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The Research Progress of Traditional Chinese Medicine in the Treatment of Liver Cancer Based on the Microenvironment

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Abstract: *Liver cancer is a common malignancy of the digestive system. The microenvironment of liver cancer is an important factor affecting tumor recurrence and metastasis. Traditional Chinese medicine believes that the etiology of liver cancer is complex, the types of symptoms are variable, and there are many treatments. Traditional Chinese medicine compounds, single drugs, etc. can affect the microenvironment of liver cancer by regulating signaling pathways and cell proliferation. This article aims to review the impact of traditional Chinese medicine on the microenvironment of liver cancer.*

Keywords: *traditional Chinese medicine; hepatocarcinoma; tumor microenvironment*

1. Introduction

The onset of liver cancer is relatively hidden, lacks specific markers in the early stage, has rapid progression, easy metastasis, low radical resection rate and high recurrence rate [1]. Therefore, it is urgent to find a drug with high safety, small side effects and good efficacy for the treatment of liver cancer. Studies in recent years have shown that the onset and progression of liver cancer depends on its tumor micro-environment TME [2]. The biological characteristics of the microenvironment such as gene expression, immune type, and neovascularization of liver cancer and pericancerous tissues are closely related to the occurrence, development and clinical efficacy of liver cancer. Liver cancer belongs to the categories of "fistula", "accumulation", "rib pain" and "jaundice" in traditional Chinese medicine, and successive generations of scholars believe that the invasion of tumors is "evil qi", and the patient's own confrontation is "right qi". In the treatment of tumors and the regulation of tumor microenvironment, traditional Chinese medicine plays a significant role in regulating the microenvironment of liver cancer disorder, inhibiting the growth and metastasis of tumor "evil qi", etc., and provides ideas for the prevention and treatment of liver cancer in clinical Chinese medicine [3].

2. Modern medicine's understanding of the microenvironment of liver cancer

Studies have found that cancer growth and metastasis occur as a result of destruction between cancer cells and TME. The liver cancer microenvironment mainly includes stromal cells and non-stromal cells. Stromal cell components include: tumor-associated immune cells, hepatic stellate cells, tumor-associated fibroblasts, tumor-associated endothelial cells, etc. Non-cellular components include: extracellular matrix, cytokines, etc. The microenvironment of liver cancer is an important material basis for tumor survival and development, which provides conditions for tumor occurrence, development, invasion and metastasis [4].

2.1 Immune cells

HCC immune cells are considered key players in the microenvironment [5]. Tumor-infiltrating lymphocytes (TILs) and peripheral blood lymphocytes (PBLs) are the two main components of the immune microenvironment associated with liver cancer [6]. They mainly include cytotoxic T cells (CTL), regulatory T cells (Treg), natural killer (NK) cells, macrophages (TAM), etc. [7]. Among them, the balance of CTL and Treg is an important factor in the liver cancer microenvironment. If there is an

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imbalance in the microenvironment such as metabolism, hypoxia, and lactic acid accumulation in the liver cancer microenvironment, it will lead to the dysfunction of CTL and Treg, which in turn will affect the recurrence and metastasis of liver cancer. Studies have found that nerve cells-epidermal growth factor receptors (EGFRs) in treg stimulate Treg differentiation and inhibit CTL activity in patient and xenograft mouse models, thereby promoting the growth of liver cancer [8]. Studies have found that the T-cell subsets CD4, CD8, and CD25 are considered to be the main causes of inhibition of T-cell immunity and therapy [9]. NK cells are cytotoxic cells with anti-tumor functions. Intrahepatic NK cells play a central role in the innate immune response to liver pathogens and tumors, and they can directly recognize and kill cancer cells, which is closely related to the poor prognosis of liver cancer [10-11]. Studies have shown that the expression of TREM-1, a surface receptor for pro-inflammatory bone marrow cells in Kuno cells (KCs), is a key factor in the development and progression of liver cancer. Cancer cell stimulation can directly increase the expression of TREM-1 on KCs, which in turn promotes the activation of KCs and the progression of liver cancer [12]. TAMs have been found to be induced into two different polarization phenotypes: M1 and M2 [13]. There is a balance between M1 and M2 KC in a healthy liver with opposite functions. In liver cancer, KCs undergo a phenotypic transition from M1 to M2, promote cancer growth by inhibiting the adaptive immune system, and promote the recruitment of CD8 T cells and prevent liver cancer development by driving the M1 polarization of KCs. In addition, M2 macrophages also play a dominant role in tumor-associated macrophages (TAMs), forming a tumor immunosuppressive microenvironment and promoting tumor growth, invasion, and metastasis [14].

2.2 Fibroblasts

In TME, tumor-associated fibroblasts (CAFs) have been shown to play multiple roles in tumor development. They can alter the microenvironment by secreting inflammatory ligands, growth factors, and extracellular matrix proteins, among others, to promote cancer cell proliferation, therapeutic resistance, and immune rejection [15]. CAFs can activate and secrete a variety of cytokines such as CCL2, CCL5, CCL7 and CXCL16 and matrix metalloproteinase (MMP) to promote liver cancer metastasis through relevant signaling pathways in hepatoma cells [16]. Transforming growth factor-β β (TGF-β) is highly expressed in TGF-β in cancer, which can change the phenotype of normal CAFs [17-18]. TGF-β signaling inhibits IL-1 receptor 1 (IL-1R1) expression, and IL-1-induced signaling cascade that activates JAK/STAT promotes the production of inflammatory CAFs [19]. In turn, it affects the further development of liver cancer.

2.3 Tumor-associated endothelial cells

Tumor-associated endothelial cells (TECs) are the key to tumor neovascularization and tumor progression, TECs are mainly derived from vascular endothelial differentiation and proliferation, and angiogenic factors stimulate the differentiation of vascular endothelial growth factor (VEGF) into endothelial cells (ECs), and obtain new cell phenotypes in specific tumor microenvironments and transform into endothelial cells [20]. In hepatoma cells, activation of oncogenes and mutations in tumor suppressor genes lead to upregulation of VEGF. VEGF activates ECs through paracrine signaling, stimulates cell migration and cell proliferation, thereby inducing angiogenesis and enhancing vascular permeability [21]. While angiogenesis is essential for the formation, development and metastasis of liver cancer, eEF2K (eExtension factor 2 kinase) stimulates PI3K/Akt and STAT3 signaling through SP1/KLF5-mediated VEGF expression, promoting tumor vascular generation and tumor progression [22]. TECs have the effect of promoting tumor angiogenesis and regulating cytotoxic T cells in the tumor microenvironment, and studies have found that TECs may promote the escape of liver cancer cells from immune surveillance through the glycoprotein non-metastatic melanoma protein GPNMB [23]. Thus, inhibition of tumor vascularization is a strategy to control tumor progression and proliferation and reduce recurrence [24].

2.4 Hepatic stellate cell microenvironment

Hepatic stellate cells (HSCs) are resident perisinus cells in the liver, and activated HSCs can promote apoptosis of effector T cells and NK cells, causing damage to tumor immunity [25]. Bone morphogenetic protein (BMP), another member of the TGF-β superfamily, can significantly promote the invasion and stemness of hepatoma cells by increasing differentiation inhibitor 1 (ID1) expression and inducing an imbalance of the TGF-β1/BMP-7 pathway in hepatoma cells [26]. In HSCs, TGF-β activates Smad2/3, stimulates the synthesis of ECM proteins such as collagen types I and II and inhibits

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their degradation. TGF-β promotes the further development of HSC-activated myofibroblasts and liver fibrosis through various mechanisms. Therefore, inhibition of TGF-β synthesis or overexpression contributes to the development of liver cancer [27].

2.5 Extracellular stromal cells

The extracellular matrix (ECM) is an important component of the noncellular component of liver cancer, and it is a complex combination of core proteins (e.g., collagen, fibronectin) and glycoproteins (e.g., heparan sulfate proteoglycans, chondroitin sulfate proteoglycans) and other related molecules (e.g., growth factors, cell adhesion molecules, and cytokines) [28]. The complex molecular biochemical properties in ECM regulate apoptosis, differentiation, proliferation, etc. of cells through continuous tissue construction and interaction to maintain homeostasis in the microenvironment. ECM homeostasis disorder is considered to be a major factor in the development of liver cancer. For example, excessive deposition of ECM can lead to the further development of liver fibrosis to liver cancer. Among them, collagen and metalloproteinases play an important role in the extracellular matrix liver cancer microenvironment.

3. Traditional medicine's understanding of the liver cancer microenvironment

For liver cancer in the "Yellow Emperor's Internal Canon", it is mostly believed that it is a balance imbalance of the qi, blood, jin and fluid microenvironment in the body, and the formation of tangible things such as weakness, blood stasis, and phlegm. For the occurrence of liver cancer, successive generations of scholars have discussed, such as "Anger and depression, accumulation day and night, temper obstruction, liver qi accumulation, then into a hidden nucleus", indicating that emotional depression is not comfortable, accumulation over time, will make the liver lose in drainage and lead to liver cancer. Just as the "Outline of Jin Kuang" "See the disease of the liver, know the liver and pass on the spleen", the qi of the liver wood is too much or not enough, which will affect the imbalance of the microenvironment between the liver and spleen, resulting in the same disease of the liver and spleen [29]. Traditional Chinese medicine believes that "positive qi exists inside, evil cannot be done", "where evil is made, its qi must be empty", and the development of liver cancer is due to "deficiency of healthy qi", "excessive evil qi", and "good cannot defeat evil", resulting in pathological states such as qi deficiency, blood stasis, phlegm coagulation, etc. The environment of qi stagnation, blood stasis, phlegm coagulation and other environments formed by the "evil qi" of liver cancer is consistent with the TME of modern medicine. For example, the microenvironment states such as VEGF, cancer cell proliferation, hypoxia, and hypercoagulability in the microenvironment of liver cancer are similar to those of traditional Chinese medicine, such as qi stagnation, blood stasis, and sputum turbidity. Based on these understandings, the liver cancer microenvironment can also be dialectical in traditional Chinese medicine, such as KCs pro-inflammatory bone marrow cell surface receptors TREM-1, EGFR, VEGF, M2 macrophages, TGF-β and other "evil qi" that promote the occurrence and development of liver cancer, and the "evil qi" that promotes the occurrence and development of liver cancer is similar to the "phlegm", "blood stasis" and "qi stagnation" mentioned by traditional Chinese medicine. And IL-2 (interleukin-2) and IgG (immunoglobulin G), NK cells, etc. inhibit tumor development and resist the invasion and development of diseases are considered "healthy qi". Therefore, modern research on liver cancer in Western medicine is combined with dialectical treatment in traditional Chinese medicine for systematic treatment.

4. Research on the regulation of liver cancer microenvironment by traditional Chinese medicine

4.1 Attack the drug

For example, in "Jin Kui Phlegm Drinking Cough Disease", "the patient's pulse is dormant, his people want self-interest, profit is fast, although it is profitable, the heart continues to be full, this is to stay and drink and want to go, and Gansui Banxia soup is the master", expounding that water-seeking expectorant, and medium dehumidification Fang Gansui Banxia soup has the dual role of inhibiting cancerous ascites, inhibiting the STAT3/AKT/ERK signaling pathway in MDSCs, and playing a dual role in inhibiting the development of liver cancer and regulating immunity [30]. It has also been shown that gansui root extract has a significant inhibitory effect on the growth of BEL-7402 cells in human epithelioid liver cancer [31]. Euphorbia factor L2 inhibits TGF-β-induced hepatocyte growth and migration of hepatocellular carcinoma via AKT/STAT3 [32]. Rhubarb extract can also inhibit the activity

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of hepatoma cells by activating the p38MAPK signaling pathway [33]. The active ingredient of Morning Glory has also been shown to be able to intervene in various signaling pathways such as toll-like receptors to achieve inhibitory effects on the growth of liver cancer [34]. Therefore, all the fierce or slowing down medicine can achieve "covering the poisonous medicine, can gush up and down, and can seize the general trend of disease."

4.2 Qi and spleen medicine

"See the disease of the liver, know the liver to the spleen, and first realize the spleen", it can be seen that the method of strengthening the spleen should be implemented into the treatment of liver cancer. For example, Yiqi solid surface jade screen dispersion weakens the activation of the TSLP-STAT3 signaling pathway by inhibiting the immunocorrelation factor TSLP [35]. Peiyuan Anti-Cancer Decoction inhibits the proliferation of H22 cell liver cancer and induces apoptosis in vitro by regulating CAFs in the tumor microenvironment [36]. Spleen Detoxification Decoction can effectively regulate the serum levels of MMP-2, MMP-9, VEGF and IL-2 in patients, improve their quality of life and the occurrence of adverse reactions [37]. Thus inhibiting the formation of liver microvessels and exerting anti-liver cancer effects. The traditional Chinese medicine licorice and its main components glycyrrhizic acid and 18β-glycyrrhetinic acid (18b-GA) activate FXR (bile acid receptor) by Sirt1 for liver protection, and can also reduce the adverse reactions of anticancer drugs used to treat liver cancer [38]. The traditional Chinese medicine compound Songyou Drink (SYY astragalus, danshen, goji berry, turtle nail, hawthorn) can inhibit tumor growth through Treg immunomodulation [39]. And it can inhibit the development of liver cancer by affecting the activation of hepatic stellate cells. Remodeling the microenvironment of liver cancer to achieve the purpose of treating liver cancer.

4.3 Blood circulation and stasis removal drugs

For example, in the treatment of liver cancer in situ in mice treated by rhubarb stinging pills, it was found that after treatment, the secretion of Th1 cells and IFN-γ in peripheral blood and spleen increased, which in turn activated CD8 T cells, inhibited the production of Treg cells, and enhanced the mechanism of anti-tumor immunity, thereby inhibiting the growth of liver cancer [40]. The traditional Chinese medicine frankincense and myrrh are targeted for the treatment of tumor blood vessels, and exert anti-liver cancer effects through the EGFR-activated PI3K/Akt and MAPK signaling pathways [41]. Peach kernels can also improve intrahepatic microcirculation and inhibit the development of liver fibrosis to liver cancer. Resveratrol treatment inhibits CAF-CM-induced expression of MMP-2 and MMP-9, thereby inhibiting tumor development [42]. Traditional Chinese medicine wormwood extract can reduce the content of collagen and TIMP-1, and reduce the excessive deposition of collagen substances in the liver. It also had a positive effect on the activation of extracellular matrix and hepatic stellate cells in rats with liver fibrosis. In the treatment of blood circulation and stasis, dissipation and swelling, the tumor microenvironment can be changed by "driving away evil spirits". For example, through drug treatment to change the activation of liver stellate cells, inhibit immune cells Treg, MDSCs, etc., inhibit the production of tumor neovascularization and the change of cell signaling pathway to improve the liver cancer microenvironment, so as to achieve the role of treating tumors.

5. Conclusions

The occurrence of liver cancer is the result of a combination of a variety of complex factors, its pathogenesis is complex, positive and false, false and real, virtual and real are mixed, so in the treatment, we should pay attention to attacking evil cannot hurt the right, make up for the deficiency cannot leave the evil Chinese medicine clinical application should be used flexibly, or attack and supplement, or eliminate and use together, in order to achieve the method of dialectical treatment to change the state of TME, reshape TME, and prevent the recurrence and metastasis of liver cancer.

Traditional Chinese medicine has shown great advantages in the treatment of liver cancer, and the use of traditional Chinese medicine compounds, single drugs, active ingredients, etc. on the liver cancer microenvironment multi-target and synergistic intervention effect has been recognized, including the upregulation of immunostimulating factors and the downregulation of immunosuppressive factors, inhibition of tumor neovascularization, regulation of signaling pathways, etc,so that the liver cancer microenvironment changes, reduce side reactions, so as to achieve the purpose of treating liver cancer, and provide certain ideas and insights for the clinical treatment of liver cancer by traditional Chinese medicine. However, the pathogenesis of liver cancer is more complex, and its research lacks systematic,

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multi-target, multi-sample clinical research, which has certain limitations and feasibility. Moreover, the chemical composition of TCMs is complex, and it is difficult to explain which drugs and which components have an impact on the microenvironment of liver cancer when playing a role in clinical practice, so there is more room for innovation in the future research on the regulation of the microenvironment of TCMs in the treatment of liver cancer, and provide more ideas for clinical treatment of liver cancer.

References

[1] Fu J, Wang H. Precision diagnosis and treatment of liver cancer in China[J]. Cancer Letters, 2018, 412: 283-288.

[2] Zhang Q, Lou Y, Bai XL, Liang TB. Immunometabolism: A novel perspective of liver cancer microenvironment and its influence on tumor progression. World J Gastroenterol. 2018; 24(31): 3500-3512.

[3] Yang Lihui, Hu Kaiwen, Wang Jingxiao. Exploring the mechanism of blood circulation and phlegm detoxification in liver cancer based on the immune microenvironment of liver cancer[J]. Chinese Journal of Experimental Medical Formulae, 2022, 28(14):172-178.)

[4] Li J, Lin HS. Integrative medicine: a characteristic China model for cancer treatment. Chin J Integr Med. 2011; 17(4):243-245.

[5] Hao Y, Li D, Xu Y, et al. Investigation of lipid metabolism dysregulation and the effects on immune microenvironments in pan-cancer using multiple omics data[J]. BMC Bioinformatics, 2019, 20(S7).

[6] Gao Q, Qiu S J, Fan J, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection[J]. J Clin Oncol, 2007, 25(18):2586-2593.

[7] Jiang R, Tang J, Chen Y, et al. The long noncoding RNA lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion[J]. Nature Communications, 2017, 8(1).

[8] Liu X, Li M, Wang X, et al. Effects of adjuvant traditional Chinese medicine therapy on long-term survival in patients with hepatocellular carcinoma. Phytomedicine. 2019; 62:152930.

[9] Hao Y, Li D, Xu Y, et al. Investigation of lipid metabolism dysregulation and the effects on immune microenvironments in pan-cancer using multiple omics data[J]. BMC Bioinformatics, 2019, 20(S7).

[10] Gao Q, Qiu S J, Fan J, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection [J]. J Clin Oncol, 2007, 25(18): 2586-2593.

[11] Wu J, Li J, Salcedo R, et al. The Proinflammatory Myeloid Cell Receptor TREM-1 Controls Kupffer Cell Activation and Development of Hepatocellular Carcinoma [J]. Cancer Research, 2012, 72(16): 3977-3986.

[12] Tian Z, Hou X, Liu W, et al. Macrophages and hepatocellular carcinoma. Cell Biosci 2019; 9.

[13] Chen Z, Yu M, Yan J, et al. PNOC Expressed by B Cells in Cholangiocarcinoma Was Survival Related and LAIR2 Could Be a T Cell Exhaustion Biomarker in Tumor Microenvironment: Characterization of Immune Microenvironment Combining Single-Cell and Bulk Sequencing Technology [J]. Frontiers in Immunology, 2021, 12.

[14] Biffi G, Tuveson DA. Diversity and Biology of Cancer-Associated Fibroblasts. Physiol Rev. 2021; 101(1): 147-176.

[15] Liu J, Chen S, Wang W, et al. Cancer-associated fibroblasts promote hepatocellular carcinoma metastasis through chemokine-activated hedgehog and TGF-β pathways [J]. Cancer Letters, 2016, 379(1): 49-59.

[16] Gurzu S, Kobori L, Fodor D, Jung I. Epithelial Mesenchymal and Endothelial Mesenchymal Transitions in Hepatocellular Carcinoma: A Review. Biomed Res Int. 2019; 2019:2962580. Published 2019 Sep 29.

[17] Yoshimatsu Y, Wakabayashi I, Kimuro S, et al. TNF-α enhances TGF-β-induced endothelial-to-mesenchymal transition via TGF-β signal augmentation. Cancer Sci. 2020; 111(7): 2385-2399.

[18] Biffi G, Oni TE, Spielman B, et al. IL1-Induced JAK/STAT Signaling Is Antagonized by TGFβ to Shape CAF Heterogeneity in Pancreatic Ductal Adenocarcinoma. Cancer Discov. 2019; 9(2):282-301.

[19] De Sanctis F, Ugel S, Facciponte J, Facciabene A. The dark side of tumor-associated endothelial cells. Semin Immunol. 2018; 35:35-47.

[20] Hida K, Maishi N, Annan DA, Hida Y. Contribution of Tumor Endothelial Cells in Cancer Progression. Int J Mol Sci. 2018 Apr 24; 19(5):1272.

[21] Zhou Y, Li Y, Xu S, et al. Eukaryotic elongation factor 2 kinase promotes angiogenesis in hepatocellular carcinoma via PI3K/Akt and STAT3. Int J Cancer. 2020; 146(5):1383-1395.

[22] Sakano Y, Noda T, Kobayashi S, et al. Tumor endothelial cell-induced CD8+ T-cell exhaustion

ISSN 2706-6819 Vol.5, Issue 7: 57-62, DOI: 10.25236/IJFM.2023.050709

via GPNMB in hepatocellular carcinoma. Cancer Sci. 2022; 113(5):1625-1638.
[23] Singh M, Lima A, Molina R, et al. Assessing therapeutic responses in Kras mutant cancers using genetically engineered mouse models. Nat Biotechnol. 2010; 28(6):585-593.
[24] Hsieh CC, Hung CH, Chiang M, Tsai YC, He JT. Hepatic Stellate Cells Enhance Liver Cancer Progression by Inducing Myeloid-Derived Suppressor Cells through Interleukin-6 Signaling. Int J Mol Sci. 2019; 20(20):5079. Published 2019 Oct 13.
[25] Ning J, Ye Y, Bu D, et al. Imbalance of TGF-β1/BMP-7 pathways induced by M2-polarized macrophages promotes hepatocellular carcinoma aggressiveness. Mol Ther. 2021; 29(6):2067-2087.
[26] Dhar D, Baglieri J, Kisseleva T, Brenner DA. Mechanisms of liver fibrosis and its role in liver cancer. Exp Biol Med (Maywood). 2020; 245(2):96-108.
[27] Mouw JK, Ou G, Weaver VM. Extracellular matrix assembly: a multiscale deconstruction. Nat Rev Mol Cell Biol. 2014; 15(12):771-785.
[28] Yu Simiao, Li Ping, Li Yuan, et al. The prevention and treatment of liver cirrhosis is discussed from "seeing liver disease, knowing the liver to the spleen, and practicing the spleen first"[J]. Journal of Beijing University of Chinese Medicine, 2022, 45(01):29-33.
[29] Li J, Li L, Liu R, Lin HS. Establishing Chinese medicine characteristic tumor response evaluation system is the key to promote internationalization of Chinese medicine oncology. Chin J Integr Med. 2012; 18(10):730-736.
[30] Feng Xiaoyi. Study on anti-liver cancer efficacy and mechanism of action of Gansui Banxia Tang [D]. Kunming University of Science and Technology, 2022.
[31] Chen Liang. In vitro experimental study of Gansui root extract on human epithelioid liver carcinoma BEL-7402[J]. Northwestern Botanical Journal, 2008(09):1889-1892.
[32] Fan L, Zhu H, Tao W, et al. Euphorbia factor L2 inhibits TGF-β-induced cell growth and migration of hepatocellular carcinoma through AKT/STAT3. Phytomedicine. 2019; 62:152931.
[33] Tan Zhangbin, Xu Youcai, Liu Qi. Rhubarb extract activates p38MAPK to promote apoptosis in HepG2 hepatoma cells [J]. Modern Digestive and Interventional Diagnosis and Treatment, 2022, 27(08): 970-973+978.
[34] Wang Mengqi, Lin Haihong, Du Gangjun. Antitumor effect and mechanism of morning glory decoction on subcutaneous transplanted tumors of H22 liver cancer in mice [J]. Journal of Henan University (Medical Sciences), 2019, 38(02):77-84.
[35] Yuan Q, Yao F, Zhou L, et al. Yu Ping Feng San Exert Anti-Angiogenesis Effects through the Inhibition of TSLP-STAT3 Signaling Pathways in Hepatocellular Carcinoma. Evid Based Complement Alternat Med. 2019; 2019: 1947156. Published 2019 Oct 23.
[36] Si Hayong, Zhang Jie, Ma Yiming, et al. Experimental study on inhibition of proliferation and apoptosis of H22 hepatoma cells by regulating cancer-associated fibroblasts [J]. Journal of Integrative Medicine and Liver Diseases, 2022, 32(10):907-911.
[37] Zhou Jueyi, Feng Jihong, Zhao Liping, et al. Clinical study of spleen detoxification decoction combined with hepatic artery chemoembolization in the treatment of primary liver cancer[J]. New Chinese Medicine, 2023, 55(02):115-118.
[38] Wu SY, Cui SC, Wang L, et al. 18β-Glycyrrhetinic acid protects against alpha-naphthylisothiocyanate-induced cholestasis through activation of the Sirt1/FXR signaling pathway. Acta Pharmacol Sin. 2018; 39(12):1865-1873.
[39] Zhang QB, Meng XT, Jia QA, et al. Herbal Compound Songyou Yin and Moderate Swimming Suppress Growth and Metastasis of Liver Cancer by Enhancing Immune Function. Integr Cancer Ther. 2016; 15(3):368-375.
[40] Chen Tt, Du Sl, Wang Sj, Wu L, Yin L. Dahuang Zhechong pills inhibit liver cancer growth in a mouse model by reversing Treg/Th1 balance. Chin J Nat Med. 2022; 20(2):102-110.
[41] Zheng P, Huang Z, Tong DC, et al. Frankincense myrrh attenuates hepatocellular carcinoma by regulating tumor blood vessel development through multiple epidermal growth factor receptor-mediated signaling pathways. World J Gastrointest Oncol. 2022; 14(2):450-477.
[42] Suh J, Kim DH, Surh YJ. Resveratrol suppresses migration, invasion and stemness of human breast cancer cells by interfering with tumor-stromal cross-talk. Arch Biochem Biophys. 2018; 643: 62-71.