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Research Progress of Chinese Medicine Against Tumor Angiogenesis

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Abstract: ***With the continuous development of the society, people's life style and living environment changing, malignant tumor disease from the past rare disease rare disease gradually tends to the high incidence of common disease change, according to incomplete statistics, in 2020, the global 12. 7 million people with new tumors, death 7. 6 million people, with an annual average of 3% to 5% increment, of which 56% of new cases and deaths come from developing countries. In China, the number of new cases of malignant tumors in 2020 will be about 3. 929 million, and the incidence rate of malignant tumors in the country will be 285. 83/100, 000, and the overall situation of prevention and control of malignant tumors is becoming more and more serious. The overall situation of prevention and control of malignant tumors is becoming more and more serious. At the same time, as the occurrence and development process of malignant tumor disease, the key link of tumor angiogenesis, which is decisive, has become an important research direction to inhibit the growth of tumor cells recurrence and metastasis. In recent years, seeking effective anti-tumor angiogenesis components and treatments from traditional Chinese medicine is a hot spot for the treatment of inhibition of the continuous deterioration of malignant tumors. Especially, the effective components of herbal extracts showed strong tumor neovascularization inhibition.***

Keywords: Traditional Chinese medicine, Tumor, Anti-angiogenesis, Review.

1. Tumors and Angiogenesis

In 1971, Folkman [1] proposed the hypothesis that solid tumors over 1-2 mm in size require angiogenesis for their development and growth. Subsequently, they showed specific fragmentary evidence that solid tumors depend on new blood vessel formation for continued growth [2]. Inspired by this, anti-angiogenic strategies began to be the focus of the research team's attention, which may develop into new therapeutic approaches for the treatment of solid tumors. Researchers accumulated a large amount of data during 40 years of laborious experiments that supported Folkman's hypothesis [3]. Relying on the efforts made in this field of research, the complex mechanisms of tumor angiogenesis have been gradually exposed. The normal process of angiogenesis is under a relatively dynamic homeostasis, tightly controlled by pro- and anti-angiogenic regulatory factors. Once this homeostasis is disrupted, the phenotypic “angiogenic switch” becomes active and initiates angiogenesis [4]. Hypoxia is one of the major factors driving tumor angiogenesis, leading to increased expression of VEGF and other angiogenesis-stimulating factors in hypoxic cells [5]. Meanwhile, matrix remodeling enzymes, particularly matrix metalloproteinases, mediate multiple changes in the tumor tissue microenvironment by degrading the extracellular matrix [6]. Once hypoxia induces upregulation of vascular endothelial growth factor, angiogenesis begins with additional activation of hypoxia-inducible factor signaling to provide oxygen supply, which stimulates endothelial cells from the pre-existing vascular system to germinate and migrate into hypoxic tissues, guided by a gradient of vascular endothelial growth factor [7]. Subsequently, endothelial cells differentiate into several cell types, including tip cells, stem cells, and tubular cells. Tip cells expressing δ-like 4 (DLL4) are non-proliferating cells located at the top of the neointima and direct the direction of the neointima in response to vascular endothelial growth factor signals [8]. Notch-1-expressing stem cells are highly proliferative and are able to lengthen the germinating duct by proliferation when they receive DLL4/Notch signaling [9]. Tube cells do not proliferate, which determines the final appearance of the vessels [3]. During additional vessel formation, endothelial progenitor cells are involved in the construction of the inner layer of the new vessel, pericytes such as specialized muscle cells stabilize the vessel lumen by providing structural support and forming an outer layer around the endothelial progenitor cells,, endothelial cells interconnect to form a continuous endothelium characterized by complex, tight junctions and produce rings that allow blood to circulate through adhesion molecules, followed by the construction of the basement membrane. Finally, the vasculature is mature and capable of transporting oxygen and nutrients to meet the needs of hypoxic tumor tissue [10], bridging the gap between tumor tissue growth and metastasis.

2. Chinese Medicine's Understanding of Tumor Angiogenesis

Chinese medicine is one of the most important means to prevent and treat tumors in China, and it has become a consensus among many scholars that “cancer toxin” is the specific pathogenic factor of tumors, and it is also the antecedent of tumor angiogenesis [11]. The theory of tumor-causing mechanism of “cancer toxin” was put forward by Professor Zhou Zhongying, a master of national medicine. He believed that cancer toxin is one of the poisonous evils, which is a specific pathogenic evil leading to tumor development caused by various internal and external factors acting on the organism, leading to dysfunction of internal organs or induced by various internal and external factors on the basis of dysfunction of internal organs [12]. [12]. Correspondingly, a single tumor cell is not enough to form a tumor, and any tumor has two parts: tumor parenchyma and tumor mesenchyme; tumor cells are the components of tumor parenchyma, and tumor mesenchyme refers to connective tissues containing blood vessels and lymphatic vessels, etc.,

and the complex interactions between them lead to the occurrence of tumors. Thus, it can be seen that the pathogenesis of cancer toxicity in Chinese medicine is highly consistent with the understanding of tumor pathogenesis in western medicine.

3. Effects of Traditional Chinese Medicines on Tumor Angiogenesis

3.1 Studies on the Active Ingredients of Single-flavored Herbs

3.1.1 Turmeric

Curcumin (curcumin) is a phenolic pigment extracted from turmeric, a plant polyphenol with various pharmacological activities. A study [13] applied flow cytometry to detect the effect of curcumin on the apoptosis of HUVECs at a concentration of 5-160 μmol/L, and the results showed that: 24h after the action of curcumin, the apoptosis rate of human umbilical vein endothelial cells (Human umbilical vein endothelial cells, HUVECs) was 5.5%-29.8%, compared with the control group of 2. 1% apoptosis rate. Gururaj et al [14] found that curcumin reduced the number of HUVECs in in vitro experiments, not because of curcumin toxicity to these cells, but induced apoptosis. At present, both in vitro and in vivo experimental studies have shown that the antiangiogenic effect of curcumin is closely related to angiogenic factors.

3.1.2 Berberine

Berberine, also known as berberine, accounts for about 40% of the total alkaloids of Berberis, which belongs to the quaternary isoquinoline alkaloids, and is the main alkaloid of the traditional Chinese medicine Berberis vulgaris, with a content of up to 5% to 8%, which is its main active ingredient [15]. Modern pharmacology has proved that berberine has a wide range of pharmacological effects, in which berberine as an antitumor drug has been documented with much biopharmacological and clinical evidence. Studies [16] have shown that berberine is able to inhibit the proliferation of tumor cells by inducing programmed cell death, inhibiting the synthesis of genetic information, blocking the cell cycle, and other mechanisms, and it has potential applications in tumor prevention and treatment.

3.1.3 Hirudin, Spotted Arachnid

Modern pharmacological studies have shown that the medicinal components of leeches mainly include hirudin, amino acids, phospholipid compounds, glycolipid compounds, sterols and trace elements, etc., of which hirudin is the most important active ingredient [17], and the water frog, zebra auriculae can reduce the microvessel density of sarcoma tissues and inhibit the proliferation of vascular endothelial cells The water frog, zebra auriculae have obvious inhibition of angiogenesis, and play the role of expanding angiogenic The role of angiogenesis was significantly inhibited by water frog and spotted arowana. Therefore, one of the mechanisms of the anti-tumor effects of Fritillaria aphanizomenon and Zebu aphanizomenon may be realized through the inhibition of angiogenesis. Its inhibition of angiogenesis may be achieved by reducing the microvascular density of tumor tissues and inhibiting the proliferation of vascular endothelial cells. Tumor neovascularization is not only a nutrient source for tumor proliferation, but also provides conditions for tumor cells to enter the circulatory system and complete metastasis during the invasion process to surrounding tissues.

3.1.4 Bufalin

Bufalin is an anticancer active ingredient extracted from toadflax. Liu Junshan [18] and others found that Bufalin had significant ex vivo and in vivo inhibition of angiogenesis, and hypothesized that its inhibitory effect might be related to the induction of vascular endothelial cell cycle blockade and apoptosis. Subsequently, a study [19] further indicated that saxatoxin could inhibit vascular endothelial growth factor-mediated angiogenesis by inhibiting the VEGFR-2 signaling pathway. Lee et al [20] observed the effect of added Bufalin on angiogenesis by modeling the capillary-like network structure generated by primary cultured bovine aortic endothelial cells in collagen type I three-dimensional medium. The results showed that capillary angiogenesis could be significantly inhibited by 5 nmol-L-1Bufalin. Flow cytometry (FCM) analysis showed that vascular endothelial cells were blocked in G/M phase and proliferation was inhibited. Therefore, the anti-tumor effect of Bufalin is closely related to its inhibition of tumor angiogenesis.

3.1.5 Saffron

Saffron, which has the effect of activating blood circulation and removing blood stasis, contains the active ingredient hydroxy saffron yellowness A. Hydroxy saffron yellowness A is likely to be an effective inhibitor of angiogenesis. Xi Shengyan et al. [21] found that hydroxy saffron yellowness A (HSYA) could inhibit endothelial growth factor (VEGF) protein expression, attenuate kinase-containing insertion zone receptor (KDR) protein phosphorylation and gene expression, and thus inhibit endothelial endothelial growth factor (VEGF) protein expression, and attenuate KDR protein phosphorylation and gene expression in transplanted tumor tissues. growth factor (VEGF) protein expression and attenuates kinase-containing insertion region receptor (KDR) protein phosphorylation and gene expression in transplanted tumor tissues, thereby inhibiting endothelial cell activation to impede tumor neovascularization. In the in vivo experiments of Lewis lung cancer transplantation tumor model in C57BL/6 mice and in vitro experiments of Lewis lung cancer cells, Xie Junping et al [22] observed that the appropriate dose range of HSYA not only reduced the volume and weight of the transplanted tumor, but also reduced the expression of VEGF in the transplanted tumor tissues and Lewis lung cancer cells, which indicated that the growth inhibition of HSYA on tumors was related to the down-regulation of VEGF and other angiogenic factors, thereby inhibiting the tumor endovascularization. angiogenic factors and thus blocking angiogenesis in tumors. On H22 hepatocellular carcinoma cells, YANG [23] et al. similarly found that HSYA significantly inhibited the expression of angiogenesis markers such as CD105, VEGF-A, and bFGF protein. The findings also suggest that HSYA may inhibit tumor angiogenesis by inhibiting the phosphorylation of signaling molecules (c-raf, ERK1/2) on the ERK/MAPK pathway, activation of nuclear translocation of NF-κB, and down-regulation of related

downstream transcription factors, such as the expression of CyclinD1, c-Myc etc., thus inhibiting tumor angiogenesis and exerting anti-tumor effects. Inhibitory effect on vascular endothelial cells The proliferation and apoptosis of human umbilical vein endothelial cells (HUVEC) were detected by MTT and flow cytometry, etc. Zhang Qian et al [24] found that HSYA inhibited the abnormal proliferation of human umbilical vein endothelial cells stimulated by supernatant of colorectal cancer LS180 cells. Wang Ji et al [25] showed that HSYA effectively promoted apoptosis of human umbilical vein cells under the abnormal proliferation of human umbilical vein endothelial cells induced by human lung cancer HepG2 cell culture supernatant, and the mechanism was related to the expression of apoptosis regulator TNF-α induced by HSYA. Inhibition of neovascularization Chicken embryo allantoic membrane microangiogenesis model needs to be used for the screening of drugs to inhibit tumor angiogenesis. It was found that saffron yellow pigment could make the large, medium and small blood vessels of chicken embryo allantoic membrane thinner and fewer, and inhibit neoangiogenesis [26], in which HSYA was the effective component to produce its effect. XI et al [21] also showed that HSYA could significantly reduce the density of tumor microvessels, thus inhibiting tumor growth. Studies using the chicken embryo allantoic membrane assay and the establishment of a nude mouse model of human carcinoma graft tumors found that HSYA may be a promising inhibitor of tumor angiogenesis, the mechanism of which is through the inhibition of mRNA expression of the vascular endothelial growth factor, VEGF, basic fibroblast growth factor, bFGF, and their receptors [27]. A nude mouse model test study found that one of the mechanisms of tumor growth inhibition by a certain concentration of HSYA may be related to the inhibition of the expression of bFGF and matrix metalloproteinase-9 (MMP-9), which reduces tumor tissue vascular degradation of the basement membrane, thereby inhibiting tumor vascular growth [27]. Proliferation of vascular endothelial cells is an important part of angiogenesis and development. HSYA can inhibit tumor by inhibiting the proliferation and metastasis of vascular smooth muscle [28].

4. Problems and Prospects

Tumor angiogenesis is closely related to the generation of most tumors up to the prognosis. Inhibition of tumor angiogenesis has now become a hot anti-tumor research with much attention. Anti-tumor angiogenesis is not only to inhibit the growth and metastasis of tumor cells, but also to indirectly destroy the existing tumor cells. The method of Chinese medicine anti-angiogenesis for tumor treatment opens up new ideas and new ways for Chinese medicine research on anti-tumor. The shortcoming is that, from the perspective of TCM theory, there are fewer relevant discussions, and the mechanism of action of many drugs in inhibiting tumor angiogenesis has not yet been clarified, and it is not yet possible to accurately grasp the mechanism and the advantages and potentials of inhibiting tumor angiogenesis. At the same time, there is a lack of research on the combined application with other anti-tumor methods, and there is still singularity in treatment. The influence of TCM on inhibiting tumor angiogenesis can only be brought into fuller play by using TCM theories to guide the use of medication through TCM evidence-based treatment.

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