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Impact of Angiogenic Signalling Mechanism in Cancer Progression: Interference with Herbal Drugs

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Abstract: Angiogenesis is a complex process that is involved in the pathogenesis of many diseases, including cancer and ischemic disorders. The intricate process of angiogenesis plays a pivotal role in various physiological and pathological conditions, making it a subject of profound interest in medical research. Traditional Chinese medicine (TCM) has evolved over the past few decades to explore the multifaceted aspects of the process, exploring its mechanisms, regulators, and implications in health and disease. In this review, we focus on the anti-angiogenic properties of herbal drugs in the treatment of cancer, with a focus on their anti-angiogenesis effects. In addition, we discuss the potential of herbs in preventing or inhibiting angiogenesis, thereby disrupting the blood supply crucial for tumor growth and metastasis. Furthermore, we highlight the role of vascular endothelial growth factor (VEGF) signalling pathways in the regulation of tumor growth. The integration of traditional wisdom with modern scientific methodologies can enhance our understanding of the mechanisms underlying the anticancer and anti-Angiogenic effects of herbal medicines. As our understanding deepens, herbal drugs may emerge as valuable components of comprehensive and personalized cancer treatment strategies. The combination of traditional and modern medicine may offer an individualized approach to cancer treatment, addressing the heterogeneity of tumors and patient responses.

Keywords: Angiogenesis, Angiogenic factors, Cancer, Herbal drugs.

I. Introduction

Cancer is a genetic disease which is characterized by uncontrolled growth and spread of abnormal cells in the body. Normally, Human cell grow and multiply through a process called cell division. When a cell grows old or become damaged, they die and new cell can take their place. Mortality rates of cancer has been depicted in Fig. 1 according to the data of global cancer observatory. Cancer can start almost anywhere in the body as it is made up of trillions of cells [1], [2].

There are many types of cancer each with its characteristics and treatment given. The cancer or neoplasm may be either benign or malignant; a benign cancer stays confined to the tissue of origin, while malignant cancer can spread to other organs. The advancement of cancer is often linked to genetic mutation and environmental factors [3], [4]. Also, some of the various treatment of cancer include; Surgery, chemotherapy, radiation therapy, immunotherapy.

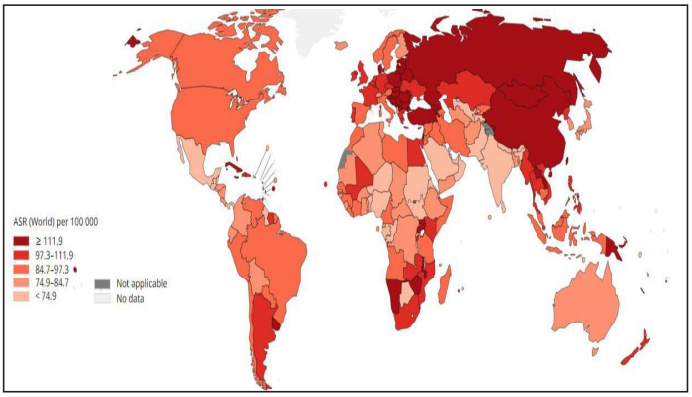

Fig. 1: Mortality Rates Due to Cancer Worldwide, All Types, Both Sexes, All Ages

Cancer progression is a complex biological process with diversified understanding [5]. However, different pathways have been extensively studied in last few decades due to advancements in imagining and analysis technology [6], [7]. Carcinogens, biological agents and inflammation may trigger deregulated metabolism which lead to genetic mutation and may result in development of cancer. These manifestations at cellular level may start interfering at cell cycle checkpoints [8]. A series of biological events are the reason for the transformation of a healthy cell into a cancerous cell including carcinogens, genetic alterations, inflammation and dysregulated metabolism. At molecular level, such factors of cancer development disbalances the levels of tumor suppressor genes and oncogenes yielding cell cycle deregulation. Further, replicative immortality and altered cell signalling mechanisms are causing the progression

of cancer and have been reported to avoid immune cells, growth suppressors and angiogenesis which yields the metastasis of cancerous cells [9].

II. Angiogenesis

Angiogenesis is a physiological process which involve formation of new blood vessels. It is a function required for growth and development as well as wound healing. But in cancer patients, angiogenesis supports tumour growth and spread by feeding it with oxygen and nutrients. Angiogenesis begins during embryo development, when the growth of new blood vessels is essential for the development of new cells and tissues [10]. The new veins are, arteries and capillaries are needed to supply cells with oxygenated blood and nutrients and take away deoxygenated blood and waste products. In adults organisms, the endothelial cells that line inside the blood vessels (the lumen) are largely dormant. However, the specific signals can reactivate these cells induce angiogenesis when environment is low in oxygen (hypoxic), after injury or in placenta formation during pregnancy [11], [12].

III. Impact of Angiogenesis in Cancer

Angiogenesis aids in cancer progression because solid tumor need blood supply to grow beyond a few millimetres in size.it also allow cancer cell to invade nearby blood vessels and travel to other parts of the body through a process called metastasis [13], [14]. Angiogenesis is a target for anti-cancer therapies. Drugs called angiogenesis inhibitors can be used to block formation of new blood vessels.

Ordinarily, angiogenesis can be thought as being "switched off". When new blood vessels are needed for wound repair or after menstruation, the process may be "switched on" however, it is carefully regulated by signals in the surrounding environment. The use of angiogenesis suppressors can promote the neovascularisation of cancer tissue as well as growth of tumor [15].

IV. Angiogenic Factors Involved in Angiogenesis and Cancer Progression

Angiogenesis is the interaction by which fresh blood vessels are shaped from prior veins. It assumes a basic part in different physiological and obsessive cycles, including wound recuperating, embryogenesis, and the growth and spread of cancers. A few factors are engaged with angiogenesis, and they can be extensively ordered into stimulatory and inhibitory factors. Following Fig. 2 consists of different angiogenic factors.

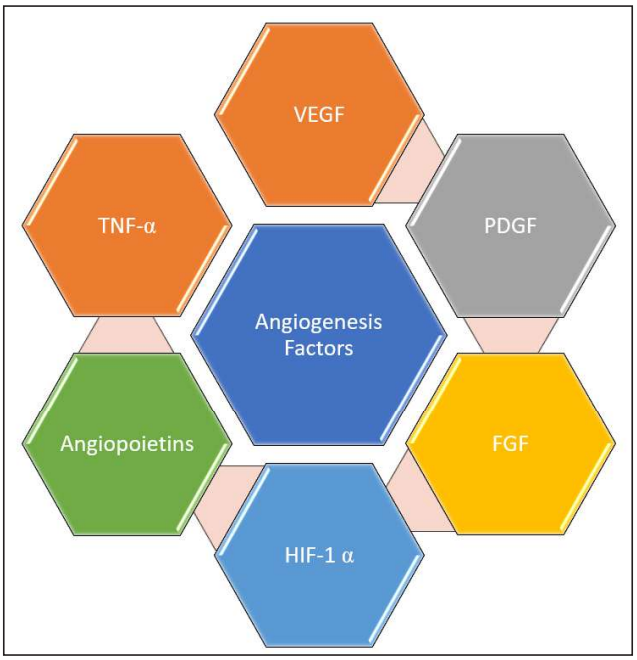

Fig. 2: Different Angiogenic Factors

- *Vascular Endothelial Growth Factor (VEGF):* VEGF is a significant supportive of angiogenic factor and a critical controller of angiogenesis. It advances the growth and movement of endothelial cells, which are the structure blocks of veins [16], [17].
- *Fibroblast Growth Factor (FGF):* FGFs, especially FGF-2, animate endothelial cell expansion and angiogenesis. They are engaged with tissue fix and advancement [18], [19].
- *Platelet-Derived Growth Factor (PDGF):* PDGF is associated with the enlistment and enactment of pericytes and smooth muscle cells to balance out recently shaped veins [20].
- *Angiopoietins:* Angiopoietins are growth factors that control vessel development and adjustment. Angiopoietin-1 advances vessel development and steadiness, while Angiopoietin-2 can weaken vessels [21].
- *Hypoxia:* Low oxygen levels (hypoxia) can set off angiogenesis. Hypoxia-inducible factors (HIFs) are key controllers that answer oxygen levels and advance the declaration of favorable to angiogenic qualities, including VEGF [22].

The balance between angiogenesis and hostile to angiogenic factors, as well as the particular microenvironment of a tissue or growth, decides the degree and guideline of angiogenesis in different physiological and neurotic settings. This equilibrium

is firmly controlled to keep up with tissue homeostasis and can be dysregulated in sicknesses like disease, where extreme angiogenesis adds to cancer growth and metastasis.

V. Angiogenic Signalling Pathways in Cancer Progression

A. AKT/PKB Pathway

The serine/threonine kinase Akt also known as protein kinase B (PKB), is a signalling pathway involved in various cellular processes like cell growth, survival, and metabolism. It`s activated by growth factors and insulin. The pathway helps regulate important cellular functions.

The key proteins involved are phosphatidylinositol 3-kinase (p13k) and akt or protein kinase B. P13k akt mTOR pathway is cell survival pathway that signals the cell to divide and grow. Blockage of AKT signalling results in apoptosis (process of programmed cell death) and inhibits growth of tumor cells. Activation of AKT/PKB promotes cell proliferation, inhibits cell death and enhances the ability of cancer cells to invade surrounding tissue and form metastases.

B. JAK-STAT Pathway

It's a pathway involved in cell signalling and gene expression. Basically, when certain molecules bind to cell surface receptors, it triggers the activation of JAKS, which then phosphorylate STAT proteins. These activated STAT proteins then move into the nucleus and regulate the expression of specific genes. It also plays a role in various biological processes.

The JAK-STAT are introduced by family. There are 4 members in JAK family; JAK1, JAK2, JAK3, TYK2. While the STAT family comprises of 7 members; STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6 (Wang Wei *et al*., 2021). In cancer dysregulation of the JAK-STAT pathway can occur through various mechanisms such as abnormal activation of JAK or STAT proteins or mutations. This dysregulation can contribute to uncontrolled cell growth, evasion, promoting tumor development and progression. Targeting the JAK STAT pathway has become an important therapeutic strategy in certain types of cancer.

C. VEGF-R Pathway

VEGF-R Pathway is also known as the vascular endothelial growth factor receptor pathway, is a signalling pathway involved in angiogenesis, which is formation of new blood vessels. VEGF-R are receptors found on the surface of endothelial cells which line the inner walls of blood vessels. When VEGF (Vascular endothelial growth factor) binds to these receptors, it triggers a cascade of signals that promote the growth and survival of blood vessels.

VEGF promotes tumor angiogenesis through some various mechanisms including enhanced endothelial cell proliferation and survival; increased migration and invasion of endothelial cells; increased permeability of existing vessels, and enhanced chemotaxis and homing of bone marrow derived vascular precursor cells.This pathway plays a crucial role in processes like wound healing and development, also it is involved in cancer and retinal disorder.

VI. Intervention of Angiogenesis using Phytochemicals

Nature is the biggest source of phytochemicals. Majority of nature derived chemicals have been reported for various pharmacological activities. Such active secondary metabolites have been used as lead molecules for synthetic library of chemicals. These active compounds of nature have been evaluated for activity against angiogenic factors [23]. We have identified numerous chemical agents which have shown effects on different angiogenic factors (VEGF, HIF-1a, Angiopoietins, FGF, PDGFs etc.) Following section of manuscript involves such herbal drugs/phytochemicals active against cancer progression and angiogenesis.

For eons, humanity has struggled to overcome the obstacles in his path and experimented with many approaches to manage illness. Among these efforts is the study of medicinal herbs, which have been used for eons to treat illnesses and retain their benefits in spite of scientific and technological advancements as well as the more prevalent use of chemicals in modern medicine. It is obvious that additional research on these substances is needed given the abundance of these herbs, their potential medical benefit, and the fact that most of them remain undiscovered. The process of angiogenesis, which helps meet cellular demands, involves regrowing existing blood vessels. There is no denying that angiogenesis is involved with some (some) physiological processes, including diabetic foot healing and deteriorating [24], [25].

The creation of new blood vessels—which are necessary for both pathologic and physiological situations, the latter of which includes the growth, development, and metastasis of tumours—is a tightly regulated process known as angiogenesis. In order to provide cancer patients with the best possible outcome, blocking angiogenesis in addition to other anticancer treatments like chemotherapy appears to be essential. Certain naturally occurring substances produced from plants have demonstrated the ability to both stop the growth and division of cancer cells as well as stop the development of these new blood vessels within the tumour [26], [27]. We want to introduce anti-angiogenic herbs and talk about their characteristics in this review.

- *Sculellaiabaicalensis:* Sculellaiabaicalensis a medicinal plant also referred to as Baikal slcuullcap, contains the primary active chemical ingredient, baicalin. Baicalin and a S.baicalensis extract were evaluated for their effects on

VEGF production, and it was shown that they had a dual effect on angiogenesis, inhibiting it at high concentrations (5 mg/ml) [28].

- *C. Roseus:* C. Roseus, the Nithyakalyani sample, Catharanthus roseus, was obtained using ethyl acetate extraction. This study specifically evaluates Catharanthus roseus utilizing fertilized eggs and the anti-angrogenesis approach. The 0.5 ml solution's concentration demonstrated notable anti-cancer effectiveness.
- *Japan's Coptis Maximo:* The main isoquinoline alkaloid found in C.chinensis is berberine. A genus of plants in the ranunculaceae family is called Coptis. Due to its potent anti-tumor properties, Coptis chinensis, a common toxin-resolving herb in traditional Chinese medicine, has drawn more attention. The extract inhibits angiogenesis by controlling issues linked to the cell cycle. CJME exhibits its effects by preventing the G1 cell cycle shift brought on by VEGF. The method that was dose-dependent and reached significance at 25 μg/ml.
- *Curcuma Longa:* Curcuma longa is a perennial herbaceous plant with rhizomata that is a member of the Zingerberaceae family of gingers. It turns out to be a polyphenol present in nature. According to a report, curcumin has the ability to stop the rate at which tumors develop by decreasing the levels of VEGF and cyclocoxygenase-2 and activating the NF-κB signalling effector. The ideal dosage required to inhibit NF-κB and signal transducer was 500 mg/kg taken orally [29].
- *Gingiber Officinalis:* The ginger family of flowering plants, or zigiberaceae, is made up of roughly 56 genera. Phenolic groups are among the many significant bioactive chemicals and compounds found in ginger. One ingredient that has anti-carcinogenic and antioxidant qualities is zingiber officinale. Of all the ginger components examined, 6-shagoal is the most active. It inhibited NF-κB activation and reduced VEGF and IL-8 GE secretion. When given orally to mice once a day for 28 days, 250 mg/kg of ginger exhibited 68% reduction of tumor growth.
- *Ginkgo Biloba:* Antioxidant-rich ginkgo biloba has anti-inflammatory properties. The exocarp extract of ginkgo biloba suppresses the effects of angiogenesis on the cancerous Wnt/β-calen VEGF signalling pathway.
- *Panax Ginseng:* Axel. The phrase panacea, which meaning "a cure for all diseases and a source of longevity," is where the name "panax," which refers to ginseng, originates. Growing to a height of 30 to 60 cm, ginseng is a herbaceous perennial. The family Araliaceae and genus Panax are widely utilized in East Asia. The components that volatile oil is composed of contains components of fatty easter in ginseng.
- *Extract from Grape Seeds:* Vitis vinifora grape seeds are members of the Vitaceae family. The tannins in grape seed extract function as potent antioxidants and may shield other tissues, like the lining of blood vessels, from harm. GSE may prevent VEGF-induced endothelial cell migration, proliferation, and sprouting from the aortic ring. VEGF-induced migration was eliminated by GSE at a concentration of 3 g/ml [30].
- *Scrophularia Striata:* Scrophularia striata is a member of the family Scrophulariace. On 1321 cell line, a filtered leaf extract of S. statata exhibited potent anticancer properties. Filtered leaf extract at a concentration of 9 μg/ml heals the 1321 cell.
- *Plantae Chinensis:* T. chinensis belongs to the genus Taxus and the family Taxaccae. In non-small cell lung cancer, an aqueous extract of Taxus chinensis targeting CD47 improved anti tumor effects.

VII. Conclusion

In conclusion, the intricate process of angiogenesis plays a pivotal role in various physiological and pathological conditions, making it a subject of profound interest in medical research. This paper has delved into the multifaceted aspects of angiogenesis, exploring its mechanisms, regulators, and implications in health and disease. The intricate interplay of pro-angiogenic and anti-angiogenic factors orchestrates the formation of new blood vessels, influencing tissue development, wound healing, and tumor progression.

Understanding the molecular signaling pathways involved in angiogenesis has provided valuable insights for developing therapeutic interventions. Targeting specific angiogenic factors or pathways holds promise for treating diseases characterized by aberrant angiogenesis, such as cancer and ischemic disorders. Moreover, advancements in imaging techniques and biomarker identification contribute to diagnostic and prognostic strategies, facilitating early intervention and personalized medicine approaches.

As our comprehension of angiogenesis continues to deepen, it opens new avenues for innovative research and clinical applications. Collaborative efforts across disciplines, including molecular biology, biochemistry, and clinical medicine, will further enhance our ability to harness the potential of angiogenesis for therapeutic purposes. Ultimately, unraveling the complexities of angiogenesis holds great promise for revolutionizing medical treatments, offering hope for improved outcomes in a myriad of health conditions.

In conclusion, the exploration of herbal drugs in the treatment of cancer, with a focus on their impact on angiogenesis, represents a captivating and promising avenue in modern oncology. The multifaceted nature of cancer demands a comprehensive approach, and herbal drugs offer a diverse array of bioactive compounds that exhibit anti-cancer properties, including the modulation of angiogenesis.

The reviewed studies and research findings underscore the potential of herbal drugs in inhibiting angiogenesis, thereby

disrupting the blood supply crucial for tumor growth and metastasis. Compounds derived from various medicinal plants exhibit anti-angiogenic effects through the regulation of key signaling pathways involved in blood vessel formation. This not only highlights the importance of herbal drugs in targeting specific aspects of cancer biology but also emphasizes their potential as adjuncts to conventional cancer therapies.

While the field of herbal medicine holds great promise, it is essential to approach it with a balanced perspective, considering the need for rigorous scientific validation and standardization of herbal formulations. The integration of traditional wisdom with modern scientific methodologies can enhance our understanding of the mechanisms underlying the anti-cancer and anti-angiogenic effects of herbal drugs.

Moreover, the holistic nature of herbal medicine aligns with the growing interest in personalized and integrative cancer care. The synergistic interactions among various bioactive compounds in herbal formulations may offer a more nuanced and individualized approach to cancer treatment, addressing the heterogeneity of tumors and patient responses.

In conclusion, the integration of herbal drugs into the treatment of cancer, particularly focusing on their anti-angiogenic properties, represents a dynamic and evolving field. Continued research, clinical trials, and collaboration between traditional and modern medicine practitioners are essential for unlocking the full potential of herbal drugs in the fight against cancer and angiogenesis-related disorders. As our understanding deepens, herbal drugs may emerge as valuable components of comprehensive and personalized cancer treatment strategies.

VIII. Conflict of Interest

Authors declare no conflict of interest.

IX. Animal Ethical Approval

Not Applicable.

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