Microbial Avengers: How Microorganisms Drive Angiogenesis for Good and Bad?

Md. Fakruddin[1*], Zarifah Chowdhury [1], Sayed Ul Alam Shibly [2], SM Bakhtiar Ul Islam [1], Jinath Sultana Jime [1], Nayeema Bulbul [1], Mohammad Badrul Anam [3], Khanjada Shahnewaj Bin Mannan [4], Md. Asaduzzaman Shishir [5]

Abstract

Angiogenesis is the formation of new blood vessels from pre-existing ones, and it plays a pivotal role in both the initiation and spread of cancer. Microorganisms have been recognized as influential regulators of angiogenesis, with certain strains fostering (angiogenic) while others impeding (antiangiogenic) this biological process. According to recent studies, microbes can control angiogenesis via various pathways, making them intriguing options for therapies meant to prevent cancer growth. This review provides a comprehensive overview of current understanding regarding how microbes modulate angiogenesis in cancer. It emphasizes the involvement of different bacterial and fungal species and elucidates the mechanisms through which they exert their effects. This review addresses how numerous microbes produce diverse bioactive substances that suppress the BCL-2 gene, leading to the disruption of mitochondrial outer membranes. Consequently, the release of cytochrome c from mitochondria serves to inhibit angiogenesis through the formation of the apoptosome, a complex involving cytochrome c, Apaf-1, and procaspase-9, which catalyzes the activation of caspases. Ultimately, this cascade of events culminates in programmed cell death, thereby impeding the process of angiogenesis. Some bacteria produce proteins like basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), promoting angiogenesis whereas certain bacteria induce angiogenesis by decreasing microRNA-203a levels, leading to increased production of proangiogenic factors which facilitates angiogenesis. Proangiogenic bacteria show promise in tissue regeneration and addressing vision impairment. These findings indicate potential for novel strategies to improve healing and vision in patients with diverse medical conditions. Nevertheless, additional investigation is required to refine the effectiveness and safety profiles of these bacterial-derived therapies for eventual clinical implementation. This review highlights the yet-to-be-explored capacity of microorganisms in cancer treatment through the suppression of angiogenesis, paving the way for innovative therapeutic strategies that could yield highly potent anti-cancer medications.

Keywords: Antibiotic resistance, Nosocomial infections, ICU morbidity, Multidrug-resistant bacteria, Empirical antibiotic therapy

Significance | The significance of microbe-induced angiogenesis and anti-angiogenesis lies in their pivotal roles in the pathogenesis and treatment of infectious diseases.

*Correspondence. Md. Fakruddin, Ph.D., Assistant Professor, Department of Biochemistry & Microbiology, North South University, Dhaka, Bangladesh. E-mail: md.fakruddin@northsouth.edu

Editor Mohammad Mamun Alam, and accepted by the Editorial Board May 05, 2024 (received for review Mar 04, 2024)

1. Introduction

Angiogenesis, the process by which pre-existing blood vessels give rise to new ones, is essential to the development of cancer (Kerbel, 2008; Jain, 2014). Tumor angiogenesis makes it easier for the expanding tumor to get oxygen and nutrients, which helps it to

Author Affiliation.
[1] Department of Biochemistry & Microbiology, North South University, Bashundhara, Dhaka-1229, Bangladesh.
[2] Department of Basic Science, Primeasia University, Banani, Dhaka, Bangladesh
[3] Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, New York-13210.206
[4] H Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA
[5] Department of Microbiology, Dhaka International University, Badda, Dhaka, Bangladesh

Please cite this article.
Md. Fakruddin et al. (2024). Microbial Avengers: How Microorganisms Drive Angiogenesis for Good and Bad?, Journal of Angiotherapy, 8(5), 1-12, 9650

spread and elude the immune system. Anti-angiogenic therapies, which block the growth of blood vessels supplying the tumor, have become a promising way to target the progression of cancer (Folkman, 1995). Unfortunately, the clinical usefulness of currently available anti-angiogenic agents has been limited due to their side effects and the emergence of drug resistance (Hanahan & Weinberg, 2011). Lately, lowering cholesterol through microbial-mediated angiogenesis modulation has become a viable strategy for developing anti-cancer therapeutics (Chang et al., 2017; Kerbel et al., 2011; Nafsi et al., 2024).

Angiogenesis is the process of creating new blood vessels from pre-existing ones is known as angiogenesis, and it is essential in the development of many physiological and pathological conditions, including cancer (Belkaid & Hand, 2014). Angiogenesis facilitates the continuous supply of nutrients and oxygen needed for the growth and metastasis of solid tumors (Bergers & Benjamin, 2003). Furthermore, angiogenesis contributes to tissue repair and wound healing. (Carmeliet & Jain, 2000; Fakruddin et al., 2022a)

Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are two examples of the signaling pathways that are activated during the highly regulated process of angiogenesis (Ferrera, 2002; Carmeliet & Jain, 2011a). The development and progression of diseases like cancer can be attributed to the dysregulation of these pathways, which can result in excessive angiogenesis (Carmeliet & Jain, 2011b; Al-Rawi et al., 2023)

To summarize, angiogenesis is a multifaceted process that involves the creation of new blood vessels from pre-existing ones. It is essential for the development and spread of solid tumors and is also involved in tissue repair and wound healing. Angiogenesis dysregulation has been linked to a number of illnesses, including cancer.

2. The role of angiogenesis in cancer development

Angiogenesis is a crucial factor in the initiation and advancement of cancer. Angiogenesis, the process of creating new blood vessels, facilitates the continuous supply of nutrients and oxygen needed for the growth and metastasis of solid tumors (Belkaid & Hand, 2014). Furthermore, angiogenesis contributes to the capacity of cancer cells to invade and spread to different areas of the body (Bergers & Benjamin, 2003).

Excessive and aberrant blood vessel formation in tumors can result from dysregulation of angiogenesis, which fosters tumor growth and invasion (Carmeliet & Jain, 2000). The upregulation of pro-angiogenic factors, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), frequently mediates this (Carmeliet & Jain, 2011a). Furthermore, the production of extracellular matrix proteins and the activation of signaling pathways like the hypoxia-inducible factor (HIF) pathway are two more ways that the tumor microenvironment can affect angiogenesis (Carmeliet & Jain, 2011b).

With the advent of medications that block pro-angiogenic factors like VEGF, targeting angiogenesis has grown in importance as a therapeutic approach for the treatment of cancer (Cerimele et al., 2003). Preclinical and clinical studies have demonstrated the effectiveness of these agents in preventing tumor growth and metastasis (Chang et al., 2017).

3. The potential of angiogenesis modulation for cancer treatments

Modulating angiogenesis has become a viable treatment approach for cancer. Anti-angiogenic treatments can starve tumors of the nutrients and oxygen they require to grow and spread by preventing the growth of new blood vessels (Sherwood et al., 1971). Anti-angiogenic drugs have been demonstrated in clinical trials to enhance overall survival and progression-free survival in patients with specific cancer types (Potente et al., 2011). However, the emergence of resistance and unfavorable side effects like bleeding and hypertension may restrict the effectiveness of these treatments (Jain et al., 2009).

To get around these restrictions and maximize the therapeutic potential of angiogenesis modulation, a number of strategies are being researched. To increase efficacy and decrease resistance, combination therapies that target several signaling pathways involved in angiogenesis are being investigated (Lei et al., 2022). Additionally, new anti-angiogenic drugs that focus on various angiogenic processes, like lymphangiogenesis and vessel normalization, are being developed (Ferrara & Adamis, 2016). Furthermore, in an effort to enhance treatment outcomes, personalized medicine strategies that take into account unique patient attributes like immune and genetic profiles are being investigated (Jang et al., 2018)

Angiogenesis modulation has promising potential for treating cancer, despite certain obstacles. It is anticipated that ongoing studies and clinical trials will enhance and optimize these treatments to enhance patient outcomes.

4. The need and demand of novel metabolites and bio actives modulating angiogenesis as anti-cancer therapeutics

Angiogenesis is the process by which preexisting blood vessels divide to form new ones, and it is essential to the growth and metastasis of tumors. As a result, focusing on angiogenesis has become a viable cancer treatment approach (Bhatt et al., 2017; Naidu et al., 2024). Although there are a number of anti-angiogenic medications on the market today, their effectiveness is restricted, and resistance may eventually arise (Carmeliet & Jain, 2011a; Al-deeb et al., 2021). Novel therapeutics that can control angiogenesis and get around drug resistance are therefore required.

The microbiome is one possible source of new anti-angiogenic compounds. Numerous bioactive metabolites that have the ability to control host angiogenesis have been demonstrated to be produced by the gut microbiome (Gouda et al., 2016; Fakruddin et

al., 2023). For instance, preclinical research has demonstrated that the production of secondary bile acids, which are produced by certain gut microbes, inhibits angiogenesis (de Menezes et al., 2023). Furthermore, some gut microbes have the ability to produce short-chain fatty acids (SCFAs), which have the ability to control the activity of regulatory T cells, which are implicated in angiogenesis (Francescone et al., 2014; Amin et al., 2023).

All things considered, the discovery and synthesis of new metabolites and bio actives with the ability to influence angiogenesis offers a viable path toward the creation of anti-cancer medications.

5. Microbial-mediated angiogenesis modulation

The human gut microbiome is essential for controlling immunity and host metabolism. An imbalance in the gut microbiome known as dysbiosis has been connected to a number of illnesses, including cancer (Dabrowska & Witkiewicz, 2016). Tumor angiogenesis is known to be significantly influenced by host cholesterol metabolism, which is modulated by the gut microbiome (Tran et al., 2022). The biosynthesis of steroid hormones, such as estrogen, which can encourage the growth of tumors, requires cholesterol as a precursor. Furthermore, cholesterol may facilitate the activation of angiogenesis-regulating signaling pathways like the PI3K/AKT/mTOR pathway (Zhu et al., 2019).

Numerous investigations have demonstrated that tumor angiogenesis can be suppressed by microbially mediated modifications of host cholesterol metabolism. The production of short-chain fatty acids (SCFAs) by the gut microbiome, for instance, has been demonstrated to lower host cholesterol levels by promoting the excretion of cholesterol and inhibiting its synthesis (Nafsi et al., 2024). The activity of regulatory T cells, which can stop tumor growth and angiogenesis, can also be modulated by SCFAs. Furthermore, some bacteria in the gut can create secondary bile acids, which have the ability to control the host's metabolism of cholesterol and prevent angiogenesis (Zhu et al., 2019).

5.1. The mechanisms of microbial induced angiogenesis

The process by which microorganisms encourage the development of new blood vessels in the tissues of their hosts is known as "microbial-induced angiogenesis." This mechanism can be advantageous or disadvantageous based on the situation. The mechanisms underlying microbially-induced angiogenesis are summarized as follows:

Release of Pro-Inflammatory Cytokines: Microbial infections result in the release of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α). These cytokines start the inflammatory process, which draws immune cells and causes the angiogenic factors to be produced (Wan et al., 2021).

Production of angiogenic factors: Microbes have the ability to either directly or indirectly stimulate the production of angiogenic factors, which include matrix metalloproteinases (MMPs), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). These elements encourage endothelial cell migration, proliferation, and differentiation, all of which are critical for the development of new blood vessels (Yoda et al., 2013).

Extracellular matrix remodeling: Certain microbes have the ability to secrete enzymes that break down the extracellular matrix surrounding blood vessels. One such enzyme is called an MMP. New blood vessel elongation and sprouting are facilitated by this remodeling process (Schirbel et al., 2013).

Induction of host signaling pathways: Certain signaling pathways, such as the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the mitogen-activated protein kinase (MAPK) pathway, can be triggered in host cells by microbes. These pathways support endothelial cell survival and proliferation, which helps to regulate angiogenesis (Uusi-Mäkelä & Rämet, 2018).

Immune cell recruitment and activation: Immune cells such as neutrophils and macrophages are drawn to the infection site by microbial infections. By releasing cytokines and growth factors, these immune cells can stimulate the growth of blood vessels and release angiogenic factors (Vieira et al., 2013).

Direct contact with endothelial cells: Toxins or surface molecules on some microbes interacts with endothelial cells directly, causing angiogenic reactions. As an illustration, some bacterial lipopolysaccharides (LPS) can cause endothelial cells to secrete factors that promote angiogenesis (Sevcikova et al., 2023). It is crucial to remember that although microbially induced angiogenesis can aid in tissue repair and wound healing, it can also hasten the course of some illnesses, including persistent inflammation and tumor growth.

5.2. The examples of microorganisms modulating angiogenesis

Numerous mechanisms have been demonstrated by microorganisms to modulate angiogenesis. As an illustration, some bacteria secrete pro-angiogenic factors like VEGF, whereas other bacteria produce anti-angiogenic factors like endostatin (Bhatt et al., 2017).

According to one study, the probiotic strain *Lactobacillus rhamnosus* GG promoted angiogenesis by producing more VEGF and fibroblast growth factor (FGF) in a mouse model of colorectal cancer (Dehghani et al., 2020). In a different investigation, it was discovered that the bacterium *Helicobacter pylori* stimulates angiogenesis in gastric cancer by upregulating the expression of matrix metalloproteinase-9 (MMP-9) and VEGF (Malespín-Bendaña et al., 2023).

However, it has been discovered that some bacterial strains prevent angiogenesis. For instance, in a mouse model of melanoma, the probiotic strain *Bifidobacterium bifidum* produced the anti-angiogenic factor endostatin, which inhibited angiogenesis (Procaccianti et al., 2023). In a similar vein, it was discovered that

the commensal bacteria *Lactobacillus acidophilus* prevented angiogenesis in a mouse model of breast cancer by producing pigment epithelium-derived factor (PEDF), an anti-angiogenic factor (Adiyoga et al., 2022).

Furthermore, it has been discovered that fungi metabolites influence angiogenesis. For instance, the fungus *Aspergillus fumigatus* produces the metabolite fumagillin, which targets endothelial cells to inhibit angiogenesis (Guruceaga et al., 2021).

Overall, these findings imply that microbes can control angiogenesis by producing pro- and anti-angiogenic factors, which may have effects on the onset and course of a number of illnesses, including cancer.

5.2.1 Mechanisms employed by microbes to inhibit angiogenesis:

***Lactobacillus rhamnosus* GG**

Lactobacillus rhamnosus is helpful in the treatment of cancer because it has probiotic qualities and the ability to degrade carcinogens. According to a number of researches, *Lactobacillus rhamnosus* may help shield against esophageal and colon cancers (Hashemi-Khah et al., 2022). Moreover, it can inhibit the transformation of procarcinogens into carcinogens and increase anti-cancer enzymes (Hashemi-Khah et al., 2022). By down-regulating BCL-2 genes and up-regulating BAD, BAX, Caspase3, Caspase8, and Caspase9, *Lactobacillus rhamnosus* GG induces apoptosis (Rajoka et al., 2019). Research revealed that *Lactobacillus rhamnosus* supernatant inhibited HT-29 cancer cell growth in a time- and dose-dependent manner (Rajoka et al., 2019). Bacterial supernatant activated genes involved in programmed cell death, including caspase-3, caspase-9, and Bax. Moreover, they led to the downregulation of Bcl2 and a reduction in the expression levels of the ERBB2 gene, cyclin D1, and cyclin E (Figure-1). Cancer cells were consequently stopped at the G0/G1 stage of the cell cycle (Dehghani et al., 2020).

Bifidobacterium bifidum

The human digestive tract is frequently colonized by the probiotic and commensal bacterium *Bifidobacterium bifidum*. According to a study, it can prevent colon cancer by up- and down-regulating pro- and anti-apoptotic genes, which exhibit anticancer activity on colorectal cancer cells (Konishi et al., 2016). The expression levels of the pro-apoptotic genes Caspase 3 and Caspase 8 increased, whereas the expression of the anti-apoptotic gene Bcl-2 decreased, in colon cancer cell lines treated with bacterial cell-free supernatant (Procaccianti et al., 2023). It alters the cancer cells' cell cycle, inhibiting their proliferation and increasing their susceptibility to apoptosis (Faghfoori et al., 2021).

Lactobacillus acidophilus

Consuming probiotic bacteria, such as *Lactobacillus acidophilus*, has been shown in numerous studies to strengthen the immune system. Probiotics are a promising candidate for the prevention of colorectal cancer because they may alter gut flora (Adiyoga et al., 2022). It has been demonstrated in numerous studies to be helpful in the treatment of colon cancer, and in an experimental mouse model, *Lactobacillus acidophilus* induces cancer cell death via the mitochondrial-mediated apoptosis pathway (Yoda et al., 2013). It causes Cyt c to be released from the mitochondria into the cytoplasm and activates Caspase-3 and Caspase-9 by upregulating Bax, IFN-γ, and TNF-α and downregulating Bcl-2 expression (Sankarapandian et al., 2022). It helps restore the apoptotic pathway in colon cells and lessens the signs and symptoms of colon cancer (Figure 1).

Aspergillus fumigatus

Aspergillus species are common opportunistic molds that have therapeutic and ethological significance (Vadlapudi et al., 2017). It can prevent a number of cancers, such as breast cancer, hepatocellular carcinoma, and cervical cancer. It does not have cytotoxic effects on healthy cells, only on cancerous ones. Owing to their antioxidant qualities, the biomolecules dehydromevalonic lactone, methyl ester, 11-Hexadecynoic acid, and 9-Tetradecynoic acid lessen the harmful effects of oxidative stress on human health (Hassan et al., 2024). The secondary metabolites of the fungus include bioactive chemicals with anticancer properties (Almanaa et al., 2020).

***Streptomyces* sp**

The largest genus of bacteria that produces antibiotics is *Streptomyces*, which also produces a wide range of other bioactive compounds. Antibacterial, antifungal, and antiparasitic drugs are produced by this genus (Jang et al., 2022). The substances prevent cancer cells from growing and spreading because of their anticancer qualities. Bioactive compounds with cytolytic and anti-oxidative properties are produced by streptomyces, especially those that thrive in unfavorable environments. These compounds can be utilized to make medications that prevent cancer and chemotherapy (Han et al., 2020). Numerous of the produced drugs have already shown therapeutic benefits after their efficacy was proven on cell lines. Numerous cancers, including those of the colon, lung, breast, GI tract, cervix, and skin, may be treated with these substances (Sethi et al., 2023).

Penicillium citrinum

An endophytic fungus called *Penicillium citrinum* produces a range of bioactive compounds that have the potential to treat human lung and colon cancer, among other cancers. These substances have anti-inflammatory properties, and they frequently show this by inducing the death of cancer cells through mechanisms involving the mitochondria and caspase-3 (Chu et al., 2021). When it comes to human colorectal cancer cell line cytotoxicity, the compound Epiremisporine is the most potent. Human colorectal adenocarcinoma and human alveolar cell carcinoma underwent

Table 1. Examples of Microbial induced angiogenesis

Microorganism	Mechanism	Reference
Inhibited Angiogenesis		
Lactobacillus rhamnosus GG	Downregulation of the BCL-2 gene	Hashemi-Khah et al., 2022
Bifidobacterium bifidum	Production of anti-angiogenic factor (endostatin)	Faghfoori et al., 2021
Lactobacillus acidophilus	Production of anti-angiogenic factor (PEDF)	Adiyoga et al, 2022
Aspergillus fumigatus	Production of anti-angiogenic compound fumagillin targeting endothelial cells	Hassan et al., 2024
Streptomyces sp.	Production of anti-angiogenic compound (enduracidin)	Jang et al., 2022
Penicillium citrinum	Production of anti-angiogenic compound (citrinin)	Chu et al., 2021
Serratia marcescens	Production of prodigiosin	Ho et al., 2009
Pseudomonas aeruginosa	Production of pyocyanin	Mudaliar & Prasad, 2024
Promoted angiogenesis		
Helicobacter pylori	Upregulation of VEGF and MMP-9	Malespín-Bendaña et al., 2023
Bartonella henselae	Upregulation of VEGF which suppresses cell death	Tsukamoto et al., 2020
Bartonella quintana	Production of a mitogen that promotes the development of vasoproliferative lesions.	Liberto et al., 2003
Bartonella bacilliformis	Production of proangiogenic autotransporter BafA	Tsukamoto et al., 2022

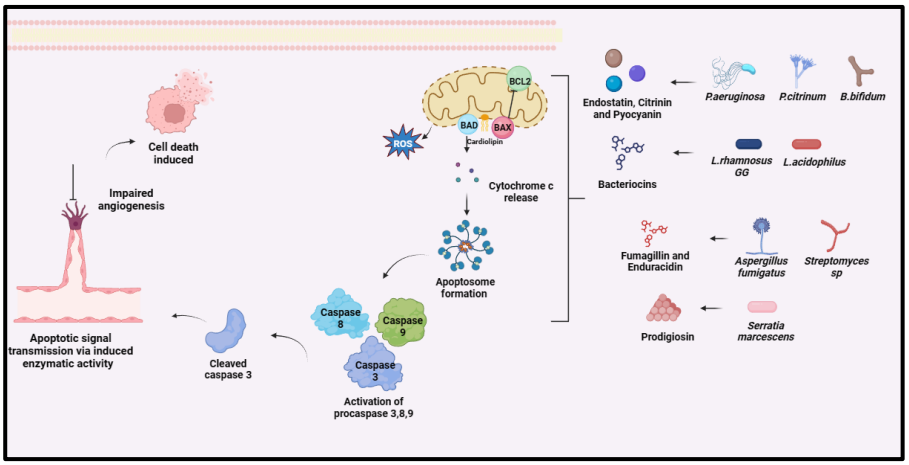

Figure 1. Several bacteria may generate diverse compounds that inhibit BCL-2 in the outer mitochondrial membrane, resulting in the release of cytochrome C from the intermembrane space of the mitochondria into the cytoplasm. Cytochrome C, together with additional factors, triggers a cascade of processes that contributes to cell death.

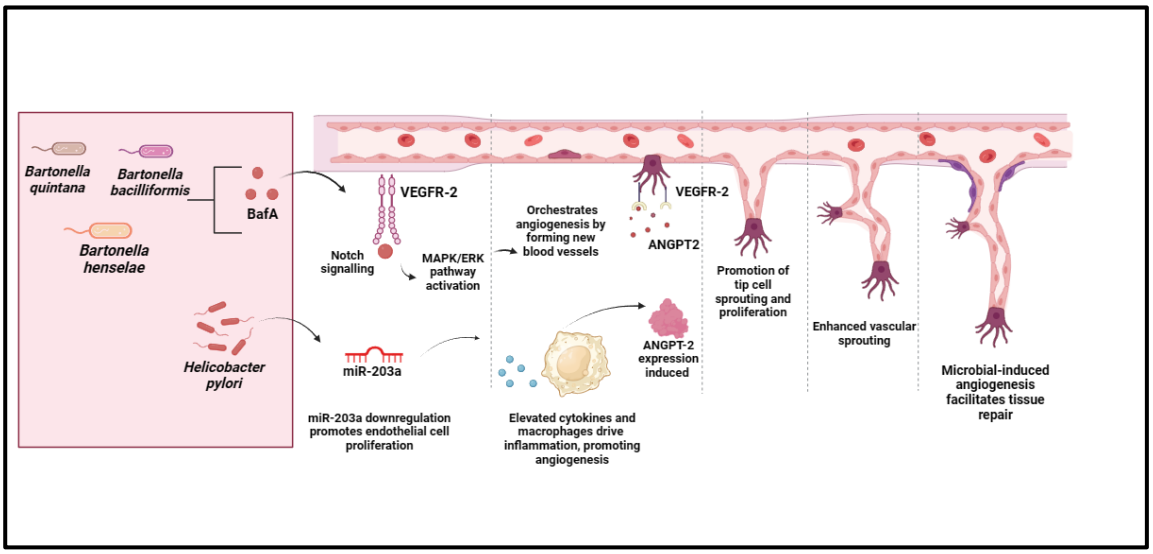

Figure 2. a) BafA promotes angiogenesis by exerting direct effects on endothelial cells, inducing pro-angiogenic factors, activating signaling pathways, and modulating the inflammatory response. BafA promotes blood vessel development, which is an essential step in angiogenesis. b) H. pylori induces angiogenesis through directly affecting endothelial cells, activating host signaling pathways, and manipulating host immunological responses. Downregulation of miR-203 by H. pylori infection may alleviate the inhibition of pro-angiogenic factors such as vascular endothelial growth factor A (VEGF-A) and Angpt2, which destabilizes blood vessels and promotes angiogenesis. H. pylori infection downregulates miR-203, which leads to an increase in Angpt2 levels.

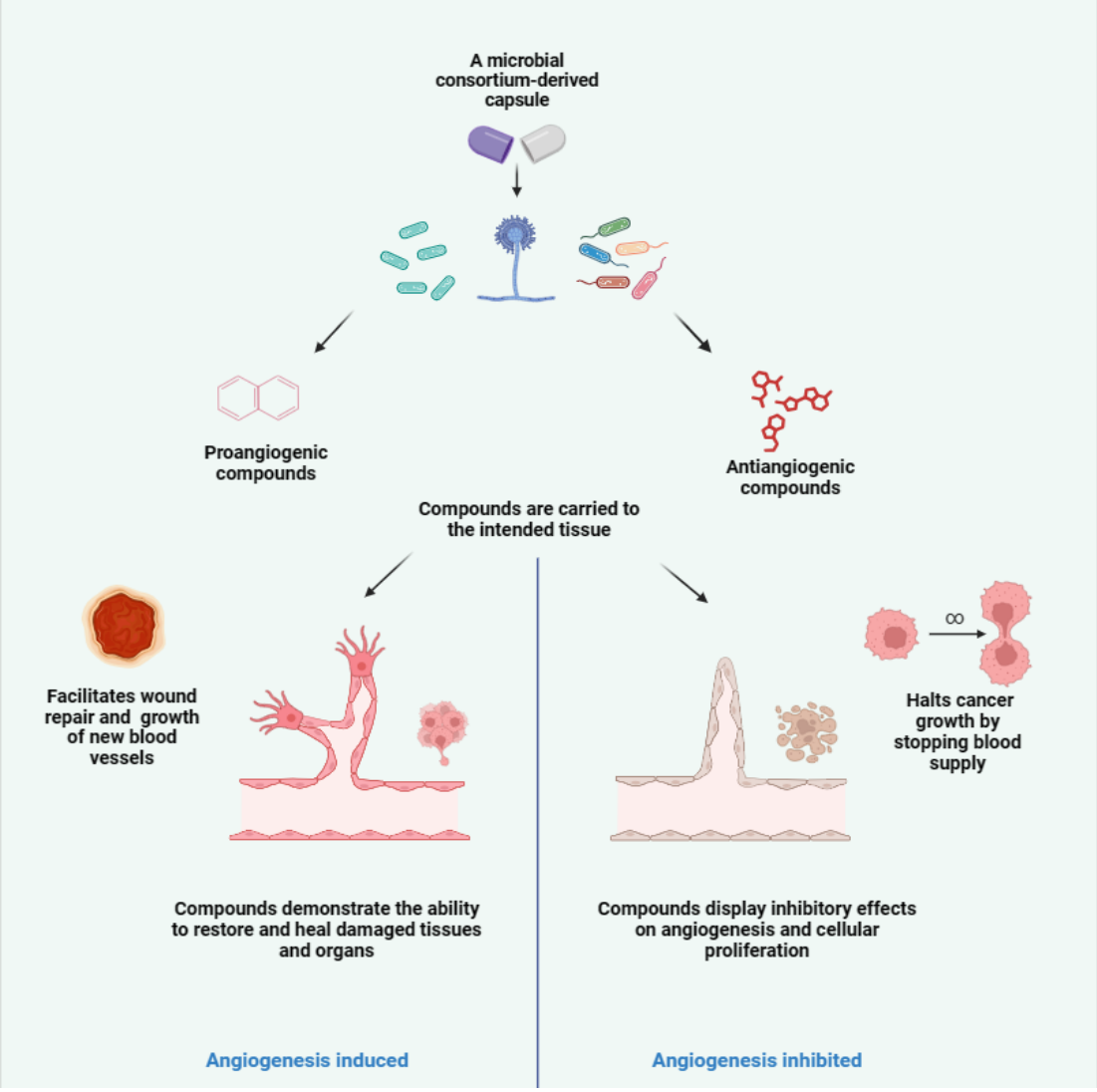

Figure 3. Microbiome-mediated angiogenesis and anti-angiogenesis have enormous therapeutic potential. The potential of microbial-based therapeutics in conjunction with traditional anti-cancer therapies has also been examined in a number of studies (Al-Ostoot et al., 2021; Ansari et al., 2022; Somani & Bhanushali, 2013). For instance, a recent study demonstrated that giving mice A. muciniphila along with chemotherapy increased the death of tumor cells and decreased the growth of tumors (Xue et al., 2023). Moreover, a clinical trial is being conducted to look into the possibility of using probiotics and anti-angiogenic therapy in conjunction to treat metastatic colorectal cancer.

apoptosis as a result of the drug's inhibition of pro-caspase 3 and elevation of cleaved caspase 3, which were both dependent on caspase 3 (Chu et al., 2021).

Serratia marcescens

Without harming healthy cells, *Serratia marcescens* produces a red pigment known as prodigiosin, which has antitumor qualities in a variety of cancers, including stomach and breast cancer (Ho et al., 2009). It stimulates several cancer cell lines to undergo apoptosis. As an immunomodulator, prodigiosin reprograms the metabolism of T and B lymphocytes, natural killer (NK) cells, tumor-associated dendritic cells (TADCs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) (Anwar et al., 2022).

Pseudomonas aeruginosa

Pyocyanin, a blue-green, water-soluble phenazine pigment produced by *Pseudomonas aeruginosa*, is an extracellular secondary metabolite that is toxic and has redox activity in mammalian cells (DeBritto et al., 2020). One exciting new cancer treatment option is pyocyanin. Numerous studies have demonstrated its effectiveness in treating human lung cancer, human cervical cancer, leukemia, and breast adenocarcinomas. Pyocyanin is a strong contender for use as a chemotherapeutic agent because it has shown cytotoxic effects against a variety of human cancer cell lines at specific doses (Mudaliar & Prasad, 2024). Pyocyanin is a promising chemotherapeutic agent for treating various types of cancer due to its ability to suppress cancer cell growth and decrease cell viability, as well as its strong anti-proliferative and cytotoxic properties that increase with concentration (DeBritto et al., 2020). Apart from triggering caspase 3, pyocyanin additionally stimulates oxidative stress by augmenting the production of reactive oxygen species (ROS) via glutathione oxidation. Caspase 3 must be activated for apoptosis, while oxidative stress causes DNA damage through strand breaks, base-pair changes, and apyrimidinic or apurinic mutations. Apoptosis in cancer cells is facilitated by all of the earlier processes (Mudaliar & Prasad, 2024).

5.2.2. Mechanisms employed by microbes to promote angiogenesis:

Helicobacter pylori

An infection with *Helicobacter pylori* is one of the main causes of stomach cancer. It invades the stomach and causes an inflammatory reaction that can result in stomach diseases like cancer (Malespín-Bendaña et al., 2023). Chronic gastritis, which is thought to be the first stage of stomach cancer development, is brought on by *Helicobacter pylori*. Because of its unique virulence factors, which include vacuolating cytotoxin A, cytotoxin-associated gene A, and the kinds of outer membrane proteins, this bacterium causes gastric cancer (Alipour, 2020). Due to its ability to downregulate miR-203a, *Helicobacter pylori* may contribute to the carcinogenesis process by increasing angiogenesis and ANGPT2 expression in the stomach mucosa (Malespín-Bendaña et al., 2023).

Bartonella henselae

Gram-negative *Bartonella henselae* causes angiogenesis and vasoproliferative lesions when it infects a host. In mice, the passenger domain of BafA promotes angiogenesis, tube formation, microvessel sprouting, and cell proliferation. *B. henselae* inhibits cell death in infected macrophages or monocytes by secreting VEGF (Tsukamoto et al., 2022). BafA functions as a VEGF analog by interacting with the vascular endothelial growth factor (VEGF) receptor-2 and inducing the downstream signaling cascade (Tsukamoto et al., 2020). Angiogenesis triggered by BafA is primarily responsible for the establishment of vasoproliferative lesions in cases of Bartonella infection (Figure 2).

Bartonella quintana

A gram-negative bacterium called *Bartonella quintana* causes pathological angiogenesis in people. It is possible that *B. quintana* produces a mitogen similar to BafA, which could aid in the formation of vasoproliferative lesions in bacillary angiomatosis (Figure-2). Variably expressed outer membrane proteins (VOMPs) are also expressed by them (Tsukamoto et al., 2020). Despite the initial escalation of inflammation in endothelial cells, *Bartonella quintana* seems to be able to prevent programmed cell death by triggering intracellular signals that promote survival and growth through the expression of the bcl-2 gene (Liberto et al., 2003).

Bartonella bacilliformis

Pathologic angiogenesis is caused by the Gram-negative bacterial pathogen *Bartonella bacilliformis*. The proangiogenic autotransporter BafA is synthesized, which in turn promotes the angiogenic process and the proliferation of endothelial cells (Tsukamoto et al., 2022). BafA stimulates the vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathway, which is the cellular/molecular basis for angiogenesis (Liberto et al., 2003).

6. The factors affecting angiogenesis modulation by microorganisms

The timing, dose, and mode of administration of a treatment can all have an impact on how microorganisms modulate angiogenesis.

Administration route: The way that microorganisms are administered can affect both their safety and effectiveness when it comes to modulating angiogenesis. For instance, systemic administration of microorganisms may result in toxicity and off-target effects, whereas local administration may be more effective in targeting particular tissues or diseases (Osheroy & Ben-Ami, 2016; Belkaid & Hand, 2014).

Dose: Angiogenesis modulation may also be impacted by the number of microbes present. A dosage that is too high can cause side effects like infection or inflammation, while a dosage that is too low might not have any therapeutic effect (Mueller et al., 2022; Bergers & Benjamin, 2003).

Treatment timing: One crucial element that may influence the effectiveness of microorganisms in modulating angiogenesis is the timing of the treatments. Certain microorganisms might, for instance, be more successful at promoting angiogenesis during tissue repair or regeneration, while others might be more successful at suppressing angiogenesis in the early stages of tumor development (Gopalakrishnan et al., 2020; Carmeliet & Jain, 2000).

Host genetics: Microorganisms and angiogenesis can interact differently depending on the genetic composition of the host. For instance, the host's genetic variations may impact the expression of genes linked to angiogenesis and the way the body reacts to microbe-mediated modulation of angiogenesis (Hooper et al., 2012; Carmeliet & Jain, 2011a).

Microbiome composition: Microbe-mediated angiogenesis modulation may also be impacted by the microbiome composition of the host. The microbiome has the ability to produce metabolites and other substances that affect angiogenesis and alter the immune response of the host (Lok, 2017; Carmeliet & Jain, 2011b).

In conclusion, a number of variables may affect the effectiveness and security of treatments involving microbe-mediated angiogenesis modulation. Additional investigation is required to enhance these variables and create safe and efficient treatments for microbe-mediated angiogenesis modulation.

7. The host-microbe interaction during angiogenesis modulation by microorganisms

During angiogenesis modulation, microorganisms engage with the host by generating a variety of bioactive molecules that control the host's cellular signaling pathways (Vieira et al., 2013; Schwabe & Jobin, 2013). Additionally, the host immune system is essential in controlling the relationship between microbes and angiogenesis. Cytokines and chemokines, which further control angiogenesis, are produced by immune cells in response to their recognition of microbial molecules (Rooks & Garrett, 2016; Sevcikova et al., 2023; Sawant et al., 2020). Furthermore, it has been demonstrated that the gut microbiota contributes to angiogenesis by generating short-chain fatty acids that influence host cell signaling pathways. As a result, the host-microbe relationship is essential to the control of angiogenesis in microbes (Uusi-Mäkelä & Rämet, 2018; Sajib et al., 2017).

8. Anti-cancer therapeutics targeting microbial-mediated angiogenesis modulation

Numerous microbial-based treatments have been created to reduce cholesterol and target tumor angiogenesis. For instance, anti-cancer treatments have been developed using the gut microbe *Akkermansia muciniphila*, which has been demonstrated to lower host cholesterol levels. According to a recent study, giving mice oral *A. muciniphila* lowered tumor growth and angiogenesis. Furthermore, a number of prebiotics and probiotics have been created to specifically target tumor angiogenesis (Marmé, 2018; Fakruddin et al., 2022b). It has been demonstrated that probiotics, like *Lactobacillus acidophilus*, reduce angiogenesis and tumor growth by altering the host's metabolism of cholesterol (Figure-3). Prebiotics, like inulin, can encourage the development of gut microbes that generate SCFAs, which lowers host cholesterol and inhibits angiogenesis (Liu et al., 2023; Shishir et al., 2023).

9. The potentials and prospects of microorganisms to module angiogenesis

Promising potential has been demonstrated by microorganisms in modulating angiogenesis for therapeutic purposes (Figure-3). It has been discovered that some microbes generate anti-angiogenic substances, which stop cancer cells from proliferating and spreading. It has been discovered that these substances specifically target different phases of the angiogenic process, such as the synthesis of growth factors and the initiation of signaling pathways (Zhao et al., 2023; Franks, 2013). Conversely, some microbes create substances known as pro-angiogenic agents, which encourage the formation of new blood vessels and support tissue regeneration. It has been discovered that these substances improve tissue repair and wound healing (Sater et al., 2022; Wan et al., 2021).

Furthermore, the possibility of using microorganisms to deliver therapeutic agents to specific tissues has been investigated. Because microorganisms can home to particular parts of the body, it is possible to engineer them to express and secrete particular therapeutic proteins that can then be targeted to particular tissues. With encouraging outcomes, this strategy has been investigated for the treatment of cancer and other illnesses (Schirbel et al., 2013; Visconti et al., 2019).

In order to fully understand the mechanisms involved and maximize their therapeutic potential, more research is required. The use of microorganisms for angiogenesis modulation is still in its early stages of development. On the other hand, the use of microbes to modulate angiogenesis offers a promising strategy for creating efficient and focused cancer and other disease treatments.

10. Conclusion

Reducing cholesterol levels to modulate microbial-mediated angiogenesis has become a viable strategy for the creation of anti-cancer medications. The gut microbiota can produce metabolites that prevent tumor angiogenesis and is essential in regulating the host's metabolism of cholesterol. Probiotics, prebiotics, and gut microbes are a few examples of microbial-based therapies that have been created to target tumor angiogenesis by lowering cholesterol. These treatments have the potential to increase the effectiveness and lessen the side effects of traditional anti-cancer therapies, and they have demonstrated encouraging results in preclinical and clinical investigations.

In conclusion, microbes have shown promise as targets for the creation of cutting-edge anti-angiogenic cancer treatments.

Microorganisms modulate angiogenesis through a variety of mechanisms, such as their interaction with the host immune system and the secretion of pro- or anti-angiogenic factors. The development of microbial-based anti-cancer therapies faces both opportunities and challenges due to the diversity of microorganisms involved and the complexity of their interactions with the host. The specificity, low toxicity, and potential to overcome drug resistance are among the potential benefits of using microbial-based approaches; however, there are a number of challenges that must be addressed, such as the need for a deeper comprehension of the interactions between microorganisms and host cells and the risk of microbial infections in patients with compromised immune systems. Notwithstanding these difficulties, research on the modulation of microbe-mediated angiogenesis presents a viable path toward the creation of potent anti-cancer medications that may supplement currently available anti-angiogenic drugs. To fully realize the potential of this strategy and apply the research's conclusions to clinical settings, more study is required.

Author contributions

M.F., Z.C., S.B.I., M.B.A., K.S.B.M., and M.A.S. Conceptualized, M.F., Z.C., J.S.J., M.B.A., K.S.B.M., and MAS drafted, wrote, MF, Z.C., S.B.I., J.S.J., N.B., and M.A.S. reviewed and edited the article.

Acknowledgment

None

Competing financial interests

The authors have no conflict of interest.

References

Adiyoga, R., Arief, I. I., Budiman, C., & Abidin, Z. (2022). In vitro anticancer potentials of Lactobacillus plantarum IIA-1A5 and Lactobacillus acidophilus IIA-2B4 extracts against WiDr human colon cancer cell line. Food Science and Technology, 42, e87221. https://doi.org/10.1590/fst.87221

Al-deeb, I., Joseph, J., Majid, A. M. S. A., Samad, N. A. (2021). Phytochemicals with Direct and/or Indirect Anti-angiogenic Properties Against Various Cancer Types Focusing on Their Mechanism of Action. Journal of Angiotherapy, 5(1), 226-233. https://doi.org/10.25163/angiotherapy.51212406111121

Al-Ostoot, F. H., Salah, S., Khamees, H. A., & Khanum, S. A. (2021). Tumor angiogenesis: Current challenges and therapeutic opportunities. Cancer Treatment and Research Communications, 28, 100422. Doi: https://doi.org/10.1016/j.ctarc.2021.100422

Al-Rawi, S. S., Ibrahim, A. H., Hamde, M. A., Babu, D., Nazari, M, Ab Kadir M. O., …., Shah, A. M. (2023). Antiangiogenic and Anticancer Potential of Supercritical Fluid Extracts from Nutmeg Seeds; In vitro, Ex vivo and in silico studies. Journal of Angiotherapy, 7(1), 1-13. https://doi.org/10.25163/angiotherapy.719371

Alipour, M. (2020). Molecular mechanism of Helicobacter pylori- Induced gastric Cancer. Journal of Gastrointestinal Cancer, 52(1), 23–30. https://doi.org/10.1007/s12029-020-00518-5

Almanaa, T. N., Yassin, M. A., El-Mekkawy, R. M., Ahmed, N. S., & Rabie, G. H. (2020). Anticancer and Antioxidant Activity by Secondary Metabolites of Aspergillus fumigatus Advances in Animal and Veterinary Sciences, 9(2), 265-273. https://doi.org/10.17582/journal.aavs/2021/9.2.265.273

Amin, T., Karim, A. B., Oyshe, I. I., Hossain, A., Karim, T., Jime, J. S., ….& Fakruddin, M. (2023). Unlocking Nature's Treasure Trove: Exploring Microorganisms for Novel Bioactives, Journal of Angiotherapy, 7(1), 1-8. Doi: https://doi.org/10.25163/angiotherapy.719345

Ansari, M. J., Bokov, D., Markov, A., Jalil, A. T., Shalaby, M. N., Suksatan, W., …. & Dadashpour, M. (2022). Cancer combination therapies by angiogenesis inhibitors; a comprehensive review. Cell Communication and Signaling, 20(1), 49. https://doi.org/10.1186/s12964-022-00838-y

Anwar, M. M., Albanese, C., Hamdy, N. M., & Sultan, A. S. (2022). Rise of the natural red pigment 'prodigiosin' as an immunomodulator in cancer. Cancer Cell International, 22(1), 419. https://doi.org/10.1186/s12935-022-02815-4

Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. Cell, 157(1), 121–141. https://doi.org/10.1016/j.cell.2014.03.011

Bergers, G., & Benjamin, L. E. (2003). Tumorigenesis and the angiogenic switch. Nature Reviews Cancer, 3(6), 401–410. https://doi.org/10.1038/nrc1093

Bhatt, A. P., Redinbo, M. R., & Bultman, S. J. (2017). The role of the microbiome in cancer development and therapy. CA Cancer Journal for Clinicians, 67(4), 326-344. doi: 10.3322/caac.21398

Carmeliet, P., & Jain, R. K. (2000). Angiogenesis in cancer and other diseases. Nature, 407(6801), 249–257. https://doi.org/10.1038/35025220

Carmeliet, P., & Jain, R. K. (2011a). Molecular mechanisms and clinical applications of angiogenesis. Nature, 473(7347), 298–307. https://doi.org/10.1038/nature10144

Carmeliet, P., & Jain, R. K. (2011b). Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nature Reviews Drug Discovery, 10(6), 417–427. https://doi.org/10.1038/nrd3455

Cerimele, F., Brown, L. F., Bravo, F., Ihler, G. M., Kouadio, P., & Arbiser, J. L. (2003). Infectious Angiogenesis: Bartonella bacilliformis Infection Results in Endothelial Production of Angiopoetin-2 and Epidermal Production of Vascular Endothelial Growth Factor. American Journal of Pathology, 163(4), 1321-1327. https://doi.org/10.1016/S0002-9440(10)63491-8

Chang, E. L., Ting, C. Y., Hsu, P.H., Lin, Y. C., Liao, E. C., Huang, C. Y., …. & Yeh, C. K. (2017). Angiogenesis-targeting microbubbles combined with ultrasound-mediated gene therapy in brain tumors. The Journal of Controlled Release, 255, 164-175. doi: 10.1016/j.jconrel.2017.04.010

Chu, Y. C., Chang, C., Liao, H. R., Fu, S. L., & Chen, J. J. (2021). Anti-Cancer and Anti-Inflammatory Activities of Three New Chromone Derivatives from the Marine-Derived Penicillium citrinum. Marine Drugs, 19(8), 408. https://doi.org/10.3390/md19080408

Dabrowska K, Witkiewicz W. Correlations of Host Genetics and Gut Microbiome Composition. Frontiers in Microbiology 2016: 7:. DOI: 10.3389/fmicb.2016.01357

de Menezes A-APM, Aguiar RPS, Santos JVO, Sarkar C, Islam MT, Braga AL, Hasan MM, da Silva FCC, Sharifi-Rad J, Dey A, Calina D, Melo-Cavalcante AAC, Sousa JMC. Citrinin as a potential anti-cancer therapy: A comprehensive review. Chemico-Biological Interactions, 2023; 381: 110561. Doi: https://doi.org/10.1016/j.cbi.2023.110561

DeBritto, S., Gajbar, T. D., Satapute, P., Sundaram, L., Lakshmikantha, R. Y., Jogaiah, S., & S, I. (2020). Isolation and characterization of nutrient dependent pyocyanin from Pseudomonas aeruginosa and its dye and agrochemical properties. Scientific Reports, 10(1). https://doi.org/10.1038/s41598-020-58335-6

Dehghani, N., Tafvizi, F., & Jafari, P. (2020). Cell cycle arrest and anti-cancer potential of probiotic Lactobacillus rhamnosus against HT-29 cancer cells. Bioimpacts, 11(4), 245–252. https://doi.org/10.34172/bi.2021.32

Faghfoori, Z., Faghfoori, M. H., Saber, A., Izadi, A., & Khosroushahi, A. Y. (2021). Anticancer effects of bifidobacteria on colon cancer cell lines. Cancer Cell International, 21(1). https://doi.org/10.1186/s12935-021-01971-3

Fakruddin M, Shishir MA, Oyshe II, Amin SMT, Hossain A, Sarna II, Jerin N, Mitra DK. Microbial Architects of Malignancy: Exploring the Gut Microbiome's Influence in Cancer Initiation and Progression. CP 2023, 5(1), 1. https://doi.org/10.18063/cp.397

Fakruddin, M., Shishir, M. A., Mouree, K. R., Khan, S. S. (2022a). Environmental and physiological angiogenesis in causing CVD with oxidative pattern. Journal of Angiotherapy, 6(2), 663-667. https://doi.org/10.25163/angiotherapy.622129

Fakruddin M, Shishir MA, Yousuf Z, Khan SS (2022b). Next Generation Probiotics- The Future of Biotherapeutics. Microbial Bioactives, 5(1), 156-163. DOI: https://doi.org/10.25163/microbbioacts.514309

Ferrara, N. (2002). VEGF and the quest for tumour angiogenesis factors. Nature Reviews.Cancer,2(10),795–803.https://doi.org/10.1038/nrc909

Ferrara, N., & Adamis, A. P. (2016). Ten years of anti-vascular endothelial growth factor therapy. Nature Reviews. Drug Discover/Nature Reviews. Drug Discovery, 15(6), 385–403.https://doi.org/10.1038/nrd.2015.17

Folkman, J. (1995). Angiogenesis in cancer, vascular, rheumatoid and other disease. Nature Medicine (Print), 1(1), 27–30. https://doi.org/10.1038/nm0195-27

Francescone R, Hou V, Grivennikov SI. Microbiome, inflammation, and cancer. Cancer J. 2014 May Jun;20(3):181-9. doi: 10.1097/PPO.0000000000000048. PMID: 24855005; PMCID: PMC4112188.

Franks, I. Gut microbes might promote intestinal angiogenesis. Nat Rev Gastroenterol Hepatol 10, 3 (2013). https://doi.org/10.1038/nrgastro.2012.227

Gopalakrishnan V, Weiner B, Ford CB, Sellman BR, Hammond SA, Freeman DJ, Dennis P, Soria J-C, Wortman JR, Henn MR. Intervention strategies for microbial therapeutics in cancer immunotherapy. Immuno-Oncology Technology, 2020; 6: 9-17. Doi: https://doi.org/10.1016/j.iotech.2020.05.001.

Gouda, S., Das, G., Sen, S. K., Shin, H., & Patra, J. K. (2016). Endophytes: a treasure house of bioactive compounds of medicinal importance. Frontiers in Microbiology, 7. https://doi.org/10.3389/fmicb.2016.01538

Guruceaga X, Perez-Cuesta U, Pellon A, Cendon-Sanchez S, Pelegri-Martinez E, Gonzalez O, Hernando FL, Mayayo E, Anguita J, Alonso RM, Keller NP, Ramirez-Garcia A, Rementeria A. Aspergillus fumigatus Fumagillin Contributes to Host Cell Damage. J Fungi (Basel). 2021 Nov 3;7(11):936. doi: 10.3390/jof7110936. PMID: 34829223; PMCID: PMC8619997.

Han JM, Jang JP, Jang JH, Ahn JS, Jung HJ. Antiangiogenic potentials of ahpatinins obtained from a Streptomyces species. Oncol Rep. 2020 Feb;43(2):625-634. doi: 10.3892/or.2019.7446. Epub 2019 Dec 24. PMID: 31894333.

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of Cancer: The next generation. Cell, 144(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hashemi-Khah, M., Soleimani, N. A., Forghanifard, M. M., Gholami, O., Taheri, S., & Amoueian, S. (2022). An In Vivo Study of Lactobacillus rhamnosus (PTCC 1637) as a New Therapeutic Candidate in Esophageal Cancer. BioMed Research International, 2022, 1–9. https://doi.org/10.1155/2022/7607470

Hassan, M., Elmezain, W. A., Baraka, D., Abo-Elmaaty, S. A., Elhassanein, A., Ibrahim, R. M., & Hamed, A. A. (2024). Anti-Cancer and Anti-Oxidant Bioactive Metabolites from Aspergillus fumigatus WA7S6 Isolated from Marine Sources: In Vitro and In Silico Studies. Microorganisms, 12(1), 127. https://doi.org/10.3390/microorganisms12010127

Ho, T. F., Peng, Y., Chuang, S., Lin, S. C., Feng, B., Lu, C., Yu, W. J., Chang, J. S., & Chang, C. (2009). Prodigiosin down-regulates survivin to facilitate paclitaxel sensitization in human breast carcinoma cell lines. Toxicology and Applied Pharmacology, 235(2), 253–260. https://doi.org/10.1016/j.taap.2008.12.009

Hooper, L. V., Littman, D. R., & Macpherson, A. J. (2012). Interactions between the microbiota and the immune system. Science (New York, N.Y.), 336(6086), 1268–1273. https://doi.org/10.1126/science.1223490

Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell. 2014;26(5):605-622. doi: 10.1016/j.ccell.2014.10.006

Jain, R. K., Duda, D. G., Willett, C. G., Sahani, D. V., Zhu, A. X., Loeffler, J. S., Batchelor, T. T., & Sorensen, A. G. (2009). Biomarkers of response and resistance to antiangiogenic therapy. Nature Reviews. Clinical Oncology (Print), 6(6), 327–338. https://doi.org/10.1038/nrclinonc.2009.63

Jang, J., Han, J. M., Jung, H. J., Osada, H., Jang, J., & Ahn, J. S. (2018). Anti-Angiogenesis Effects Induced by Octaminomycins A and B against HUVECs. Journal of Microbiology and Biotechnology (Print). https://doi.org/10.4014/jmb.1806.06046

Jang J, Jang M, Nogawa T, Takahashi S, Osada H, Ahn JS, Ko S, Jang J. RK-270D and E, Oxindole Derivatives from Streptomyces sp. with Anti-Angiogenic Activity. J. Microbiol. Biotechnol. 2022;32:302-306. https://doi.org/10.4014/jmb.2110.10039

Kerbel RS. (2008) Tumor angiogenesis. N Engl J Med.;358(19):2039-2049. doi: 10.1056/NEJMra0706596

Kerbel RS. Improving conventional or targeted anticancer therapy with complementary, not alternative, antiangiogenic treatment strategies. J Clin Oncol. 2011;29(10):1239-1242. doi: 10.1200/JCO.2010.32.9504

Konishi, H., Fujiya, M., Tanaka, H., Ueno, N., Moriichi, K., Sasajima, J., Ikuta, K., Akutsu, H., Tanabe, H., & Kohgo, Y. (2016). Probiotic-derived ferrichrome inhibits colon cancer progression via JNK-mediated apoptosis. Nature Communications, 7(1). https://doi.org/10.1038/ncomms12365

Lei ZN., Teng QX., Tian Q, Chen W, Xie Y, Wu K, Zeng Q, Zeng L, Pan Y, Chen Z-S, He Y. Signaling pathways and therapeutic interventions in gastric cancer. Sig

Transduct Target Ther 7, 358 (2022). https://doi.org/10.1038/s41392-022-01190-w

Liberto, M. C., Matera, G., Lamberti, A. G., Barreca, G. S., Quirino, A., & Focà, A. (2003). In vitro Bartonella quintana infection modulates the programmed cell death and inflammatory reaction of endothelial cells. Diagnostic Microbiology and Infectious Disease, 45(2), 107–115. https://doi.org/10.1016/s0732-8893(02)00461-3

Liu, ZL., Chen, HH., Zheng, LL. et al. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Sig Transduct Target Ther 8, 198 (2023). https://doi.org/10.1038/s41392-023-01460-1

Lok, B. (2017). Angiogenesis and its potential role in the growth and proliferation of pathogens. Journal of Angiotherapy (Print), 1(1), E001-E011. https://doi.org/10.25163/angiotherapy.11000121421300417

Malespín-Bendaña, W., Ferreira, R. M., Pinto, M., Figueiredo, C., Alpízar-Alpízar, W., Une, C., Figueroa-Protti, L., & RamíRez, V. (2023). Helicobacter pylori infection induces abnormal expression of pro-angiogenic gene ANGPT2 and miR-203a in AGS gastric cell line. Brazilian Journal of Microbiology, 54(2), 791–801. https://doi.org/10.1007/s42770-023-00940-4

Marmé D. Tumor Angiogenesis: A Key Target for Cancer Therapy. Oncol Res Treat 9 April 2018; 41 (4): 164. https://doi.org/10.1159/000488340

Mudaliar, S. B., & Prasad, A. S. B. (2024b). A biomedical perspective of pyocyanin from Pseudomonas aeruginosa: its applications and challenges. World Journal of Microbiology & Biotechnology, 40(3). https://doi.org/10.1007/s11274-024-03889-0

Mueller, A., Brockmueller, A., Fahimi, N., Ghotbi, T., Hashemi, S., Sadri, S., Khorshidi, N., Kunnumakkara, A. B., & Shakibaei, M. (2022). Bacteria-Mediated Modulatory Strategies for Colorectal Cancer treatment. Biomedicines, 10(4), 832. https://doi.org/10.3390/biomedicines10040832

Naidu, J. R., Sreenivasan, S., Ruhi, S., Chen, H. W. J., Naidu, S. R., Khan, D., …., Rammohan, S. (2024). Review on Angiogenesis Modulation by Natural Compounds as Therapeutic Potential and Mechanisms. Journal of Angiotherapy, 8(2), 1-6. https://doi.org/10.25163/angiotherapy.829507

Nafsi NN, Rahman MA, Shishir MA, Arefin MS, Jime JS, Bulbul N, Safa A, Fakruddin M. Unleashing the Potential of Gut Microbiota: Cholesterol Reduction Through Microbial Bile Acid Metabolism, Current Biotechnology, 2024; 13(1): 6-14. Doi: 10.2174/0122115501282536240301055402

Osherov N, Ben-Ami R. Modulation of Host Angiogenesis as a Microbial Survival Strategy and Therapeutic Target. PLoS Pathog. 2016 Apr 14;12(4):e1005479. doi: 10.1371/journal.ppat.1005479. Erratum in: PLoS Pathog. 2016 Aug;12(8):e1005838. PMID: 27078259; PMCID: PMC4831739.

Potente, M., Gerhardt, H., & Carmeliet, P. (2011). Basic and therapeutic aspects of angiogenesis. Cell (Cambridge), 146(6), 873–887. https://doi.org/10.1016/j.cell.2011.08.039

Procaccianti G, Roggiani S, Conti G, Brigidi P, Turroni S, D'Amico F. Bifidobacterium in anticancer immunochemotherapy: friend or foe? Microbiome Res Rep. 2023 Jul 10;2(3):24. doi: 10.20517/mrr.2023.23. PMID: 38046824; PMCID: PMC10688788.

Rajoka, M. S. R., Zhao, H., Mehwish, H. M., Li, N., Lū, Y., Lian, Z., Shao, D., Jin, M., Li, Q., Zhao, L., & Shi, J. (2019). Anti-tumor potential of cell free culture supernatant of Lactobacillus rhamnosus strains isolated from human breast milk. Food Research International, 123, 286–297. https://doi.org/10.1016/j.foodres.2019.05.002

Rooks, M., & Garrett, W. S. (2016). Gut microbiota, metabolites and host immunity. Nature Reviews. Immunology (Print), 16(6), 341–352. https://doi.org/10.1038/nri.2016.42

Sajib, S., Zahra, F. T., Lionakis, M. S., German, N., & Mikelis, C. M. (2017). Mechanisms of angiogenesis in microbe-regulated inflammatory and neoplastic conditions. Angiogenesis, 21(1), 1–14. https://doi.org/10.1007/s10456-017-9583-4

Sankarapandian, V., Maran, B. a. V., Rajendran, R. L., Jogalekar, M. P., Sridharan, G., Krishnamoorthy, R., Gangadaran, P., & Ahn, B. (2022). An update on the effectiveness of probiotics in the prevention and treatment of cancer. Life, 12(1), 59. https://doi.org/10.3390/life12010059

Sater AHA, Bouferraa Y, Amhaz G, Haibe Y, Lakkiss AE, Shamseddine A. From Tumor Cells to Endothelium and Gut Microbiome: A Complex Interaction Favoring the Metastasis Cascade. Front Oncol. 2022 May 5;12:804983. doi: 10.3389/fonc.2022.804983. PMID: 35600385; PMCID: PMC9117727.

Sawant, S. S., Patil, S. M., Gupta, V., & Kunda, N. K. (2020). Microbes as Medicines: Harnessing the power of bacteria in advancing Cancer treatment. International Journal of Molecular Sciences (Online), 21(20), 7575. https://doi.org/10.3390/ijms21207575

Schirbel A, Kessler S, Rieder F, West G, Rebert N, Asosingh K, McDonald C, Fiocchi C. Pro-Angiogenic Activity of TLRs and NLRs: A Novel Link Between Gut Microbiota and Intestinal Angiogenesis. Gastroenterology, 2013; 144(3): 613-623.e9. Doi: https://doi.org/10.1053/j.gastro.2012.11.005

Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer. 2013;13(11):800-812. doi:10.1038/nrc3610

Sethi, Y., Vora, V., Anyagwa, O. E., Turabi, N., Abdelwahab, M., Kaiwan, O., Chopra, H., Attia, M. S., Yahya, G., Emran, T. B., & Padda, I. (2023). Streptomyces Paradigm in Anticancer therapy: A State-of-the Art review. 19: 1-16. Doi: 10.2174/0115733947254550230920170230

Sevcikova A, Mladosievicova B, Mego M, Ciernikova S. Exploring the role of the gut and intratumoral microbiomes in tumor progression and metastasis. International Journal of Molecular Sciences 2023; 24(24): 17199.

Sherwood, L. M., Parris, E. E., & Folkman, J. (1971). Tumor angiogenesis: therapeutic implications. The New England Journal of Medicine (Print), 285(21), 1182–1186. https://doi.org/10.1056/nejm197111182852108

Shishir MA, Sultana S, Turna JT, Akter T, Mim SJ, Islam R, Tanvir M, Akther Y, Jahan I, Ferdous UT, Prima MJ, Fakruddin M. Non-Ribosomally Synthesized Lipopeptides (NRLP): Novel Potential Therapeutics for Cancer Treatment. CP 2023, 5(2), 2569. https://doi.org/10.36922/cp.2569

Somani RR, Bhanushali UV. Targeting angiogenesis for treatment of human cancer. Indian J Pharm Sci. 2013 Jan;75(1):3-10. doi: 10.4103/0250-474X.113529. PMID: 23901154; PMCID: PMC3719146.

Tran, P. M., Tang, S., & Salgado-Pabón, W. (2022). Staphylococcus aureus β-Toxin Exerts Anti-angiogenic Effects by Inhibiting Re-endothelialization and Neovessel Formation. Frontiers in Microbiology, 13. https://doi.org/10.3389/fmicb.2022.840236

Tsukamoto K, Kumadaki K, Tatematsu K, Suzuki N, Doi Y. The of Bartonella bacilliformis BafA Promotes Endothelial Cell Angiogenesis via the VEGF Receptor Signaling Pathway. mSphere. 2022 Apr 27;7(2):e0008122. doi: 10.1128/msphere.00081-22

Tsukamoto, K., Shinzawa, N., Kawai, A., Suzuki, M., Kidoya, H., Takakura, N., Yamaguchi, H., Kameyama, T., Inagaki, H., Kurahashi, H., Horiguchi, Y., & Doi, Y. (2020). The Bartonella autotransporter BafA activates the host VEGF pathway to drive angiogenesis. Nature Communications, 11(1). https://doi.org/10.1038/s41467-020-17391-2

Uusi-Mäkelä, M., & Rämet, M. (2018). Hijacking host angiogenesis to drive mycobacterial growth. Cell Host & Microbe, 24(4), 465–466. https://doi.org/10.1016/j.chom.2018.09.016

Vadlapudi, V., Borah, N., Yellusani, K. R., Gade, S., Reddy, P. S. R., Rajamanikyam, M., Vempati, L., Gubbala, S. P., Chopra, P., Upadhyayula, S. M., & Amanchy, R. (2017). Aspergillus Secondary Metabolite Database, a resource to understand the Secondary metabolome of Aspergillus genus. Scientific Reports (Nature Publishing Group), 7(1). https://doi.org/10.1038/s41598-017-07436-w

Vieira AT, Teixeira MM, Martins FS. The Role of Probiotics and Prebiotics in Inducing Gut Immunity. Front Immunol. 2013;4:445. doi: 10.3389/fimmu.2013.00445

Visconti, A., Roy, C. I. L., Rosa, F., Rossi, N., Martin, T., Mohney, R. P., Li, W., De Rinaldis, E., Bell, J. T., Venter, J. C., Nelson, K. E., Spector, T. D., & Falchi, M. (2019). Interplay between the human gut microbiome and host metabolism. Nature Communications, 10(1). https://doi.org/10.1038/s41467-019-12476-z

Wan X, Song M, Wang A, Zhao Y, Wei Z, Lu Y. Microbiome Crosstalk in Immunotherapy and Antiangiogenesis Therapy. Front Immunol. 2021 Oct 21;12:747914. doi: 10.3389/fimmu.2021.747914. Erratum in: Front Immunol. 2022 Apr 21;13:887775. PMID: 34745119; PMCID: PMC8566949.

Xue C, Li G, Gu X, Su Y, Zheng Q, Yuan X, Bao Z, Lu J, Li L. Health and Disease: Akkermansia muciniphila, the Shining Star of the Gut Flora. Research (Wash D C). 2023;6:0107. doi: 10.34133/research.0107. Epub 2023 Apr 3. PMID: 37040299; PMCID: PMC10079265.

Yoda, K., Miyazawa, K., Hosoda, M., Hiramatsu, M., Yan, F., & He, F. (2013). Lactobacillus GG-fermented milk prevents DSS-induced colitis and regulates intestinal epithelial homeostasis through activation of epidermal growth factor receptor. European Journal of Nutrition, 53(1), 105–115. https://doi.org/10.1007/s00394-013-0506-x

Zhao, LY., Mei, JX., Yu, G. et al. Role of the gut microbiota in anticancer therapy: from molecular mechanisms to clinical applications. Sig Transduct Target Ther 8, 201 (2023). https://doi.org/10.1038/s41392-023-01406-7

Zhu L, Gu Q, Fang L. Cholesterol-mediated regulation of angiogenesis: An emerging paradigm. Cardiol Plus 2019;4:1-9. DOI:10.4103/cp.cp_5_19