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Cover Page Footnote

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Angiogenesis' Overall Effect on Health and Diseases

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ABSTRACT

Angiogenesis is the process of forming new blood vessel and capillaries from pre-existing vessels. Angiogensis is the foundation of reproduction and growth and as well as, responsible for healing of wounds and tissue repair. Angiogenesis is a multistep process that involves the induction of angiogenesis by VEGF, destabilization of extracellular matrix membranes, sprouting of vessels, migration of cells, and maturation. However angiogenesis is also the root of cancer and age related dieseases such as muscular degeneration and several other major cardiovascular diseases. There is evidence of various angiogenesis inhibiting therapies that are effective as a treatment method by interfering with the development and growth of blood vessels and tumors. This article focuses on the the mechanism of angiogenesis and how inhibiting angiogenesis is a crucial step in combatting cancer and disease. The article discusses the potential of treatment therapies such monoclonal antibodies and consumption of foods that exhibit anti-angiogenic properties such as fruits, vegetables, and berries.

INTRODUCTION

What is the leading cause of death in the U.S.? In 2019, the leading cause of death was due to heart disease and following behind is cancer according to the National Vital Statistics System, Mortality, which remained the same in 2018. To understand the emergence of cancers and diseases, the role of angiogenesis in disease and cancers must be understood.

Angiogenesis is the process of forming new blood vessel and capillaries from pre-existing vessels. Cell growth is regulated by normal cell division, checkpoints and cell signaling. Angiogenesis brings in oxygen and nutrients to the body's tissues allowing for the repair and healing of developing or injured tissues. In pathologies, specifically cancer, chemical signals and regulations are ignored by the cells, and they continue to divide and become cancerous. In abnormal angiogenesis, the blood vessel is formed by angiogenic stimulators released to the surrounding cells of a tumor mass that encourages the growth of new blood vessels. In turn, angiogenesis supplies the growth and metastasis of cancer cells supplying the area with nutrients and creating a perfect tumor microenvironment with angiogenic activators that are manipulated to create more blood vessels. In conclusion, angiogenesis plays both a crucial role in health and disease. However, currently knowledge on the effects of angiogenesis and angiogenic therapies are limited and aren't widely used**.** In this paper I review the importance of relevant studies that explore a potentially exciting treatment using anti angiogenic therapies for disease and cancer treatment. This article will be an overview of the promising anti-angiogenic therapies as well as the methods and results of studies previously done using angiogenesis inhibitors in various diseases such as lung cancer and cardiovascular diseases. Without a doubt regulating angiogenesis will benefit the advancement of treatment in the field of medicine.

ANGIOGENESIS

The matrix is a dynamic structure undergoing consistent deposition, degradation and modifications of its components [1]. There are two types of known angiogenesis, sprouting and the intussusceptive splitting of preexisting blood vessels; both of which are triggered by hypoxic tissues and are not very well understood [2]. Sprouting angiogenesis is the formation of new vessels from existing blood vessels characterized by the sprouting of endothelial cells triggered by VEGFs [2]. Without the vascular network, the spread of cancer tissue would not proliferate but be hindered in growth due to the lack of angiogenesis [3].

The process of sprouting angiogenesis starts by the activation of endothelial cells through growth factor molecules or VEGF. VEGF are released by nearby hypoxic tumor tissues and will later play an important factor in sprouting angiogenesis, as they are sufficient in triggering angiogenesis [4]. Endothelial cells are found in the inner blood vessels lined by a single cell layer that contains VEGF receptors. The expressions of these specific receptors are bound by VEGF ligands on the blood vessels of endothelial cells triggering a signaling cascade and activates angiogenesis [5]. The binding of

VEGF to VEGFR releases proteases, which encourages the loosening of nearby blood vessel cells. Proteases, specifically matrix metalloproteinases (MMPs) have the ability to target many proteins, their targets include growth factors-binding proteins, cell surface receptors, cell-cell, cell adhesion molecules [6]. MMPs are the key participant in tip cell functioning and breaking down the basement and extracellular matrix (ECM) [7]. The ECM is present in all cells and consists of various components of different signaling molecules that are secreted from mesenchymal cells that are important for development. The loosening of the vessel cell allows for the sprouting mechanism that forms an extension of endothelial cells as a new vessel grow towards an angiogenic stimulus VEGF-A [2]. As the capillary sprout emerges from endothelial cells that will elongate, it extends the filopodia and explores the microenvironment becoming tip and stalk cells.

The mechanisms of notch signaling pathways and VEGFs enforce a cascade that continuously re-evaluates with the aid of many other signaling pathways that participate in the regulation of specializing into tip cells [8]. Morphically, the tip cells will soon be joined cell to cell by the merging of the vacuoles, which creates a uniform lumen shared by many cells but a separated cytoplasm. Tip cells contain receptors and exhibit migratory behavior in endothelial cells during sprouting angiogenesis and they sense the environment for guidance cues. The tip cell expresses Netrin receptor uncoordinated-5B (UNC5B) and Neuropilin (NRP), which will help detect attractive signals from the tissue microenvironment and then follow into a multistep processes of adhesion and detachment, and leading to directed migration [7].

The tip cells form filopodia and lamellipodia which are involved in cell migration. Filopodia are plasma membranes that contain bundles of actin filament that aids in the tip cells to probing their environment [7]. Lamellipodia are thin fan-like projections that are found in the leading edge of many moving cells, such as endothelial tip cells [9]. Lamellipodia are regarded as the major driving force of mesenchymal cell migration in both normal and disease-causing environments [10]. The movements of cell migration are in the protrusion of the leading edge, adhesion of the leading edge, de-adhesion of the trailing edge, and then movement of the cell body [11]. The mechanism starts with determining the direction of the cell body, and then the cell extends a protrusion in the direction of the movement via actin polymerization in the leading edge. The cell then adheres the leading end to the surface in the direction in which it is moving then de-adheres the cell body from the rear [11]. On the contrary, stalk cells are endothelial and proliferative but do not form filopodia and follow behind tip cells [8]. Stalk cells form the body and elongate as the sprouting occurs [12]. However, it has been found that previously inhibited stalk cells can be relieved from their inhibition and then become tip cells [8]. In other words, tip-stalks do not exhibit a fixed cell fate but instead, a dynamically exchangeable phenotype specification fluctuation [8].

The uniform lumen will provide direct supply of oxygen and glucose to the hypoxic tissue, providing a perfect microenvironment. When the tissue flourishes because of the oxygen it will increase in size, further develop, and possibly exhibit more harm by metastasis. If the tumor metastasis occurs, the tumor will travel to new places in the body through blood vessels and capillaries in search for a new environment to grow. In essence, the blood vessels provide a route by which tumor cells exit the tumor site and enter circulation [13]. Overall, tip cells and stalk cells work together to form a vascular sprout that grows towards the VEGR in response to the chemical, mechanical factors, and some degree of random motility [14].

Intussusceptive Angiogenesis is the lesser understood angiogenesis method discovered after sprouting angiogenesis, yet it is faster and lacks dependence on endothelial cell proliferation for growth. The major difference between this two angiogenesis' is the presence of pillars in the intussusceptive method, which are made of connective tissue called tissue pillars, and inserted into the lumen resulting in division of the lumen and an increase in the density of the capillary network [15]**.** Sprouting and intussusceptive angiogenesis are both critical to processes involving wound healing and embryonic development. However over 70 diseases, such as cancer and occlusive vascular disease relay on angiogenesis for development and proliferation [16].

Angiogenesis plays such a huge role in disease and illness, theocratically inhibiting angiogenesis could prevent a lot of diseases and illnesses, since without these factors (oxygen and nutrients) they wouldn't adequately meet the requirements to promote angiogenesis. Tumors that grow bigger than a few millimeters will need oxygen and nutrients in order to enlarge. Similarly, diseases like cancer will need oxygen and nutrients in order to invade nearby tissues and metastases, without it the cancer will remain in a dormant state. In another relevant study done, a region that lacked blood circulation the tumors grew to a size of approximately 1-2mm^3 before they halted. Unfortunately, it was found that these tumors grew beyond 2mm^3 when placed in an area with angiogenic support [17]. Therefore, if oxygen and nutrients are inhibited from nourishing pathological tissues including hypoxia, and the biochemical and physiologic pathways that facilitate development of these tissues are altered and intercepted in some way, then some diseases and illnesses will not be successful in the development malignancy.

Angiogenesis inhibitors express anti-angiogenesis activity, while the tumor angiogenic switch seems to be activated when the balance shifts from angiogenic inhibitors to angiogenic stimulators [18]. Angiogenesis inhibitors work by blocking the growth of the blood vessels that support the tumor development rather than inhibiting the growth of the tumor tissues.

MOLECULAR MEDIATORS IN ANGIOGENESIS

There are many molecular mediators that play a part in angiogenesis. The vascular endothelial growth factor (VEGF) is one of the most crucial molecular mediators in the development of new blood vessels from existing blood vessels. These molecular mediators that aid angiogenesis keep the body healthy. Other growth factors that are a part of the formation of new blood vessels like VEGF include fibroblasts growth factor (FGF), tumor necrosis factor-alpha (TNF- α), transforming growth factor (TGF-β), and the angiopoietins (Ang) [19]. Expression of VEGF is fundamental as it has an extensive range of functions and acts jointly on many varieties of cell types, in essence allowing for homeostasis in the human body. The ligands of the VEGF family include VEGF-A, VEGF-B, VEGF-C and VEGF-D and bind to VEGF receptors such as VEGFR1, VEGFR2 and VEGFR3. VEGF plays a role in the physiological processes of development that supply blood and oxygen to cells through a series of vessels, which allows for wound healing and increasing blood flow to an area [20]. The ligand VEGF-A/receptor VEGFR-2 signaling appears to be more frequent and distinguished as the predominant mediator involved in the angiogenesis pathway [14]. Increasing blood flow and angiogenesis can benefit certain health related problems like heart disease, arterial disease, and promote wound healing. Other physiological processes that are associated with upregulation of VEGF/VEGFR- system include VEGF being widely expressed during the female reproductive cycle, reproductive cycle, as well as bone repair [21].

On the other hand, increased angiogenesis is non-therapeutic and harmful in the case of tumor development and growth, sepsis, arthritis and other diseases. Tumor angiogenesis is stimulated by VEGF through several mechanisms, including enhancing endothelial cell proliferation and survival; increased migration through the formation of lattice network and invasion of endothelial cells; and enhancing chemotaxis [22]. Therefore, it has been concluded that inhibiting VEGF would interrupt the growth of tumors as it plays such a vital role in the formation of blood vessels. Inhibition of VEGF signaling with anti-VEGF strategies were designed to target abnormal angiogenic production and used in anticancer therapy. Many molecules and proteins such as small molecules (kinase inhibitors), peptides, antibodies and aptamers play a critical role in the body in the formation of complex macromolecules and immunological protection from intrinsic and extrinsic factors. These important agents create essential building blocks that allow for the healthy functioning of the body. Interestingly enough, it has been confirmed that using these agents and combination of other treatments, have the potential to work against and block VEGF and be used as a treatment in cancer patients. Cancers lacking angiogenesis will remain latent and tumors do not grow if blood isn't supplied which is why angiogenesis is an important topic in medicine. In clinical trial patients with lower levels of VEGF expression, survival was significantly greater than patients with higher levels of VEGF expression found in the body. The first FDA inhibiting angiogenesis target therapy drug, bevacizumab was officially approved in patients with metastatic colorectal cancer, metastatic breast cancer, lung cancer, renal cell carcinomas and glioblastoma multiforme [23].

ANGIOGENESIS INHIBITORS

There are various therapies including angiogenesis inhibitors being used as a treatment method by interfering with development and growth. Monoclonal antibodies are laboratory made molecules that act as a human antibody protecting our immune system by mimicking natural immune system functions. Monoclonal antibodies are one of the most significant strategies for treatment of cancer and other diseases. Examples of some monoclonal antibodies that act as angiogenesis inhibitors are Bevacizumab (Avastin), Aflibercept (Zaltrap) and Ramucirumab (Cryramza) [24]. These monoclonal antibodies work by targeting VEGF and VEGFR in the body.

Bevacizumab (Avastin) is a recombinant humanized immunoglobulin G (IgG) monoclonal antibody that targets VEGF-A and inhibits formation of the VEGF-A and VEGFR-2 complex [24, 25]. In 2004, US FDA approved Bevacizumab for treatment of metastatic colorectal cancer with a combination of chemotherapy [26]. Currently Bevacizumab is used on patients with various cancers, metastatic renal cell carcinoma, breast cancer, epithelial ovarian cancer, glioblastoma [24, 27-31]. As a result of successful clinical validation in patients who had taken bevacizumab to as act the specific inhibitor of VEGF-A/VEGFR2 interactions, there has been an increase of monoclonal antibody development to target VEGFR2 since it showed promising results for anti-angiogenesis [24].

Aflibercept (Zaltrap) is another monoclonal antibody that suppresses tumor angiogenesis by tricking VEGF-A, VEGF-B and PIGF [24]. In 2012, the FDA approved aflibercept to be used as a treatment on patients with resistant and progressive metastatic colorectal cancer

[32]. The FDA also approved aflibercept (Eylea) to be used as treatment on patients with wet age-related muscular degeneration, which is responsible for one most common cause of blindness in the elderly [32, 33].

Ramucirumab (Cyramza) is a monoclonal antibody that targets VEGFR-2 and is used in combination with paclitaxel to treat patients with advanced gastroesophageal cancer and have progressed after initial treatment [34]. It was approved by the FDA for non-small cell lung cancer patients, results from phase 3 of clinical trial showed promising results and even greater benefit for patients with aggressive tumor behavior of this antibody, however it has been found that Ramucirumab can cause severe toxicity in patients [35]. Other treatment therapies include consumption of foods that exhibit anti-angiogenesis properties. For example, these include fruits, vegetables, berries, parsley, and green tea.

GREEN TEA ANTI-INFLAMMATORY AND ANTI-CANCER PROPERTIES

The consumption of tea, specifically green tea, has been shown to inhibit the growth of angiogenesis. Green tea comes from dried tea plants of the *Camellia sinensis* family. Green tea has many benefits for the body, besides being rich in antioxidants research has found that drinking green tea may promote the prevention of disease. Polyphenols are the chemicals found in green tea that have antioxidant potential and are classified as catechins. Researchers have found that the extract of green tea contains high amount catechins that reveal anti-tumorigenic activity and anti-inflammatory capabilities [36]. Recent scientific research suggests that catechins exhibits efficient prevention of lung cancer, liver cancer, esophageal cancer, and prostate cancer [37]. Another research suggests that green tea consumption improves circulation and promotes vessel dilation which can be a preventive measure in chronic smokers from cardiovascular related diseases [38]. Overall catechins found in green tea have exhibited anti-carcinogenic, antimutagenic, anti-inflammatory mechanisms [39]. This is the reason why green tea has been heavily focused on as an anti-cancer and anti-inflammatory preventative.

GREEN TEA AND NSAIDS COMBINATION SYNERGISTIC ANTI-CANCER EFFECTS

In a study done in Japan in 1983, at the National Cancer Center Research Institute in Tokyo and Saitama Cancer Center Research Institute they have found that the main catechins found in green tea includes 10-15% of epigallocatechin gallate (EGCG), 6% to 10% epigallocatechin (EGC), 2% to 3% epicatechin gallate (ECG), and 2% epicatechin (EC) [40]. Out of the main catechins found, EGCG is the most abundant and active catechin found in green tea followed by EGC and ECG, it has been found that all of the catechin exhibit cancer preventive activity besides EC. It appears to be an inactive tea catechin and does not reveal effective anticancer activity, however when EC is combined with EGCG as a treatment it showed synergistic effects on apoptosis performance [41]. Many studies have been done on rodents targeting many organs with EGCG, the results reported that EGCG and green tea catechins can have systemic effects on cells towards anticariogenic activity [42]. Consuming a certain amount of green tea per day has seen a potentially preventative effect on lung , colorectal, liver and stomach [43, 44] and breast cancer [45]. In patients with breast cancer, it has shown that EGCG interfered with the function of estrogen receptors, inhibited cell proliferation of estrogen-induced breast cancer and increased the sensitivity of the tumor to drugs that target steroid receptors [46-48].

The outcome and success level of using EGCG as an anti-malignant and repressor of cancer differs in different types of cancer and per individual. It has been found that a combination of EGCG and nonsteroidal anti-inflammatory drugs (NSAIDs), like sulindac, acting synergistically for enhanced anticancer activity while treatment with either EGCG or sulindac alone have only a minor effect on promoting anticancer activity [49]. In conclusion when EGCG and green tea catechins are used in combination with other anticancer compounds, repression of tumor growth and anticancer effects increased in various human cancer cells [40].

SUBJECT AND METHODS

Angiogenesis inhibition in cancer prevention as a result of drinking green tea is significant because it's inexpensive, easily accessible, and not very time consuming. Drinking green tea daily can lower your risk of contracting cancer and improve your overall health. The antioxidants in green tea such as catechins inhibit angiogenesis naturally without the aid of medication. This is extremely relevant in today's society as many people are heavily reliant on medication and never have enough free time to worry about their personal health. This study focused on the preventative effects of the consumption of green tea and the significance of green tea in the prevention of and to decrease the risk of cancer and disease, like cardiovascular diseases, which are often observed in patients with lung cancer [44]. The study was done in 1986 in Saitama, Japan in residents over the age of 40 of 8,552 individuals. They first initiated this study by conducting a questionnaire covering 90 lifestyle factors, and then organized the results. From 1986 to 1997, a timespan of 11 years, there were a total of 488 cancer cases. They organized the results on green tea consumption in these categories, below 3,4-9 and over 10 cups a day on these cancer patients. They had found the

most common cancer in both sexes, in order, were cancers of the stomach, lung, colon, rectum and liver [44].

RESULTS

It was concluded among women who had high consumption of green tea, consuming over 10 cups a day had the most significant decrease in cancer by as much as 40%. Although, all categories of women who drank below 3 or 4-9 cups a day all show decreased signs of cancer [44]. Interesting enough, the results between women and men were opposite for those consuming over 10 cups a day. Among men who had high consumption of green tea, consuming over 10 cups a day suggested an increased rate of cancer incidence [44]. The reasoning for the increased cancer incidence in men when consuming over 10 cups of tea a day, was that those who were consuming the greatest amount of tea also had increased cigarette consumption. This was deemed true, as the results revealed that among men who never smoke and those who quit smoking both showed a decrease in cancer incidence with a higher amount of green tea consumption daily [44]. In both male and female, it showed a correlation and association of decrease in cancer incidence in those who were nonsmokers and those who quit smoking with consumption of over 10 cups of tea daily. Those consuming below 3, 4-9 and over 10 cups a day showed an exponential decrease in cancer incidences [44]. Proceeding, the team studied the effect of green tea based on the type of cancer. For example, consumption of a high amount of green tea daily had the greatest impact for individuals who had lung cancer in both males and females [29]. In conclusion the study showed that green tea exhibits some preventative effects of cancer, specifically lung cancer and decreased incidences of cancer for those consuming over 10 cups a day without tobacco use.

CONCLUSION

Cancer and disease are the leading causes of death in the United States every year. Angiogenesis has shown to exhibit a role in disease and health as it is the main mediator in healing as well as the proliferation of tumors and malignant diseases. While angiogenesis is a natural process that takes place in the course of life development, it ultimately exacerbates tumor growth in cancer patients. VEGF and VEGFR signal angiogenesis and play a crucial role in healing and the development of diseases; it is advantageous in cases with heart disease and arterial disease, but disadvantageous to individuals with lung and breast cancer. Treatment therapies targeting VEGF and VEGFR in the body include the consumption of foods that exhibit anti-angiogenic properties. For example, vegetables, berries, parsley and specifically green tea. Monoclonal antibodies have been developed targeting VEGF and VEGFR, these antibodies include Bevacizumab (Avastin), Aflibercept (Zaltrap) and Ramucirumab (Cryramza). Green tea contains a high content of EGCG, which has been found to inhibit angiogenesis through cell proliferation, apoptosis, and inhibition of angiogenesis expression. Particularly, this paper discussed the cohort study on the effect of green tea on disease prevention and the correlation of the decrease in cancer incidences in individuals who consumed a high amount of green tea daily. Green tea exhibits a preventative effect in cancer, specifically lung cancer and decreases the incidences of cancer for those consuming over 10 cups a day.

To conclude, angiogenesis has a major role in both healing and the development of diseases, many monoclonal antibodies have been developed to inhibit angiogenesis and the efficacy varies depending on the type of cancer. For a natural route, foods that contain EGCG, for example in fruits, vegetables, berries, parsley, and specifically green tea have shown a preventative effect on cancer.

REFERENCES

1. Neve, A., et al., *Extracellular matrix modulates angiogenesis in physiological and pathological conditions.* Biomed Res Int, 2014. **2014**: p. 756078.
2. Adair, T.H. and J.P. Montani, in *Angiogenesis*. 2010: San Rafael (CA).
3. Shahneh, F.Z., et al., *Tumor angiogenesis and anti-angiogenic therapies.* Hum Antibodies, 2013. **22**(1-2): p. 15-9.
4. Moreira-Soares, M., et al., *Angiogenic Factors produced by Hypoxic Cells are a leading driver of Anastomoses in Sprouting Angiogenesis–a computational study.* Scientific Reports, 2018. **8**(1): p. 8726.
5. Stefanini, M.O., et al., *The presence of VEGF receptors on the luminal surface of endothelial cells affects VEGF distribution and VEGF signaling.* PLoS Comput Biol, 2009. **5**(12): p. e1000622.
6. Sternlicht, M.D. and Z. Werb, *How matrix metalloproteinases regulate cell behavior.* Annu Rev Cell Dev Biol, 2001. **17**: p. 463-516.
7. Siemerink, M.J., et al., *Endothelial tip cells in ocular angiogenesis: potential target for anti-angiogenesis therapy.* J Histochem Cytochem, 2013. **61**(2): p. 101-15.
8. Chen, W., et al., *The endothelial tip-stalk cell selection and shuffling during angiogenesis.* J Cell Commun Signal, 2019. **13**(3): p. 291-301.
9. DeLisser, H.M., *Modulators of endothelial cell filopodia: PECAM-1 joins the club.* Cell Adh Migr, 2011. **5**(1): p. 37-41.
10. Innocenti, M., *New insights into the formation and the function of lamellipodia and ruffles in mesenchymal cell migration.* Cell Adh Migr, 2018. **12**(5): p. 401-416.
11. Ananthakrishnan, R. and A. Ehrlicher, *The forces behind cell movement.* Int J Biol Sci, 2007. **3**(5): p. 303-17.
12. Palm, M.M., et al., *Computational Screening of Tip and Stalk Cell Behavior Proposes a Role for Apelin Signaling in Sprout Progression.* PLoS One, 2016. **11**(11): p. e0159478.
13. Zetter, B.R., *Angiogenesis and tumor metastasis.* Annu Rev Med, 1998. **49**: p. 407-24.
14. Abhinand, C.S., et al., *VEGF-A/VEGFR2 signaling network in endothelial cells relevant to angiogenesis.* J Cell Commun Signal, 2016. **10**(4): p. 347-354.

15. Paku, S., et al., *A new mechanism for pillar formation during tumor-induced intussusceptive angiogenesis: inverse sprouting.* Am J Pathol, 2011. **179**(3): p. 1573-85.
16. Weddell, J.C. and P.I. Imoukhuede, *Computational Systems Biology for the VEGF Family in Angiogenesis*, in *Encyclopedia of Cardiovascular Research and Medicine*, R.S. Vasan and D.B. Sawyer, Editors. 2018, Elsevier: Oxford. p. 659-676.
17. Nishida, N., et al., *Angiogenesis in cancer.* Vasc Health Risk Manag, 2006. **2**(3): p. 213-9.
18. Sagar, S.M., D. Yance, and R.K. Wong, *Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer-Part 1.* Curr Oncol, 2006. **13**(1): p. 14-26.
19. Ucuzian, A.A., et al., *Molecular mediators of angiogenesis.* J Burn Care Res, 2010. **31**(1): p. 158-75.
20. Haigh, J.J., *Role of VEGF in organogenesis.* Organogenesis, 2008. **4**(4): p. 247-56.
21. Zelzer, E. and B.R. Olsen, *Multiple roles of vascular endothelial growth factor (VEGF) in skeletal development, growth, and repair.* Curr Top Dev Biol, 2005. **65**: p. 169-87.
22. Niu, G. and X. Chen, *Vascular endothelial growth factor as an anti-angiogenic target for cancer therapy.* Curr Drug Targets, 2010. **11**(8): p. 1000-17.
23. Pircher, A., et al., *Biomarkers in tumor angiogenesis and anti-angiogenic therapy.* Int J Mol Sci, 2011. **12**(10): p. 7077-99.
24. Kong, D.H., et al., *A Review of Anti-Angiogenic Targets for Monoclonal Antibody Cancer Therapy.* Int J Mol Sci, 2017. **18**(8).
25. Braghiroli, M.I., J. Sabbaga, and P.M. Hoff, *Bevacizumab: overview of the literature.* Expert Rev Anticancer Ther, 2012. **12**(5): p. 567-80.
26. Ellis, L.M., *Bevacizumab.* Nat Rev Drug Discov, 2005. **Suppl**: p. S8-9.
27. Cohen, M.H., et al., *FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme.* Oncologist, 2009. **14**(11): p. 1131-8.
28. Garcia, A. and H. Singh, *Bevacizumab and ovarian cancer.* Ther Adv Med Oncol, 2013. **5**(2): p. 133-41.
29. Planchard, D., *Bevacizumab in non-small-cell lung cancer: a review.* Expert Rev Anticancer Ther, 2011. **11**(8): p. 1163-79.
30. Rinne, M.L., et al., *Update on bevacizumab and other angiogenesis inhibitors for brain cancer.* Expert Opin Emerg Drugs, 2013. **18**(2): p. 137-53.
31. Shih, T. and C. Lindley, *Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies.* Clin Ther, 2006. **28**(11): p. 1779-802.
32. Ashraf, M. and A.A.R. Souka, *Aflibercept in age-related macular degeneration: evaluating its role as a primary therapeutic option.* Eye (Lond), 2017. **31**(11): p. 1523-1536.
33. Sarwar, S., et al., *Aflibercept for neovascular age-related macular degeneration.* Cochrane Database Syst Rev, 2016. **2**: p. CD011346.
34. Smyth, E.C., N. Tarazona, and I. Chau, *Ramucirumab: targeting angiogenesis in the treatment of gastric cancer.* Immunotherapy, 2014. **6**(11): p. 1177-86.
35. Arrieta, O., et al., *Ramucirumab in the treatment of non-small cell lung cancer.* Expert Opin Drug Saf, 2017. **16**(5): p. 637-644.
36. Yuan, J.M., *Green tea and prevention of esophageal and lung cancers.* Mol Nutr Food Res, 2011. **55**(6): p. 886-904.
37. Musial, C., A. Kuban-Jankowska, and M. Gorska-Ponikowska, *Beneficial Properties of Green Tea Catechins.* Int J Mol Sci, 2020. **21**(5).
38. Kim, W., et al., *Effect of green tea consumption on endothelial function and circulating endothelial progenitor cells in chronic smokers.* Circ J, 2006. **70**(8): p. 1052-7.
39. Lamy, S., D. Gingras, and R. Beliveau, *Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation.* Cancer Res, 2002. **62**(2): p. 381-5.
40. Fujiki, H., et al., *Primary cancer prevention by green tea, and tertiary cancer prevention by the combination of green tea catechins and anticancer compounds.* J Cancer Prev, 2015. **20**(1): p. 1-4.
41. Fujiki, H., *Two stages of cancer prevention with green tea.* Journal of Cancer Research and Clinical Oncology, 1999. **125**(11): p. 589-597.
42. Fujiki, H. and M. Suganuma, *Green tea and cancer prevention.* Proceedings of the Japan Academy, Series B, 2002. **78**(9): p. 263-270.
43. Imai, K., K. Suga, and K. Nakachi, *Cancer-preventive effects of drinking green tea among a Japanese population.* Prev Med, 1997. **26**(6): p. 769-75.
44. Nakachi, K., et al., *Preventive effects of drinking green tea on cancer and cardiovascular disease: Epidemiological evidence for multiple targeting prevention.* BioFactors, 2000. **13**(1-4): p. 49-54.
45. Li, M.J., et al., *Green tea compounds in breast cancer prevention and treatment.* World J Clin Oncol, 2014. **5**(3): p. 520-8.
46. Farabegoli, F., et al., *(-)-Epigallocatechin-3-gallate downregulates estrogen receptor alpha function in MCF-7 breast carcinoma cells.* Cancer Detect Prev, 2007. **31**(6): p. 499-504.
47. Sartippour, M.R., et al., *The combination of green tea and tamoxifen is effective against breast cancer.* Carcinogenesis, 2006. **27**(12): p. 2424-33.
48. Tu, S.H., et al., *Tea polyphenol (-)-epigallocatechin-3-gallate inhibits nicotine- and estrogen-induced alpha9-nicotinic acetylcholine receptor upregulation in human breast cancer cells.* Mol Nutr Food Res, 2011. **55**(3): p. 455-66.
49. Fujiki, H., et al., *Synergistic enhancement of anticancer effects on numerous human cancer cell lines treated with the combination of EGCG, other green tea catechins, and anticancer compounds.* J Cancer Res Clin Oncol, 2015. **141**(9): p. 1511-22.