

## A novel insight into anti-angiogenic foods

Anindita Deb Pal

Department of Food Science & Nutrition Management, J.D. Birla Institute, 11, Lower Rawdon Street, Kolkata, India

### Abstract

Angiogenesis is an important physiological process which is essential for tissue growth and development. It is the formation of new blood vessels from the already existing vasculature that is controlled by chemical signaling. These signals stimulate both the formation of new blood vessels as well as the repair of damaged vasculature. The ongoing research on cancer and other diseases has mainly focused on development of therapeutic agents. Since angiogenesis has been well documented to contribute to tumorigenesis, numerous efforts have been employed for screening and development of anti-angiogenic products. Interestingly, many natural food sources have been found to have components that possess the potential to inhibit angiogenesis. Considering the drawbacks and limitations of the existing treatment strategies, anti-angiogenic foods may serve as a better and safer line of therapy which may also be employed for prevention of chronic diseases. Also, these may serve as economically viable approaches against the above diseases. Moreover, they can also be used as combination therapy along with the prevailing strategies which may lead to an improved prognosis. The present review will mainly focus on the various edible food products and their involvement in anti-angiogenesis.

**Keywords:** angiogenesis; carcinogenesis; endothelial cells; pro-angiogenic factors; anti-angiogenic factors; bioactive compounds

### 1. Introduction

Angiogenesis, the phenomenon of formation of new blood vessels occurs throughout the life in both health and disease. These ensure an adequate supply of nutrients and oxygen together with the removal of wastes. Angiogenesis is a key event during embryogenesis where new blood vessels are formed for proper development. Moreover, this natural process is also required for healing and reproduction. Being an extremely critical phenomenon, the process is well balanced by various stimulating and inhibitory factors in the human body. Alteration of this careful balance may lead to a plethora of diseases including cardiovascular disease, skin diseases and most importantly cancer<sup>[1]</sup>. Vasculogenesis is a dynamic process that involves interactions between cell–cell and cell–extracellular matrix (ECM) under the influence of growth factors. Angiogenesis is generally stimulated by hypoxia that leads to perivascular detachment and disassembly of the existing vessels followed by digestion of the basement membrane, migration of the endothelial cells and their differentiation into blood vessels in the newly acquired site<sup>[2]</sup>. Previous studies have identified numerous pro-angiogenic factors which include basic Fibroblast Growth Factor (bFGF), angiogenin, Transforming Growth Factor (TGF)- $\alpha$ , Tumor Necrosis Factor (TNF)- $\alpha$ , Platelet-derived Endothelial Growth Factor (PDEGF), Granulocyte Colony Stimulating Factor (GCSF), Placental Growth Factor (PGF), Interleukin-8 (IL-8), Hepatocyte Growth Factor (HGF), Epidermal Growth Factor (EGF) and most importantly Vascular Endothelial Growth Factor (VEGF)<sup>[3]</sup>. Binding of pro-angiogenic ligands and cytokines to their receptors is followed by receptor activation which further initiates complex signaling cascades including the Extracellular Signal-Regulated Kinases (ERK), Mitogen-Activated Protein Kinases (MAPK) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF $\kappa$ B) pathways. These pathways lead to the downstream activation of Nitric Oxide Synthase (NOS) which thereafter results in survival, migration and invasion of endothelial cells.

Furthermore, Hypoxia also aids in angiogenesis. Conditions of hypoxia lead to upregulation of the expression of VEGF and its receptor through Hypoxia-Inducible Factor-1 $\alpha$  (HIF-1 $\alpha$ ). Binding of VEGF to receptors on the surface of normal endothelial cells signals the growth and survival of new blood vessels. Activation of VEGF signaling further activates endothelial cells which in turn secrete Matrix Metalloproteinases (MMPs). The MMPs break down the extracellular matrix which aid in the migration of endothelial cells. Endothelial cells possess the ability of rapid multiplication and are induced to do so in conditions of wound healing, menstruation and pregnancy. Angiogenesis is also induced in a number of pathological conditions such as rheumatoid arthritis and diabetic retinopathy.

### 2. Angiogenesis and cancer

The era of modern angiogenesis began with the work of Judah Folkman, who hypothesized that tumor growth is angiogenesis-dependent<sup>[4]</sup>. During early stages of cancer development, their nutrient requirements are satisfied via diffusion from normal vessels. Beyond a certain size, new blood supply becomes essential for further growth of the tumor. It has been observed that cancer cells develop this new blood supply either by directly activating pathways that stimulate angiogenesis or by stimulating the nearby normal cells for the same. The resulting new blood vessels feed growing tumors with oxygen and other essential nutrients, allowing the cancer cells to grow and metastasize. Vascular angiogenesis promotes the growth and invasion of tumor cells and their absence may lead to necrosis or apoptosis of the same. Tumor cells secrete cytokines and pro-angiogenic factors that aid in increasing vascular permeability thereby promoting angiogenesis. However, the demand for oxygen and nutrients differ amongst the different kinds of tumors depending on their size, location and developmental stage. Although cancer cells have been shown to undergo aerobic glycolysis to meet their oxygen requirements, angiogenesis becomes a necessity during the

exponential phase of tumor growth. The increased demand for oxygen stimulates the angiogenic switch and alters the balance of angiogenesis towards increased blood vessel formation, aiding further tumor growth [2]. Angiogenesis is regulated by both activator and inhibitor molecules. Sustained tumor growth requires upregulation of pro-angiogenic factors along with downregulation of anti-angiogenic factors. It has been observed that cancerous cells release pro-angiogenic proteins that stimulate formation of new blood vessels in tumors, providing it with oxygen and nutrients. Furthermore, immunohistochemical analysis have revealed the VEGF family and their receptors to be expressed in about half of the human cancers investigated [5]. VEGF has been associated with colorectal cancers, breast cancers, lung cancers, head and neck cancers as well as Kaposi's sarcoma. Levels of expression of angiogenic factors indicate the stage and severity cancer and other chronic ailments. Moreover, recognition of the fact that control of angiogenesis could lead to cancer therapies have stimulated intensive research in the field. Henceforth, employment of anti-angiogenic therapy should interfere with the process of blood vessel growth and may be targeted to inhibit the progress of cancer and other chronic diseases.

### 3. Anti-angiogenic agents

Angiogenesis based medicine is an upcoming approach to fight disease. Recently, a large number of angiogenesis inhibitors have been discovered and developed ranging from monoclonal antibodies, small organic molecules to microRNAs. These inhibitors interfere with various steps in the angiogenic process. For example, bevacizumab (Avastin®) is a monoclonal antibody that specifically recognizes and binds to VEGF. When VEGF is attached to bevacizumab, it is unable to activate the VEGF receptor. Other angiogenesis inhibitors, including sorafenib and sunitinib, bind to receptors on the surface of endothelial cells or to other proteins in the downstream signaling pathways, blocking their activities. By using new medical treatments that interfere with angiogenesis, doctors are prolonging the lives of patients suffering from a range of chronic diseases. Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. Angiogenesis inhibitor therapy does not necessarily kill tumors but instead may prevent tumors from growing. Therefore, this type of therapy may need to be administered over a long period.

Our diet has been shown to improve the prognosis of various diseases including cancer. Moreover, studies have also highlighted the role of a number of edible foods in inhibiting angiogenesis. Apart from modulating other biological processes, the dietary components influence the angiogenic switch for the benefit of the individual. Many of these bioactive food components target the genetically stable endothelial cells and inhibit their ability to form new vasculature during tumor growth thereby leading to tumor regression. These compounds alter the balance of the angiogenesis towards anti-angiogenesis by targeting some of the important genes of the pathway such as NOS, VEGF, Vascular Endothelial Growth Factor Receptor (VEGFR), Epidermal Growth Factor Receptor (EGFR), (TNF- $\alpha$ ) and Cyclooxygenase 2(COX 2). The mitochondria, being the hub of apoptosis has also been shown to play a role in anti-angiogenesis by inducing endothelial cell death. Extensive researches in this area have implicated the mechanism of anti-

angiogenesis by the above and have laid down the possibility of diet related angiogenesis modulation.

## 4. Anti-angiogenic foods

### 4.1 Fruits & Vegetables

The health effects of fruits and vegetables have been well established over the past years. These products not only contribute to overall nutrition but are also endowed with properties of disease prevention and treatment owing to their anti-oxidant, anti-inflammatory and anti-angiogenic potentials. Different classes of anti-angiogenic and anti-carcinogenic bioactive plant compounds present in fruits and vegetables include flavonoids, antioxidants, carbohydrates and triterpenoids. Amongst others, berries have been thoroughly studied for their anti-angiogenic potential. It has been observed that extracts of berries especially wild blueberries, bilberries, cranberries, elderberries, raspberries and strawberries significantly decreased hydrogen peroxide as well as TNF- $\alpha$  induced angiogenesis via downregulation of the expression of VEGF [6]. Moreover *in vitro* matrigel analyses have also displayed the anti-angiogenic potential of berries. The above effect has been demonstrated to correlate with reduction in tumor mass. The proanthocyanidin compounds from the cranberry extracts have displayed the potential to inhibit VEGF induced receptor phosphorylation in endothelial cells thereby blocking endothelial cell migration [7]. These proanthocyanidins are naturally occurring flavonoids that provide protection against pathogenic infections and other diseases. Berries, especially black raspberries contain significant quantities of antioxidant polyphenols that have been reported to offer protection against inflammatory diseases and cancers. The extracts of black raspberries have been observed to reduce the expression of pro-inflammatory cytokines accompanied with a concomitant reduction of VEGF dependent vascularization and angiogenesis as evident in studies of cell migration, proliferation and tube formation. Furthermore, previous studies have highlighted the capability of grape seed extract to affect angiogenesis by downregulating MMPs and inhibiting capillary tube formation by endothelial cells [8]. Moreover, resveratrol present in grape skin suppresses angiogenesis [9]. Flavonoids isolated from *Lycium barbarum* fruits has also been observed to inhibit angiogenesis by interfering with VEGF stimulated endothelial cell migration. Furthermore, *Psidium Guajava* commonly known as guava has been found to have the capacity to inhibit angiogenesis [10]. This plant is common to Africa, America and Asia, where all parts have been used for a variety of purposes including food and medicine. It is also a good source of fiber and vitamin C apart from iron, calcium, phosphorus and vitamins A and B. It contains numerous polyphenols, most of which display anti-cancer abilities. Studies have displayed guava leaf extracts to inhibit NF $\kappa$ B, COX-2 and NOS mediated pathways implying its role in anti-angiogenesis [11]. Moreover, previous studies have also highlighted the effect of proanthocyanidins isolated from fruit peels of *Choerospondias axillaris* on angiogenesis. These compounds were detected to arrest all stages of angiogenesis including migration of endothelial cells and the formation of capillary tubes. Additionally, the proanthocyanidins inhibited the cellular signaling associated with angiogenesis without causing any toxicity [12]. Fisetin is a dietary polyphenol found in numerous vegetables and fruits including apples, grapes, strawberries, onions and cucumber at concentrations in the range of 2–160

lg/g. These polyphenols have portrayed a protective action against different malfunctions such as cancers, neuronal disorders, diabetes, obesity and pulmonary diseases and hence have emerged as a potent nutraceutical [13]. Their role in anti-carcinogenesis has been well studied where they have been shown to reduce the incidence and progression of tumors of the lung, colon, pancreas and prostate by influencing MMPs and key signaling pathways, thereby indicating their role in anti-angiogenesis. Dietary polyphenols have shown numerous benefits on human health by interfering with important signaling cascades. Therefore, the identification of dietary polyphenols that alter angiogenesis has become a significant area in health-related research. Reports portray that polyphenols have the capacity of altering important events in the angiogenesis signaling pathways. These include inhibition of Epidermal Growth Factor Receptor (EGFR) and VEGFR activation as well as decrease in expression of VEGF, MMPs and HIF- $\alpha$ , all of which lead to inhibition of capillary tube formation. Additionally, *Punica granatum* or pomegranate has been established a good anti-tumor agent owing to its capability to decrease inflammation and angiogenesis [14]. Moreover, the fruit has also displayed protection against cardiovascular, neurological and metabolic diseases. Pomegranate juice contains bioactive agents such as organic acids, vitamins, sugars, as well as phenolic components all of which contribute to the above. Previous reports have shown the juice to own the capability of inhibition of migration and invasion of endothelial cells [15]. Gallic acid, a natural phytochemical in numerous fruits and vegetables has also been shown to inhibit tumor growth by targeting the HIF- $\alpha$  and VEGF dependent angiogenic pathways. *In vitro* matrigel and western blot analysis have indeed demonstrated the decrease in protein expression of the above in ovarian cancer cells [16]. Tomato forms a major part of the diet in many countries since it serves as a good source of nutrients, vitamins, minerals, dietary fibers, anti-oxidants and phytonutrients. Interestingly, consumption of tomato has been linked to reduced incidences of cardiovascular diseases and cancers. Tomato cysteine knot miniproteins isolated from the tomato fruit has been well researched for its anti-angiogenic potential. Cystine knot miniproteins generally contain less than 50 amino acids, have a unique three-dimensional structure possessing three intra-molecular disulphide bonds forming a cystine-knot and play an important role in cell growth and development. Many of these proteins have been studied and exploited for their therapeutic potential. Notably, these proteins have proven their role in anti-angiogenesis. They interfere with endothelial cell migration by effecting nitric oxide mediated VEGF receptor activation [17]. Additionally, bioactive flavonoids such as Galangin and Myricetin that is present in many vegetables and fruits also display anti-angiogenesis potential. These phytochemicals have been found to affect the secretion and expression of important mediators of angiogenesis both *in vitro* and *in vivo* [18]. The anti-angiogenic activity of *Morinda citrifolia* L. also known as the starvation fruit or Noni has also been evaluated. The fruit extracts, especially the compound scopoletin have shown a potential of angiogenesis inhibition as observed in chick chorioallantoic membrane assays [19]. Moreover, scopoletin isolated from *Nicotiana glauca* extract have also been demonstrated to exhibit vascularization inhibition *ex vivo*, *in vivo* as well as *in silico*. This anti-vascularization has been further correlated with anti-tumorigenesis. Date fruit (*Phoenix dactylifera* L.) has long been

used as for the treatment of a variety of inflammatory ailments such as intestinal diseases, fever, bronchitis, wound healing and also cancer. Interestingly, date fruit has been implicated in anti-angiogenesis apart from other anti-cancer effects such as protection of oxidative stress. The polyphenols of date syrup obtained from date fruit had been noted to decrease angiogenic responses by affecting the expressions of VEGF and COX-2 [20]. Vitamins such as Riboflavin and Niacin that are present in a range of fruits and vegetables have been documented to reduce angiogenesis mediated breast cancer progression since they decrease the expression of pro-angiogenic factors and increase the expression of anti-angiogenic factors [21]. Additionally, several cruciferous vegetables have been implicated in inhibiting iNOS influenced angiogenesis [22]. Moreover, leaf extracts of *Nelumbo nucifera* have shown the potential to attenuate VEGF dependent angiogenesis [23]. Several dietary agents have surfaced in laboratory studies as potential anti-angiogenic agents. Therefore, consumption of fruits and vegetables are essential not only for maintaining a balanced diet but also for protection against a range of ailments including cancer owing to their anti-angiogenic potential.

#### 4.2 Cereals, legumes and oils

Similar to fruits and vegetables, several bioactive compounds present in cereals, legumes and oils also display potent anti-angiogenic potential. Numerous natural polyphenols have indeed been studied with respect to diabetes, cardiovascular diseases and cancer. The polyphenols such as hydroxycinnamic acids and ferulic acid found in cereals have been associated with angiogenesis inhibition. These generally target EGFR mediated VEGF signaling pathways. These compounds also exert their effect on other angiogenic mediators including MMPs and NOS. Nitric Oxide is produced by a family of Nitric Oxide Synthase (NOS) enzymes that are concerned with interconversion of L-arginine to citrulline in the presence of oxygen and Nicotinamide Adenine Dinucleotide phosphate (NADPH). Inducible NOS (iNOS) dependent signal transduction pathways boost angiogenesis by targeting cytokine expression which further leads to increase in vascular permeability and blood flow followed by neo-vascularization [24]. Evidences have shown iNOS to be elevated during inflammation and hypoxia induced VEGF dependent tumor angiogenesis. Dietary inositol hexaphosphate present in cereals, legumes as well as nuts have been documented to decrease VEGF expression and suppress *in vitro* migration and invasion of endothelial cells thereby implicating them to be potential anti-angiogenic agents [25]. Diabetic nephropathy (DN) is a disease characterized by loss of kidney function, hyperglycemia, renal injury and inflammation. Interestingly, rice bran proteins have been shown to reduce the incidence of diabetes nephropathy by decreasing the expression of pro-angiogenic factors including HIF- $\alpha$ , TGF- $\beta$  and VEGF [26]. Rice bran which is a by-product of rice processing has recently received much attention due to its nutritional significance. Therefore, the benefits of the same may be exemplified by its further role in anti-angiogenesis. Additionally, 3-O-Acetyloleanolic acid, a bioactive agent isolated from cowpea seeds has been studied to inhibit migration, invasion and capillary tube formation by endothelial cells [27]. Soybean is one of the widely cultivated crops since it is considered a valuable source of proteins, polyunsaturated fatty acids, carbohydrates and dietary fibers. Although being a part of the human diet since many years, soybean and soybean derived

food is gaining increased popularity recently because of their ability to reduce the incidences of chronic illnesses like cardiovascular diseases and cancer. Moreover, they are also a good source of phytochemicals such as isoflavones, phytosterols and lecithins, which along with the nutrients confer significant health benefits. Dietary patterns are known to play a role in development of cancers. Consumption of soy isoflavones has indeed been found to inversely correlate with breast cancer progression [28]. Previous reports have highlighted the role of soy isoflavones in interfering with the estrogen receptors, apoptosis, cell proliferation and angiogenesis. These have been shown to inhibit the expression of VEGF, MMPs and other pro-angiogenic chemokines and hence influence the endothelial cell migration and tumor metastasis [29]. Furthermore, soybean kunitz trypsin inhibitor has been shown to exert strong inhibitory action against migration and capillary tube formation of endothelial cells along with decreasing tumor metastasis [30]. Additionally, tempeh, a fermented soy product has been associated with anti-angiogenesis. Isoflavones isolated from tempeh such as genistein, daidzein, factor 2 and orobol has been experimentally proved to inhibit in vivo endothelial cell proliferation, migration as well expression of pro-angiogenic factors [31]. The above effects have been found to be responsible for decreasing the progress of solid tumors. Lunasin, another peptide present in seeds and legumes including soybean has been associated with anti-inflammatory and anti-carcinogenic effects [32]. Moreover, hazelnuts, corn derived peptides and canola seed oils have also been related with anti-cancer effects [33, 34]. Olive oil has also been connected with the ability of anti-angiogenesis owing to its ability to reduce the expression of VEGF as well as MMP-2 and 9 [35]. Silibinin, a flavonoid derived from the seeds of *Silybum marianum*) has been associated with anti-carcinogenic properties which are mainly attributed to its pro-apoptotic, anti-proliferative as well as anti-angiogenic capacity. This compound affects the expression levels of important mediators of angiogenesis leading to tumor arrest [36]. Hence cereals, oils and legumes like soybean can serve as promising candidate for preparation of new generation anti-tumor drugs.

#### 4.3 Beverages

Natural beverages like tea, coffee and milk have also shown substantial anti-angiogenic effects. Tea is the most popular of all non-alcoholic beverages in the world. About two-thirds of the world population drinks tea. Tea has now become the worlds cheapest and is the second most consumed liquid after water. The different varieties of teas are all derived from the leaves of *Camellia sinensis* that are subjected to differential processing and fermentation methods. Tea and coffee are known to contain polyphenols such as flavan-3-ols that are associated with a range of health benefits which include reduction of symptoms of chronic and inflammatory diseases via anti-angiogenesis [37]. Furthermore, studies have shown Green Tea, Black Tea and Oolong Tea to aid in reduction of body fat and inflammation. The bioactive polyphenols isolated from the above tea extracts were also documented to effect VEGF moderated angiogenesis. Additionally, epigallocatechin-3-gallate (EGCG) present in green tea has been shown to decrease iNOS and VEGF expression [38]. It has also been found to be responsible for blocking cancer progression by inhibiting tumor induced angiogenesis [39]. Moreover, leaves of *Origanum onites* L. that are sometimes used as condiments in tea have also portrayed anti-angiogenic potential as analyzed by cell migration and tube

formation assays. Coffee is another worldwide beverage which contains a mixture of many bioactive compounds. Administration of caffeic acid has proven to decrease in incidence of diabetes. The caffeic acid has been associated with a decrease in the process of angiogenesis as evident from the expression levels of MMPs and other pro-angiogenic markers [40]. Another bioactive compound, cafestol, found in unfiltered coffee has been associated with anti-inflammatory, anti-tumorigenic as well as anti-angiogenesis effects. The above compound has been shown to exert angiogenic inhibition by blocking the VEGF signaling induced processes of cell proliferation, endothelial cell migration and capillary tube formation [41]. Interestingly, camel milk has been found to play a role in anti-angiogenesis. The milk of camel has traditionally been used to treat chronic diseases like cancer. This anti-cancer effect has mainly been attributed to its ability to downregulate the expression of VEGF with a concomitant decrease in the rate of neo-vascularization during tumorigenesis [42]. Moreover, previous studies have documented the ability of milk lactoferrin in promoting anti-tumor effects. The above has been ascribed due to its capability to alter important tumor signaling pathways that influence cell cycle progression, apoptosis and also angiogenesis [43]. Therefore, exploitation of biologically active compounds from beverages normally consumed by population at large may lead to improved prognosis in chronic diseases.

#### 4.4 Mushrooms

Mushrooms although biologically distinct from plant and animal foods are classified in the vegetable food group and are endowed with unique nutrition and health benefits. They comprise of the fruiting bodies of filamentous fungi and have long been part of the human diet. The edible mushrooms are a significant source of proteins, fats, potassium, calcium, Vitamin D and fibers. Polysaccharides from many edible mushrooms have been documented to contribute to reduction in tumor growth and progression. The role of mushrooms in anti-angiogenesis is now well established. The fruit extract of *Ganoderma lucidum* has been shown to reduce NO mediated endothelial cell invasion [44]. Moreover, *Antrodia cinnamomea*, a precious *edible* mushroom endemic to Taiwan has also been claimed to exert anti-angiogenic effects according to results of *in vitro* and *ex vivo* analysis [45]. *Grifola frondosa* or maitake mushroom, a health food especially in China and Japan has also been associated with inhibition of VEGF dependent angiogenesis via downregulation of angiogenesis signaling accompanied with reduction of oxidative stress [46].

#### 4.5 Spices and sweeteners

Spices and sweeteners have always been of prime importance in our diet. These not only enable flavor enhancement but also offer protection from diseases owing to their anti-oxidant, anti-inflammatory and anti-tumorigenic potential. Interestingly, many of the upcoming compounds possessing therapeutic potential against chronic diseases are derived from spices. Many of these herbs and spices have been shown to protect against microbial diseases and cancer. The role of spices and sweeteners in anti-angiogenesis is also well documented. *Brassica juncea* or mustard extracts have been associated with anti-cancer effects mainly by downregulation of pro-angiogenic genes like VEGF and bFGF [47]. Curcumin, chemically known as diferuloylmethane is one of the most active polyphenol present in turmeric. It has been used as medicine for treatments of

ailments including jaundice, arthritis, asthma, heart disease, skin infections and many others. The above compound also possesses significant anti-tumor potential due to its ability to interfere with signaling pathways involved in generation of reactive oxygen Species (ROS), angiogenesis and metastasis. Moreover, existing evidences clearly portray the ability of curcumin to reduce the expression of iNOS, COX2 and VEGF in addition to decreasing microvessel density in cancer cells [48]. Curcumin has also shown the ability to inhibit the secretion of angiogenesis promoting interleukins thereby reducing the rates of endothelial tube formation and invasion [49]. Isoliquiritigenin, a flavonoid isolated from *Glycyrrhiza uralensis* is generally used for culinary purposes in the West. This compound has been shown to possess anti-inflammatory, anti-angiogenic and anti-cancer properties. Studies have proven Isoliquiritigenin to inhibit neo-angiogenesis mediated tumor progression by targeting VEGF, VEGFR and HIF- $\alpha$  [50]. Nutmeg (*Myristica fragrans*) is another widely used spice and flavoring agent and has been associated with anti-inflammatory and anti-microbial effects. The oil of nutmeg has been documented to decrease the process of angiogenesis as evident from rat aortic ring assays [51]. Moreover, previous reports have also highlighted the anticancer properties of phytochemicals derived from pepper [52]. Additionally, extracts of *Alpinia caerulea* fruit that is used as a flavoring agent and ginger substitute, prevents proliferation and migration of endothelial cells and hence interferes with angiogenesis [53]. The growth and expansion of adipose tissue has been correlated with angiogenesis. Korean red ginseng has been found to reduce angiogenesis mediated obesity in mouse models by reducing the expression of pro-angiogenic genes such as VEGF, FGF and MMPs [54]. Honey is one of the most popular natural sweeteners also endowed with a range of medicinal properties. Studies have documented honey to induce the property of anti-inflammation in cells by interfering with VEGF dependent angiogenesis [55]. Moreover, Mogroside V, a natural food sweetener has been found to exert potent anti-tumor effects. Hence, regular consumption of virgin herbs used as spices along with natural sweeteners may prevent the incidences of chronic diseases.

## 5. Conclusion and future perspectives

An unhealthy diet is an established cause of disease. The link between nutrition and health benefits has been well proven. Our daily diet not only provides us with essential nutrients and energy but also aid our body in prevention and treatment of a range of chronic disorders. The health benefits of medicinal foods are subject to immense interest amongst the public, pharmaceutical companies and health professionals. Angiogenesis plays a significant part in the growth and dissemination of cancer and other chronic diseases. Novel approaches of cancer treatments that block angiogenesis are now approved and available. These strategies are mainly based on interference with angiogenic ligands, receptors and downstream signaling. This has proven to contribute significantly to treat tumors of the colon, kidney, lung, breast, liver, brain, ovaries and thyroid. Amongst others, several dietary bioactive compounds have also surfaced as potent anti-angiogenic agents. These are also gaining popularity more so because their economic affordability, non-toxic nature, diminished side effects, easy availability and their high acceptance by consumers. Hence, it has become essential to explore food items for new angiogenic inhibitors along with understand the detailed mechanism of the same. These inhibitors may help to normalize

the blood supply of tumor cells thereby aiding in the delivery of other anti-tumor agents. However, certain limitations are associated with the numerous anti-angiogenic therapies available such as increased tumor resistance, increased hypoxia and decreased delivery of chemotherapeutic drugs. Therefore, selecting the optimum dosage and combinations in addition to searching for new therapeutic targets may be required to achieve adequate benefits. In this regard, a thorough investigation of the different diet components along with screening of new food for their anti-angiogenic potential may help in augmenting the severity of many diseases apart from serving as a potential source of treatment.

## 6. Acknowledgment

The author acknowledges the support from J.D. Birla Institute for writing this article. There is no conflict of interest.

## 7. References

1. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med.* 2000; 6:389-95.
2. Petrovic N. Targeting Angiogenesis in Cancer Treatments: Where do we Stand? *J Pharm Pharm Sci.* 2016; 19:226-38.
3. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenesis in Cancer. *Vasc Health Risk Manag.* 2006; 2:213-19.
4. Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med.* 1995; 333:1757-63.
5. Salven P, Lymboussaki A, Heikkilä P, Jääskela-Saari H, Enholm B, Aase K, *et al.* Vascular endothelial growth factors VEGF-B and VEGF-C are expressed in human tumors. *Am J Pathol.* 1998; 153:103-8.
6. Bagchi D, Sen CK, Bagchi M, Atalay M. Anti-angiogenic, Antioxidant, and Anti-carcinogenic Properties of a Novel Anthocyanin-Rich Berry Extract Formula. *Biochemistry (Moscow).* 2004; 69:75-80.
7. Kim KK, Singh AP, Singh RK, DeMartino A, Brard L, Vorsa N, *et al.* Anti-angiogenic activity of cranberry proanthocyanidins and cytotoxic properties in ovarian cancer cells. *Int J Oncol.* 2012; 40:227-35.
8. Singh RP, Tyagi AK, Dhanalakshmi S, Agarwal R, Agarwal C. Grape Seed Extract Inhibits Advanced Human Prostate Tumor Growth and Angiogenesis and Upregulates Insulin-Like Growth Factor Binding Protein-3. *Int. J. Cancer.* 2004; 108:733-40.
9. Brakenhielm E, Cao R, Cao Y. Suppression of Angiogenesis, Tumor Growth, and Wound Healing by Resveratrol, a Natural Compound in Red Wine and Grapes. *FASEB J.* 2001; 15:1798-1800.
10. Correa MG, Couto JS, Teodoro AJ. Anticancer Properties of *Psidium guajava* - a Mini-Review. *Asian Pac J Cancer Prev.* 2016; 17:4199-204.
11. Ryu NH, Park KR, Kim SM, Yun HM, Nam D, Lee SG, *et al.* A hexane fraction of guava Leaves (*Psidium guajava* L.) induces anticancer activity by suppressing AKT/mammalian target of rapamycin/ribosomal p70 S6 kinase in human prostate cancer cells. *J Med Food.* 2012; 15:231-41.
12. Li Q, Wang X, Dai T, Liu C, Li T, Mc Clements DJ, *et al.* Proanthocyanidins, Isolated from *Choerospondias axillaris* Fruit Peels, Exhibit Potent Antioxidant Activities in Vitro

- and a Novel Anti-angiogenic Property in Vitro and in Vivo. *J. Agric. Food Chem.* 2016; 64:3546-56.
13. Pal HC, Pearlman RL, Afaq F. Fisetin and Its Role in Chronic Diseases. *Adv Exp Med Biol.* 2016; 928:213-44.
  14. Syed DN, Chamcheu JC, Adhami VM, Mukhtar H. Pomegranate extracts and cancer prevention: Molecular and cellular activities. *Anticancer Agents Med Chem.* 2013; 13:1149-61.
  15. Tibullo D, Caporarello N, Giallongo C, Anfuso CD, Genovese C, Arlotta C, *et al.* Antiproliferative and Antiangiogenic Effects of Punica granatum Juice (PGJ) in Multiple Myeloma (MM). *Nutrients.* 2016; 8:611-28.
  16. He Z, Chen AY, Rojanasakul Y, Rankin GO, Chen YC. Gallic acid, a phenolic compound, exerts anti-angiogenic effects via the PTEN/AKT/HIF-1 $\alpha$ /VEGF signaling pathway in ovarian cancer cells. *Oncology Reports.* 2016; 35:291-7.
  17. Treggiari D, Zoccatelli G, Chignola R, Molesini B, Minuz P, Pandolfini T. Tomato cystine-knot miniproteins possessing anti-angiogenic activity exhibit in vitro gastrointestinal stability, intestinal absorption and resistance to food industrial processing. *Food Chemistry.* 2017; 221:1346-53.
  18. Huang H, Chen AY, Rojanasakul Y, Ye X, Rankin GO, Chen YC. Dietary compounds galangin and myricetin suppress ovarian cancer cell angiogenesis. *J Funct Foods.* 2015, 15:464-75.
  19. Beh HK, Seow LJ, Asmawi MZ, Abdul Majid AM, Murugaiyah V, Ismail N, *et al.* Anti-angiogenic activity of Morinda citrifolia extracts and its chemical constituents. *Nat Prod Res.* 2012; 26:1492-7.
  20. Taleb H, Morris RK, Withycombe CE, Maddocks SE. Date syrup-derived polyphenols attenuate angiogenic responses and exhibits anti-inflammatory activity mediated by vascular endothelial growth factor and cyclooxygenase-2 expression in endothelial cells. *Nutr Res.* 2016; 36:636-47.
  21. Premkumar VG, Yuvaraj S, Sathish S, Shanthi P, Sachdanandam P. Anti-angiogenic potential of CoenzymeQ10, riboflavin and niacin in breast cancer patients undergoing tamoxifen therapy *Vascul Pharmacol.* 2008; 48:4-6.
  22. Surh YJ, Chun KS, Cha HH, Han SS, Keu YS, Park KK, *et al.* Molecular Mechanisms Underlying Chemopreventive Activities of Anti-Inflammatory Phytochemicals: Down-Regulation of COX-2 and iNOS through Suppression of NF- $\kappa$ B Activation. *Mutat. Res.* 2001, 480-481,243-68.
  23. Lee JS, Shukla S, Kim JA, Kim M. Anti-Angiogenic Effect of Nelumbo nucifera Leaf Extracts in Human Umbilical Vein Endothelial Cells with Antioxidant Potential. *PLOS ONE.* 2015; 10:e0118552.
  24. Morbidelli L, Donnini S, Ziche M. Role of Nitric Oxide in Tumor Angiogenesis. *Cancer Treat Res.* 2004; 117:155-67.
  25. Vucenik I, Passaniti A, Vitolo MI, Tantivejkul K, Eggleton P, Shamsuddin AM. Anti-angiogenic Activity of Inositol Hexaphosphate (IP6). *Carcinogenesis.* 2004; 25:2115-23.
  26. Boonloh K, Lee ES, Kim HM, Kwon MH, Kim YM, Pannangpetch P, *et al.* Rice bran protein hydrolysates attenuate diabetic nephropathy in diabetic animal model, *Eur J Nutr.* 2016. doi: 10.1007/s00394-016-1366-y.
  27. Cui EJ, Hwang-Bo J, Park JH, Baek NI, Kim J, Hong SG, *et al.* 3-O-Acetyloleanolic acid exhibits anti-angiogenic effects and induces apoptosis in human umbilical vein endothelial cells. *Biotechnol Lett.* 2013; 35:1807-15.
  28. Xie Q, Chen ML, Qin Y, Zhang QY, Xu HX, Zhou Y, *et al.* Isoflavone consumption and risk of breast cancer: A dose-response meta-analysis of observational studies. *Asia Pac J Clin Nutr.* 2013; 22:118-27.
  29. Kim MH. Flavonoids inhibit VEGF/bFGF-induced angiogenesis in vitro by inhibiting the matrix-degrading proteases. *J Cell Biochem.* 2003; 89:529-38.
  30. Shakiba Y, Mansouri K, Mostafaie A. Anti-angiogenic effect of soybean kunitz trypsin inhibitor on human umbilical vein endothelial cells. *Fitoterapia.* 2007; 78:587-9.
  31. Kiriakidis S, Ho-gemeier O, Starcke S, Dombrowski F, Hahne JC, Pepper M, *et al.* Novel tempeh (fermented soyabean) isoflavones inhibit in vivo angiogenesis in the chicken chorioallantoic membrane assay. *British Journal of Nutrition.* 2005; 93:317-23.
  32. Hernández-Ledesma B, Hsieh CC. Chemopreventive Role of Food-derived Proteins and Peptides: A Review. *Critical Reviews in Food Science and Nutrition.* 2017; 57:2358-76.
  33. Aydemir LY, Gökbulut AA, Baran Y, Yemencioğlu A. Bioactive, functional and edible film-forming properties of isolated hazelnut (*Corylus avellana* L.) meal proteins. *Food Hydrocolloid.* 2014; 36:130-42.
  34. Achary AP, Thiyam U. A pursuit of the functional, nutritional and bioactive properties of canola proteins and peptides. *Crit. Rev Food Sci Nutr.* 2012; 52:965-79.
  35. Calabriso N, Massaro M, Scoditti E, D'Amore S, Gnoni A, Pellegrino M, *et al.* Extra virgin olive oil rich in polyphenols modulates VEGF-induced angiogenic responses by preventing NADPH oxidase activity and expression. *J Nutr Biochem.* 2016; 28:19-29.
  36. Tyagi A, Singh RP, Ramasamy K, Raina K, Redente EF, Dwyer-Nield LD, *et al.* Growth inhibition and regression of lung tumors by silibinin: modulation of angiogenesis by macrophage-associated cytokines and nuclear factor-kappaB and signal transducers and activators of transcription 3. *Cancer Prev Res (Phila Pa).* 2009; 2:74-83.
  37. Diniz C, Suliburska J, Ferreira IM. New insights into the antiangiogenic and proangiogenic properties of dietary polyphenols. *Mol Nutr Food Res.* 2016. doi: 10.1002/mnfr.201600912.
  38. Lamy S, Gingras D, Beliveau R. Green Tea Catechins Inhibit Vascular Endothelial Growth Factor Receptor Phosphorylations. *Cancer Res.* 2002; 62:381-5.
  39. Jung YD, Kim MS, Shin BA, Chay KO, Ahn BW, Liu W, *et al.* EGCG, a Major Component of Green Tea, Inhibits Tumor Growth by Inhibiting VEGF Induction in Human Colon Carcinoma Cells. *Br J Cancer.* 2001; 84:844-50.
  40. Abduljawad SH, El-Refaei MF, El-Nashar NN. Protective and anti-angiopathy effects of caffeic acid phenethyl ester against induced type 1 diabetes in vivo. *Int Immunopharmacol.* 2013; 17:408-14.
  41. Wang S, Yoon YC, Sung MJ, Hur HJ, Park JH. Antiangiogenic properties of cafestol, a coffee diterpene, in human umbilical vein endothelial cells. *Biochemical and Biophysical Research Communications.* 2017; 421:567-71.
  42. Alhaider AA, Gader AGA, Almehaal N, Saraswati S. Camel milk inhibits inflammatory angiogenesis via downregulation of proangiogenic and proinflammatory cytokines in mice. *APMIS.* 2014; 122:599-607.

43. De Mejía EG, Dia VP. The role of nutraceutical proteins and peptides in apoptosis, angiogenesis, and metastasis of cancer cells. *Cancer Metast Rev.* 2010; 29:511-28.
44. Song YS, Kim SH, Sa JH, Jin C, Lim CJ, Park EH. Anti-angiogenic and inhibitory activity on inducible nitric oxide production of the mushroom *Ganoderma lucidum*. *Journal of Ethnopharmacology.* 2004; 90:17-20.
45. Yang CM, Zhou YJ, Wang RJ, Hu ML. Anti-angiogenic effects and mechanisms of polysaccharides from *Antrodia cinnamomea* with different molecular weights. *Journal of Ethnopharmacology.* 2009; 123:407-12.
46. Lee JS, Park BC, Ko YJ, Choi MK, Choi HG, Yong CS, *et al.* Grifola frondosa (maitake mushroom) water extract inhibits vascular endothelial growth factor-induced angiogenesis through inhibition of reactive oxygen species and extracellular signal-regulated kinase phosphorylation. *J Med Food.* 2008; 11:643-51.
47. Kwak Y, Lee J, Ju J. Anti-cancer activities of *Brassica juncea* leaves in vitro. *EXCLI Journal.* 2016; 15:699-710.
48. Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H, Patumraj S. Effects of Curcumin on Tumor Angiogenesis and Biomarkers, COX-2 and VEGF, in Hepatocellular Carcinoma Cell-Implanted Nude Mice. *Clin Hemorheol Microcirc.* 2006; 34:109-15.
49. Sung B, Prasad S, Yadav VR, Aggarwal BB. Cancer cell signaling pathways targeted by spice-derived nutraceuticals. *Nutr Cancer.* 2012; 64:173-97.
50. Wang Z, Wang N, Han S, Wang D, Mo S, Yu L, *et al.* Dietary Compound Isoliquiritigenin Inhibits Breast Cancer Neoangiogenesis via VEGF/VEGFR-2 Signaling Pathway, *PLOS ONE.* 2013; 8:e68566.
51. Piaru SP, Mahmud R, Majid AMSA, Daoud Z, Nassar M. Antioxidant and antiangiogenic activities of the essential oils of *Myristica fragrans* and *Morinda citrifolia*. *Asian Pacific Journal of Tropical Medicine.* 2012; 5:294-8.
52. Manach, C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am. J. Clin. Nutr.* 2004; 79:727-47.
53. He ZH, Gilli C, Yue GG, Lau CB, Greger H, Brecker L, *et al.* Anti-angiogenic effects and mechanisms of zerumin A from *Alpinia caerulea*. *Food Chem.* 2012; 132:201-8.
54. Lee H, Park D, Yoon M. Korean red ginseng (*Panax ginseng*) prevents obesity by inhibiting angiogenesis in high fat diet-induced obese C57BL/6J mice. *Food Chem Toxicol.* 2013; 53:402-8.
55. Eteraf-Oskouei T, Najafi M, Gharehbagheri A. Natural honey: a new and potent anti-angiogenic agent in the air-pouch model of inflammation. *Drug Res (Stuttg).* 2014; 64:530-6.