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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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LETTER TO THE EDITOR

Use of traditional Chinese medicine bezoars and bezoar-containing preparations in hepatocarcinoma

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Abstract

This manuscript used network pharmacology and experimental verification to analyze the anti-hepatocarcinoma mechanism of action of bezoars in traditional Chinese medicine (TCM), discovering that it can affect the immune cells within the tumor microenvironment and related pathways to produce inhibitory effects in liver cancer. In TCM, bezoars have a unique therapeutic advantage in the prevention and treatment of tumors. They play an anti-tumorigenic role by regulating the immune microenvironment through multi-component, multi-target and multi-pathway mechanisms. With the application of nanotechnology, bezoars and their compound preparations have been developed into anti-cancer drugs with unique therapeutic advantages, providing novel treatment options for tumor patients.

Key Words: Bezoar; Traditional Chinese medicine; Liver cancer; Immune microenvironment; Network pharmacology

Core Tip: Liver cancer seriously affects the physical and mental health of human beings. traditional Chinese medicine (TCM) is an important part of a comprehensive treatment plan, due to its multi-component and multi-target therapeutic characteristics and its known clinical efficacy. However, its mechanism of action is unclear. As science and technology progress and in-depth research leads to the creation of new drugs, many novel treatments for liver cancer have been developed. The research and development of TCM with anti-tumor effects is a hot spot in clinical treatment. Bezoars and bezoar preparations in TCM are known to regulate the immune microenvironment in liver cancer and inhibit the progression of liver cancer through various mechanisms. Targeting these mechanisms through the development of TCM anti-tumor agents, such as nano-bezoars, is the focus of future research.

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TO THE EDITOR

In this article, we discuss the use of bezoars and compound preparations containing bezoars in traditional Chinese medicine (TCM) which have been shown to restore the immune balance of the body by regulating the expression of immune cells and related signaling pathways in the tumor immune microenvironment, thus inhibiting the occurrence and development of tumors. The research and development of bezoars and its compound preparations have broad anti-tumor prospects.

STATUS OF BEZOAR AND BEZOAR CONTAINING PREPARATIONS IN THE TREATMENT OF HEPATOCARCINOMA

According to recent epidemiological surveys, liver cancer is the sixth most common malignant tumor in the world, and also the third most common cause of cancer-related death. It poses great challenges and threats to human physical and mental health. Liver cancer most commonly occurs in Southeast Africa and Asia, however incidence and mortality rates have recently declined in East Asian countries, while incidence and mortality rates have increased in Western countries. Incidence rates of liver cancer are projected to exceed 1 million by 2025[1,2]. China is a region with a high incidence of liver cancer. Liver cancer is the second most common cause of cancer-related death in China, after lung cancer. Compared with low-incidence areas, high incidence areas demonstrate younger age of onset and faster disease progression[3]. Primary liver cancer is mainly divided into hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and mixed hepatocellular carcinoma, of which hepatocellular carcinoma accounts for about 80% of cases[4]. The main causes of liver cancer include hepatitis B infection, long-term exposure to aflatoxin, chronic liver injury, cirrhosis, alcoholic liver poisoning, and chronic bile outflow obstruction[5]. Patients with liver cancer do not have obvious clinical characteristics in the early stage, thus, when the tumor is found they are often already in the middle or late stages. Surgery is the first choice for early stage liver cancer, while chemotherapy or minimally invasive, targeting immunotherapies are the primary therapies for middle and late stage liver cancer. TCM therapy runs through the whole process of liver cancer prevention and treatment. TCM has thousands of years of history in the prevention and treatment of cancer, and has been favored by doctors and patients because of its stable curative effect, safety, and minimal side effects[6]. The use of bezoars in TCM has a significant effect in the treatment of liver cancer, effectively reducing the risks of recurrence and metastasis of liver cancer patients after surgery. Bezoars and their compound preparations have shown broad prospects in the field of hepatocarcinoma treatment.

FEASIBILITY ANALYSIS AND ADVANTAGES OF TCM BEZOARS IN TREATING LIVER CANCER

The use of bezoars in TCM has a long history of use in the treatment of diseases. First seen in the Shennong Bencaojing, a Chinese agricultural manuscript and described as "flat, bitter taste, non-toxic, main convulsive epilepsy, cold and heat", it has the effect of clearing the heart and opening the body, cooling the liver and extinguishing the wind, clearing the heat and detoxifying the liver and the heart[7]. In TCM, bezoars can be divided into natural bezoars, artificial bezoars, cultured bezoars *in vitro* and cultured bezoars. The main components of bezoars are biliverdin, free bilirubin, free bile acid, ursodeoxycholic acid, and taurocholic acid, which have remarkable effects in the prevention and treatment of various diseases[8]. Natural bezoars have the best therapeutic effects, followed by artificial and cultivated bezoars[9]. Studies have found that the application of bezoar can directly or indirectly inhibit tumors, regulate the recovery of the body's immune microenvironment, improve the body's immunity, regulate the function of macrophages, and control the further development of tumors[10]. Recent studies and a large number of experiments have shown that bezoars, alone or

in combination with other TCM, can induce apoptosis of cancer cells and regulate body immunity to inhibit tumor development. The anti-tumorigenic mechanisms of bezoars mainly occur by inhibiting cell growth and migration, inducing apoptosis of cancer cells, reversing drug resistance in cancer cells, inhibiting angiogenesis, enhancing immune function, and regulating tumor-associated signaling pathways[11]. Bezoars and Chinese herbal compounds containing bezoars can not only treat liver cancer, but also have obvious tumor inhibitory effects on other solid tumors such as breast and cervical cancer. Representative Chinese patent medicines including bezoars include Pien Tze Huang[12], Xihuang Pill [13], Kehuang Capsule[14], Niuhuang Tianlong Capsule[15], and Niuhuang Xingxiao Pill[16]. which can inhibit the development of various tumors (Table 1).

Based on the theoretical analysis and clinical trials on the efficacy and reduction of side effects of TCM bezoar for liver cancer, we found that not only bezoar, but also a variety of TCM anti-tumor principles mainly focus on regulating tumor immune activity, modulating the influence of metastasis-related signaling pathway proteins on tumor microenvironment, inhibiting cancer cell growth and blocking cancer cell metastasis. When combined with chemotherapy drugs, these treatments enhance the therapeutic effect and reduce toxic side effects[17].

MACROPHAGES AND THE IMMUNE MICROENVIRONMENT

The human immune system is a dynamic system, which can be divided into two categories: The innate and the adaptive immune system. The tumor immune microenvironment is a dynamic microenvironment composed of cancerous and non-cancerous cells, including a large number of immune cells. It consists of different quantities of T cells, B cells, dendritic cells, tumor-associated macrophages (TAMs), tumor-infiltrating lymphocytes, antigen-presenting cells (APC), tumor-associated fibroblasts, mesenchymal cells, endothelial cells, and extracellular matrix[18].

The immunosuppressive tumor microenvironment mediated by the programmed death ligand 1 (PD-L1)/programmed cell death 1 (PD-1) signaling pathway is the basis of liver cancer survival, and plays an important role in the generation and development of liver cancer, and in evading immune surveillance. PD-L1 expression in tumors is currently being used as a biomarker to guide decision making. PD-1 is an important immunosuppressive molecule, which is usually expressed on the surface of T cells, B cells, natural killer cell (NK) and other immune cells. PD-L1 is expressed on tumor cells, activated T cells, and macrophages in the tumor microenvironment. TAMs also widely express PD-L1, and its expression persists in tumor cells for a long time. The application of monoclonal antibodies to block binding between PD-1 and PD-L1, restoring immune activity in the tumor microenvironment, enhancing the activity of immune T cells, and enhances the anti-tumor immune response. Current studies have found that PD-1 and PD-L1 inhibitors have achieved ideal therapeutic effects in several cancers, including liver cancer, breast cancer, and bowel cancer[19,20].

Macrophages in the liver can differentiate into pro-inflammatory M1 and anti-inflammatory M2 macrophages. The immune factors secreted by the two types of macrophages are different, and their functions are also different. In the liver microenvironment, the proportion of the two types of macrophages maintains a delicate balance, jointly maintaining the stability of the liver internal environment. In the early stage of inflammatory disease, liver macrophages, also known as Kupffer cells, recruit neutrophils and peripheral monocytes to the site of liver injury to promote inflammation and fibrosis. M1 macrophages dominate in this stage. With the progression of disease, macrophages transform into the M2 type, to promote immunosuppression and fibrosis formation, and the inflammation gradually changes from acute to chronic leading to the formation of a tumor immune microenvironment, and promoting the generation and development of liver cancer. TAMs promote liver cancer angiogenesis, invasion and metastasis, enhance liver cancer stem cell characteristics, and inhibit tumor immunity[21].

Most macrophages in liver cancer are M2 macrophages, which plays a pro-tumor role, thus reducing the number of TAM in liver cancer is an effective anti-tumor strategy. Macrophages, located in tissues and organs, are important components of innate immunity and major APC. Macrophages have two sides in tumor immunity. On the one hand, activated macrophages can play an anti-tumor role. On the other hand, different microenvironments can promote the activation of macrophages with different properties and become immunosuppressive macrophages with different molecular characteristics and different functions, thus promoting the occurrence of tumors[22].

TAMs can be highly expressed in a variety of tumor microenvironments, such as liver cancer, stomach cancer, and bowel cancer. As a type of monocyte, macrophages can differentiate into M1 proinflammatory macrophages and M2 anti-inflammatory macrophages. M1-type macrophages can release pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, IL-12, IL-13, tumor necrosis factor-α (TNF-α), interferon gamma (INF-γ), and M2 can release IL-10, transforming growth factor-β (TGF-β) anti-inflammatory or immunosuppressive cytokines. The balance of M1 and M2 plays an important role in the balance of the body's immune system[23]. In the tumor immune microenvironment, TAMs were mostly immunosuppressive M2 and anti-inflammatory, which played an immunosuppressive role. One subtype of helper T cells, Th1, releases INF-γ, which can promote the polarization of M1 cells. When M1 macrophages are polarized, M1 macrophages release TNF-α, and INF-γ and TNF-α can promote the proliferation and activation of CTL and NK cells. These cytokines can promote cellular immunity in a pro-inflammatory environment and forming an anti-cancer environment. One subtype of helper T cells, Th2, release cytokines to promote the polarization of M2 cells. When M2 macrophages are polarized, IL-10 is released to play an immunosuppressive role. Additionally, M2 macrophages release TGF-β, which promotes the differentiation of regulatory T cells (Treg) which will release a large amount of IL-10 for immunosuppression. M2 macrophages and Tregs form a cancer-promoting environment[24]. M2 macrophages in the microenvironment are gradually transformed into M1 macrophages by reprogramming, which inhibits the polarization of M2 macrophages, reduces their immunosuppressive abilities, and restores the body's immunity. The immune microenvironment of the liver is complex and specific, and there is a certain natural immune tolerance. Various factors can cause the

Table 1 Chinese herbal compounds containing bezoars and their anti-tumor effects

Drug	Drug composition	Efficacy	Disease treated
Pien tze huang[12]	Bezoar, notoginseng, snake gall, musk	Clearing heat and detoxifying, cooling blood and removing stasis	Liver cancer, chronic hepatitis
Xihuang pill[13]	Bezoar, musk, frankincense, myrrh	Clearing heat and detoxifying, and relieving swelling	Breast cancer, scrofula
Kehuang capsule[14]	Bezoar, musk, snake gall, notoginseng, scutellaria, coptis, phellodendron Curcuma	Clearing heat and detoxifying, cooling blood and clearing knot	Liver cancer, chronic hepatitis
Niuhuang tianlong capsule[15]	Xihuang pill plus or minus	Clearing heat and detoxifying, dispersing knot and removing blood stasis	Cervical cancer, endometrial cancer
Niuhuang xingxiao pill[16]	Bezoar, musk, frankincense, myrrh	Clearing heat and detoxifying, cooling blood and removing stasis	Breast cancer, scrofula

occurrence of liver cancer. In situations of chronic inflammation, the body secretes immunosuppressive factors to suppress immune cells through excessive immunosuppression, leading to the occurrence of tumors. Notable among them are TAMs[25]. The liver is the body's parenchymatous organ containing the most macrophages, and it is also contains the highest immune cell population in the liver. As a bridge between the innate and adaptive immune system, it plays an important role in the treatment of liver cancer[26] (Figure 1).

BEZOARS AND BEZOAR-CONTAINING COMPOUNDS REGULATE THE IMMUNE MICROENVIRONMENT IN LIVER CANCER

The regulatory mechanisms by which bezoars and bezoar-containing compounds on liver cancer can occur in many ways. First, they can promote the apoptosis of liver cancer cells and inhibit their growth and metastasis by regulating liver cancer-related cells. Second, they can regulate the relevant signaling pathways, regulate and improve the tumor immune microenvironment, and inhibit the growth of tumors. The PD-1/PD-L1 signaling pathway plays a regulatory role in cell proliferation and apoptosis. By regulating the PD-1/PD-L1 signaling pathway, the polarization of macrophages and the expression of IL-6 cytokines are affected. Experimental data shows that the Xihuang Pill can prevent the further development of liver cancer by inhibiting PD-1/PD-L1 signaling[27]. NF-κB regulates immunity and inflammation in the body, and when activated, it promotes increased inflammatory cell infiltration to aggravate the inflammatory response. IL-1β and TNF-α as upstream factors of NF-κB, activate NF-κB which promotes the development of inflammation, and metastasis of cancer cells. Pien Tze Huang can reduce liver fibrosis and promote apoptosis of cancer cells by regulating the NF-κB signaling pathway. In addition, experimental studies have also found that Pien Tze Huang can reduce liver fibrosis by regulating autophagy as well as the TGF-β1/Smad signaling pathway[28-30]. The Wnt/β-catenin signaling pathway is an important signaling pathway regulating cell growth, development and differentiation. Many studies have found that activation of the Wnt/β-catenin signaling pathway promotes tumor development[31]. Studies have shown that there is a close relationship between Wnt and macrophages, and that macrophages can re-activate the Wnt signaling pathway in the tumor immune microenvironment, regulate Wnt in neighboring cells through paracysecretory, and affect the function of Wnt. In addition, Wnt signals in macrophages can change their own immune activation state and affect the homeostatic balance of surrounding organs after activation[32]. Wnt signaling in macrophages can increase the degree and progression of organ fibrosis by regulating the state of its immune response. Ye Feng found that Wnt/β-catenin signaling can promote the secretion of TGF-β and other pro-fibrotic factors by macrophages *in vitro*, and that the degree of fibrosis was reduced in mice where β-catenin was knocked out in myeloid cells. Inhibition of Wnt/β-catenin signaling can reduce the degree of bleomycin-induced pulmonary fibrosis in mice[33]. Regulating the Wnt/β-catenin signaling pathway is an effective strategy for the treatment of liver cancer. From the etiology of liver cancer, we have learned that chronic hepatitis is an important factor causing liver cancer. In some inflammatory diseases, macrophages and Wnt signaling are involved. Macrophages secrete some factors involved in immune tolerance, such as TGF-β and IL-10, and the expression of these cytokines is also a typical feature of M2 polarized macrophages, resulting in immunosuppression. When the Wnt/β-catenin signaling pathway is activated, it will promote the polarization of M2 macrophages to produce tumor promoting cytokines such as IL-10, generate Tregs, and promote the further development of tumors. The classical Wnt signal is transmitted to the upstream ligand *via* β-catenin to avoid excessive degradation of itself. M2-type macrophages promote tissue repair, and when β-catenin is silenced in macrophages, tumor cell mobility decreases. Cell experiments have shown that silenced β-catenin can slow down the cell healing rate and reduce tumor mobility to a certain extent, which can inhibit not only liver cancer but also a variety of tumors[34].

The application of bezoars and related preparations is not limited to experimental data and related basic research, and clinical applications have shown that their use in the treatment of liver cancer has also achieved effective therapeutic effects. Ning *et al*[35] found that the combined application of bezoars and imagination can promote apoptosis of liver cancer cells[35]. Xu *et al*[36] found that after TACE surgery in patients with primary liver cancer, the combination of acupuncture with the Xihuang Pill and conventional Western medicine treatments can significantly relieve patient pain,

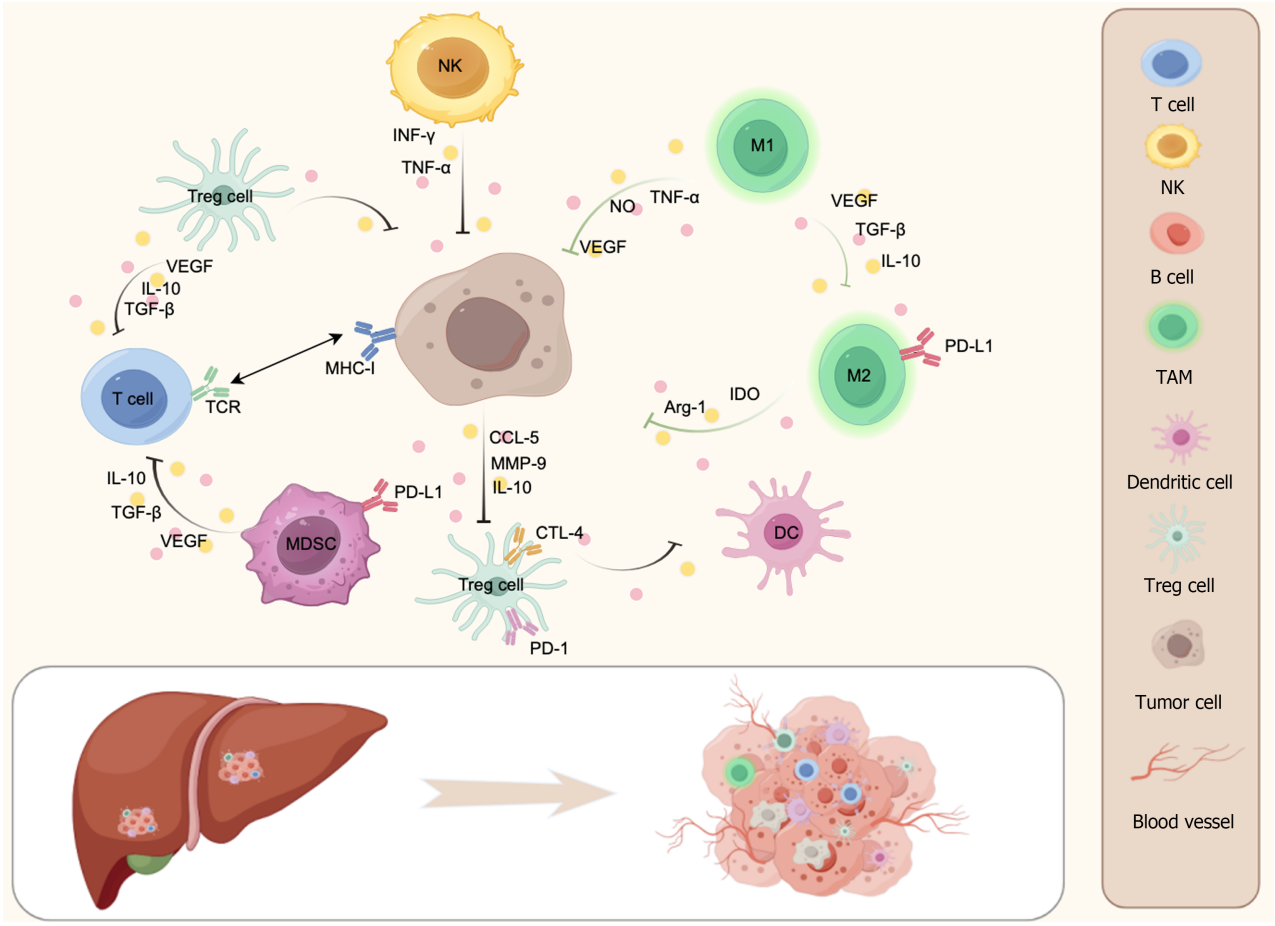

Figure 1 Liver cancer immune microenvironment. Created by Figdraw.

improve patient quality of life, and serum levels of AFP and GAS, which is worthy of clinical promotion and application [36]. Guo *et al*[37] found that Pian Zehuang combined with gamma knife stereotactic radiotherapy had fewer adverse reactions and could prolong the survival time of patients with primary liver cancer compared to radiotherapy[37].

In this paper, the TCM bezoar inhibits the polarization of M2 TAMs by inhibiting the activation of the Wnt/β-catenin signaling pathway to subsequently inhibit the development of liver cancer, which confirms the obvious effect of TCM on liver cancer.

RESEARCH AND DEVELOPMENT OF BEZOAR AND ANTI-TUMOR PREPARATIONS CONTAINING BEZOAR COMPOUND

In recent years, with the gradual deepening of the research on the prevention and treatment of cancer using TCM, we have found that TCM has the advantages of multi-pathway and multi-target effects, which translates to remarkable effects on the prevention and treatment of tumors[38]. However, the application of TCM in cancer has the disadvantages of instability and poor water solubility, which limits its clinical application and exploration. With the deepening of research on the chemistry and pharmacology of TCM, thus the use of nano preparations in TCM is quite clear. Nano preparation of TCM has the advantages of reducing toxicity and promoting more accurate targeting[39,40]. Studies have found that a variety of single herbs have shown good therapeutic effects in the treatment of malignant tumors. Nano polysaccharides can enhance the stability of TCM compounds[41]. Zhang *et al*[42] found that Sanqi compound nanoparticles had significant antithrombotic effect[42]. Reviewing the application history and value of bezoars in Linchuan may result in more accurate targeted treatments that may be achieved through the development of nano-bezoars in anti-tumor treatment. Nano-preparations can be given in multi-unit administration in the field of TCM. Bezoars can be divided into independent drug units, which are further processed by wet grinding, high pressure homogenization, liquid nitrogen freezing and other methods. It was found that the antitumor activity of the multi-unit drug delivery system for a Chinese medicine Niuhuang Xingxiao Pill was significantly higher than that of the Niuhuang Xingxiao Pill[43].

Through this article, we found that the TCM bezoar can affect the macrophages and immune microenvironment of tumor patients through relevant signaling pathways. This suggests that the nano-bezoar has great potential for future development, providing a new means for the treatment of liver cancer by the TCM bezoar and the compound preparation

containing bezoar[44].

CLINICAL IMPLICATIONS

TCM, as a traditional means of treating diseases in China, has a long history. Even with the development of molecular biology and pharmacological technology, TCM is effective in the treatment of cancer. Whether it is used alone or with multiple drugs combined, it can inhibit and reverse the tumor to some extent. The composition of TCM is complex, and it can be applied in multiple targets with high safety. The use of TCM can positively regulate the immune microenvironment in tumor patients, inhibit the negative feedback signal pathways, and restore the body's immune ability to achieve anti-tumor effects. However, the first shortcoming is that the exploration of a variety of Chinese medicines is not in-depth enough, and there is a lack of clinical trial data to reveal its anti-tumor mechanism of action. More clinical trials and data sorting are needed to further discover, reveal, and prove the mechanism of action of Chinese medicine on tumors. In addition, single drug or compound preparations need to be further optimized and developed, and modern nanotechnology is needed to improve the stability and accuracy of TCM in the treatment of tumors, and to improve clinical efficacy.

FOOTNOTES

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