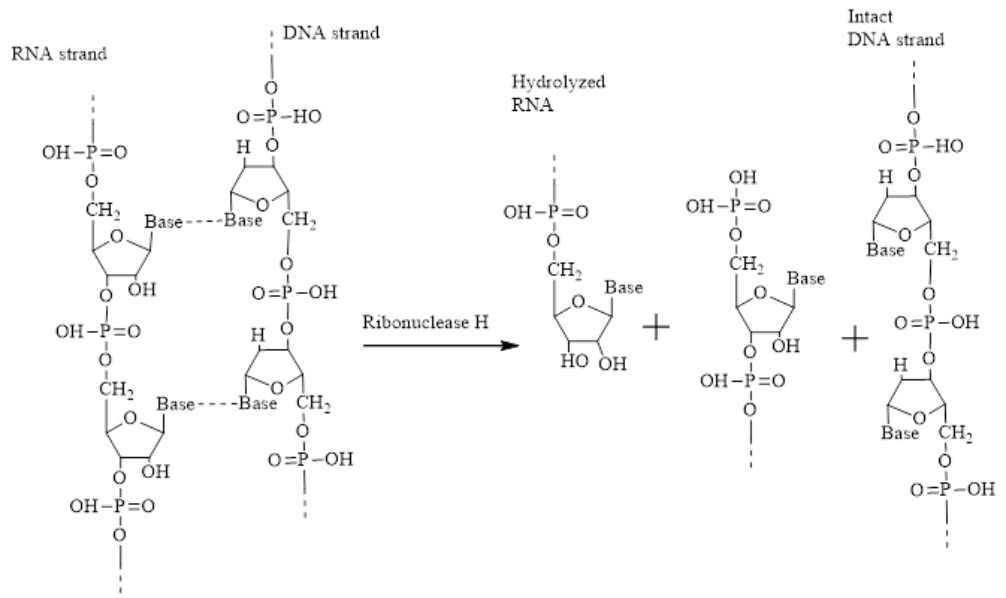

Figure 4.5 | **Working of Ribonuclease on Strands of DNA**

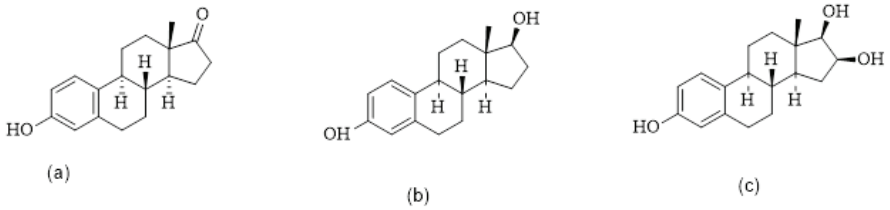

Figure 4.6 | **(a). Structure of estrone, (b) Structure of estradiol and (c) Structure of estriol**

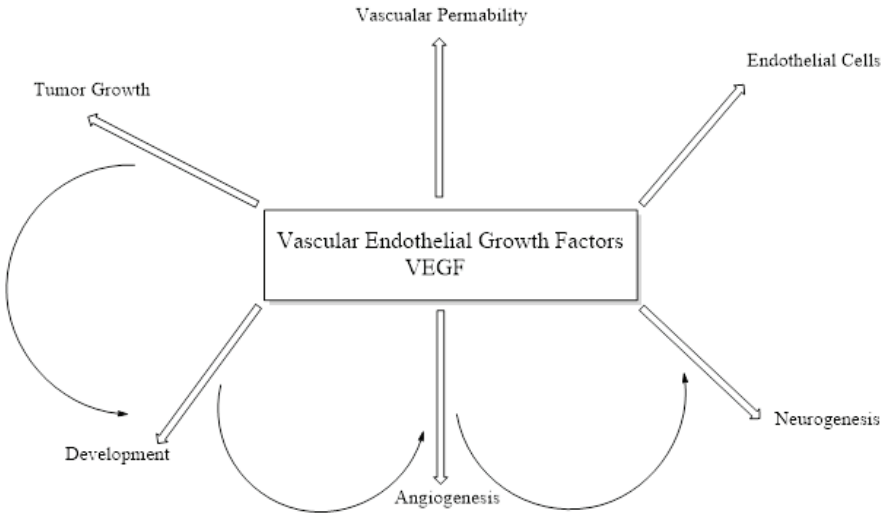

Figure 4.7 | **Shows factors for VEGF**

activity are illustrated in figure 4.7 (Suárez and Sessa, 2009).

Angiotherapy has far more encouraging impacts when contrasted with the chemotherapy. The purpose of chemotherapy is to kill he cancer cells directly or indirectly. Therefore, there are worthy chances of unexpected side effects and changes. As a result, the possibility to control the cancers will pose much tougher challenges in future.

On the other hand inhibitor instigated angiotherapy is more encouraging and safe. The purpose here is not to kill the cancerous cell however to focus on endothelial cell. This significantly diminishes the hazard reactions. At the point when the blood supply to the cancerous cells is disturbed or made restricted, the movement of cancer will be limited and slowed down.

Similarly, chemotherapeutic techniques maybe constantly pass on to death sentence to the cancerous cells but the inhibitors, I can say, give another 'expectation' to cells by doing so much to stop the tumor. For example to make the surrounding conditions more benevolent and favourable.

Some limitations

Since the movement of cancers follows very exceptional processes, therefore their comprehension is not a simple assignment. Each abnormal growth of vessels forces another challenge for the researchers on one hand and furthermore opens new horizons to be explored again. Despite everything we need authentic and valid biomarkers to highlight their clear route. Similarly, the knowledge of different signaling insruments (Suárez and Sessa, 2009) is still poorly understood and is basically based on suppositions rather than established facts. The logic behind the absence of spotlight on the auxiliary properties of different synthetics utilized. The most neglected area is perhaps the lack of focus on the structural properties of the different chemicals created. If a repository of various properties of different classes of chemicals and the groups is developed, this will truly encourage our motivation. A perfects model is the work on analogues of organosulphur compounds from garlic.

Future Possibilities

Anti-angiogenic treatment is getting increasingly advanced with the appearance of innovation. The spread of tumors presently being understood with current instruments like getting a magnetic resonance image of the affected site, HPLC, FT-IR, SEM, TEM, and likewise physico-chemical spectral analyses can also be utilized to upgrade and make the research yield more gainful, genuine and legitimite.

Suggestions

A varied methodology can be more productive in angiotherapy. The findings with encouraging results should be put to more through experimentation. This will help to limit the region of interest and make our work more focused.

Author contributions

Mr. Imran initially started the manuscript. It was further polished by Mr. Shan. The corresponding author managed these students to compile the manuscript in its final form.

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Competing financial interests

Authors have declared that no competing interest exists.

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