

Research Progress on Regulating Intestinal Microbiota with Traditional Chinese Medicine to Treat Digestive System Tumors

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Abstract: The imbalance of intestinal microbiota homeostasis is closely related to the occurrence and development of digestive system tumors. Traditional Chinese medicine plays an important role in regulating intestinal microbiota and is used in the clinical prevention and treatment of digestive system tumors. This article reviews the research progress of traditional Chinese medicine in regulating intestinal microbiota to intervene in digestive system tumors. It reveals the important role of regulating intestinal microbiota in optimizing the treatment of digestive system tumors with traditional Chinese medicine, and provides a new direction and direction for the prevention and treatment of digestive system tumors.

1. Introduction

Globally, digestive tract tumors are the main malignant tumors [1], occupying 4 of the top ten cancer incidences [2]. The global incidence and mortality rate of digestive tract tumors are approximately (23.48%, 30.91%), and China's digestive tract tumors. The incidence of tract tumors accounts for approximately 38.71% of global tumors, and the mortality rate accounts for approximately 45.03%, both of which are higher than the world average (23.48%, 30.91%) [3].

The pathogenesis of each digestive tract tumor is not yet clear, and each has its own unique disease progression process. Most tumor patients have no obvious symptoms in the early stage, and the prognosis of the patients is poor. The intestinal microbiota represents a hidden treasure trove of trillions of microorganisms that inhabit the host's intestinal epithelial barrier. The intestinal microenvironment can affect local and distant tumors by affecting the immune environment, myeloid and lymphocyte proliferation rates, metabolic patterns and inflammation [4].

In recent years, traditional Chinese medicine has played an important role in tumor treatment, especially in improving the adverse reactions of radiotherapy, chemotherapy, targeted therapy, immunotherapy, etc. [5], and enhancing the body's immunity [6]. And it can regulate intestinal microorganisms to treat diseases and achieve a certain curative effect. This article will review the research progress on the use of traditional Chinese medicine to regulate intestinal microorganisms in the treatment of digestive tract tumors.

2. Traditional Chinese medicine theory and intestinal microbiota

"Microecology" is a discipline in modern medicine that studies the structure and function of normal microorganisms in the human body and their relationship with the host from a microscopic level. It is an important part of life sciences. There is no discussion about intestinal microbiota in the theory of traditional Chinese medicine, but traditional Chinese medicine originated from ancient Chinese macroecology and is a microscopic application of macroecology. Its essence is also ecological medicine [20]. This is consistent with the concept of microecology.

The holistic view believes that the human body itself is a unified organic whole, and that people, society, and the natural environment are also unified; modern microecology believes that microorganisms, microorganisms and their hosts, and microorganisms and the social and natural environment are all unified wholes. It cannot be separated [21]. Traditional Chinese medicine believes that righteousness is the body's ability to resist evil, including the ability to adapt to changes in the external environment and the ability to heal from diseases. Evil qi is the key factor leading to the imbalance of yin and yang in the human body. The diversity and abundance of the human intestinal microbiota are relatively stable, the intestine is in a relatively balanced state, indicating sufficient righteousness and normal ability to resist evil.

Ancient Chinese medicine scientists introduced the theory of yin and yang into the theoretical system of traditional Chinese medicine. Traditional Chinese medicine believes that the normal operation of various functions of the human body is due to the relative balance of yin and yang. Just as "Suwen Qi Tongtian Lun" says: "The dynamic balance of yin and yang is the foundation of normal physiological activities in the human body. If there is an imbalance between yin and yang, it is no longer possible to maintain the active relationship between the two, causing damage to the body". Modern microecology believes that intestinal microorganisms colonize and multiply in the human intestine and are in a dynamic balance. When the balance of the intestinal microbiota is broken, a series of diseases will occur occurrence [21].

The author believes that when the relative balance of the human body is destroyed due to invasion of external evils, internal injuries caused by diet, emotional disorders and other causes, the homeostasis of the intestinal microbiota will also change, thereby affecting the progression of the disease.

3. Traditional Chinese Medicine's understanding of digestive system tumors

There is no name for "digestive tract system tumors" in ancient Chinese medicine books, but according to the Book of Rites of Zhou records, there were "ulcer doctors" in the Zhou Dynasty who took the concept of treating both internal and external diseases with both attack and tonic. Huangdi Neijing puts forward the concepts of diseases such as Ji Disease, Fuliang Disease, Tuan Disease, and intestinal mushrooms based on their syndromes, disease locations, and characteristics. "Miraculous Pivot" says: Emotional issues, improper diet, etc. can lead to the accumulation of evil energy. It is generally believed that invasion of external pathogens, improper diet, and emotional disorders are the main causes of tumor occurrence. "Miraculous Pivot" says: "People who are prone to intestinal lumps have thin and dull skin, weak and moist muscles. This will damage the intestines and stomach, leading to the retention of evil energy here". It points out that damage to the internal organs leads to imbalance of qi, blood, yin, and yang, which is the key to the occurrence of tumors.

Zhang Zhongjing of the Eastern Han Dynasty created classic prescriptions such as Biejiajian Pills based on the etiology, pathogenesis and characteristics of accumulation. Wang Shuhe of the Jin Dynasty discussed in detail the pulse method of the five internal organs in Pluse Classic, which laid the foundation for the pulse method of tumors in traditional Chinese medicine. The theory of traditional Chinese medicine developed rapidly and innovated during the Song and Yuan Dynasties.

The description of cancer in ancient Chinese medicine books is first seen in "Wei Jibao's Book", which is considered an independent disease. The name of the disease, and cancer as a malignant tumor should be the Ren Zhai Zhi Zhi Fang written in 1264 AD.

Since the Ming and Qing Dynasties, with the development of traditional Chinese medicine theory, the understanding of tumors has gradually deepened, and the etiology, pathogenesis, and treatment principles of tumors have been further understood. This has laid the foundation for the treatment of tumors of the digestive tract system by contemporary traditional Chinese medicine and traditional Chinese and Western medicine. Theoretical basis and practical experience.

4. The treatment of digestive system tumors can modulate the intestinal microbiota through traditional Chinese medicine

The intestine is a huge digestive organ in the human body. There are a large number of symbiotic microorganisms in the human intestine, including bacteria, fungi, viruses, archaea and protozoa [7]. They live on the surface of the gastrointestinal epithelial barrier and pass through the human eating habits, dynamically changing under the influence of specific physiological conditions and drug use. They exert their specific functions in the production of short-chain fatty acids (SCFA), immune system homeostasis, nutrition and drug metabolism, vitamin synthesis, and prevention of pathogen colonization [8-9]. Research has found that the microbiota is involved in regulating physiological processes, such as immune system development, pathogen replacement, and nutrient absorption[10]. Changes in its diversity and composition (dysbiosis) are related to a variety of pathologies, including the occurrence of cancer. This relationship is two-way.

4.1. Imbalance of intestinal microbiota homeostasis induces the occurrence of cancer

Microorganisms induce chronic inflammation, and inflammatory mediators (cell mediators and reactive oxygen species and nitrogen species) produce higher mutation rates and DNA damage in the tumor microenvironment [12]. Studies have proven that microorganisms promote the occurrence and development of tumors by inducing tumor inflammation or translocating to tumor sites and sustaining cancer-induced inflammation [11-12]. Using an azomethane (AOM)/dextran sodium sulfate (DSS) model, HU et al found that the microbiota of inflammasome-deficient mice was altered by inducing CCL5 (CC-chemokine ligand 5) and activating intestinal epithelium. The IL-6 signaling pathway in cells can lead to inflammation-induced colorectal cancer [13-14]. Dysregulation of microbiota balance and increased abundance of Th17-inducing bacteria can cause chronic inflammation, leading to the initiation and progression of cancer. In addition to the indirect carcinogenic mechanism of microorganisms by inducing chronic inflammation, there are also direct mechanisms by which microorganisms produce toxins and metabolites that cause cancer [15].

4.2. Anti-tumor properties of intestinal microbiota

Intestinal microorganisms in the human body play a very important role in human life and health activities. Some nutrients necessary for the human body cannot be synthesized by themselves and must be obtained by intestinal microorganisms, such as vitamin K, short-chain fatty acids, etc. [16]. Studies have proven that intestinal microbiota can promote the differentiation of human intestinal epithelial cells and regulate the body's energy metabolism [17]. Heather L and others found that human immune regulation can be achieved by the intestinal microorganism *P. mirabilis* promoting the activation of intestinal NLRP3 and the secretion of IL-1b [18]. Enhanced immune regulation can promote the activation of phagocytes, thereby clearing cancer cells at an early stage. For example: *Lactobacillus* and *Bifidobacterium* are the two most common probiotics in the digestive system.

Lactobacillus reduces inflammation and DNA damage by producing antioxidants and anti-angiogenic factors, and prevents polyamines and tumor-specific antigens expression to prevent cancer [19].

5. Treat digestive system tumors by regulating intestinal microbiota through traditional Chinese medicine.

5.1. Treatment of liver cancer

Liver cancer is one of the common clinical malignant tumors. Most patients have an insidious onset and rapid disease progression. When symptoms appear, they often develop into mid-to-late stages and lose the opportunity for surgical treatment. Targeted therapy is the mainstay in clinical practice, but single targeted therapy is ineffective. Good, and accompanied by the emergence of different adverse reactions.

Traditional Chinese medicine and its active ingredients can enhance the body's immunity by regulating intestinal microorganisms, which can enhance the anti-tumor effect of traditional Chinese medicine. Studies have proven that patients treated with traditional Chinese medicine have lower mortality and longer survival than those who do not use traditional Chinese medicine. Jiang Ruiyuan et al have shown that Jianpi Yiqi prescription can reduce the peripheral circulation of liver cancer-bearing mice under spleen deficiency and inflammation models through the abundance of Firmicutes, Bacteroidetes and Deferribacteria [22].

The expression levels of IL-1 β , IL-18, and NF- κ B in the system improve the inflammatory environment in tumor-bearing mice, thereby effectively inhibiting the proliferation of liver cancer cells. Research found that compared with the intestinal microorganisms of healthy people, patients with liver cancer have more Streptococcus species and fewer species of Bifidobacterium, Lactobacillus, Roseburia, etc [23]. After treatment with Fuzheng Xiaoliu Recipe, The abundance of Streptococcus in the intestine has decreased, while the abundance of Bifidobacterium, Lactobacillus, Roseburia, etc has increased, and its bacterial community structure tends to be that of healthy people.

Research shows that Diwu Yanggan Recipe improves the diversity, richness and evenness of intestinal flora in rats, thereby reducing the expression levels of TLR4 protein and NF- κ B protein in rats, and can effectively reduce AFP in rats, ALT and CA19-9 levels, effectively reducing tumor marker levels [24]. Tian Li et al found that tumors can cause structural changes in the intestinal microbiota of mice [25]. Salvianolic acid B can improve the changes in the intestinal microbiota caused by tumors, reduce the abundance of harmful bacteria, and increase beneficial bacteria of abundance. Studies have shown that cryptotanshinone can inhibit liver cancer activity in mice transplanted with liver cancer, improve the intestinal shielding function of mice, increase the richness and diversity of intestinal flora in mice, and further improve cellular immunity [26]. Function Zhang Yumei et al found that the imbalance of intestinal microecology and the occurrence and development of liver cancer are often related to abnormal bile acid metabolism[27]. Yinchenhao decoction may promote the production of primary conjugated bile acid T- β -MCA, thereby improving the intestinal tract. Dominant strains of bacteria can further play a role in treating liver cancer.

The above-mentioned studies have shown that regulating intestinal microorganisms through traditional Chinese medicine can treat liver cancer by increasing the abundance and diversity of intestinal flora, thereby inhibiting or delaying the occurrence and development of liver cancer by enhancing the body's immunity, and further reducing the levels of tumor markers.

5.2. Treatment of colorectal cancer

Colorectal cancer is the general term for colon and rectal cancer and is one of the common malignant tumors of the digestive tract in my country. At present, most clinical treatments for

colorectal cancer include surgery, radiotherapy, chemotherapy, immunotherapy, and palliation. Modern pharmacological research shows that traditional Chinese medicine can regulate intestinal microbiota from many aspects and play an anti-tumor effect. The relative stability of intestinal microbiota can enable traditional Chinese medicine to increase the therapeutic effect [28].

Studies have confirmed that the flavor of Dahuang Mudan Tang can improve the distribution of intestinal microbial groups after surgery of patients with hydrocytosis in colorectal cancer, which reduces the number of harmful bacteria coli, and increases the number of bisidobacterium and lactobacillus [29]. Meng Chunqin et al have shown that Jianpi Huayu Recipe can reduce the number of pathogenic bacteria *Enterococcus faecalis* and *Enterobacter* in the intestine and increase the number of beneficial bacteria *Bifidobacterium* and *Lactobacillus* in treating colorectal cancer with spleen deficiency and blood stasis type [30]. It can improve the body's immune function and reduce the level of inflammatory factors. This mechanism may be related to the regulation of TLR4/NF- κ B. Research found that Yichang Sanjie Decoction combined with chemotherapy to treat advanced colorectal cancer with spleen deficiency and phlegm stasis syndrome can positively correlate the expression level of AIM2 mRNA in serum with the level of intestinal flora diversity, and can increase the diversity of intestinal flora and increased levels of beneficial bacteria [31].

Research has proven that Sanwubaisan can significantly increase the abundance of *Enterorhabdus*, *Clostridium* and uncultured_bacterium [32]. *Enterorhabdus* is positively correlated with the anti-tumor cytokines IL-17 and IFN- γ . Sanwubaisan can regulate intestinal microorganisms group thereby exerting tumor effects. The study found that the anti-colon cancer mechanism of iron pills increased the abundance of Clostridiales and inhibited the abundance of opportunistic pathogen *Enterobacter*, thereby increasing the diversity and abundance of intestinal flora in nude mice, thereby inhibiting colon cancer the development of cancer [33].

Wang Nan et al found that in experiments on rats with colon cancer, Gegen Qinlian Decoction reduced the number of *Lactobacillus*, *Escherichia coli*, *Enterococcus* and *Bifidobacterium* in the intestinal tract of rats, and increased the diversity of intestinal flora [34]. Increase, Gegen Qinlian Decoction can effectively control the occurrence and development of colon cancer. Studies have proven that Sijunzi Decoction can increase the reduced levels of bifidobacteria and lactobacilli in mice with colon cancer, reduce the levels of enterococci and enterobacteriaceae, and make the intestinal flora of mice tend to normal levels [35]. By regulating T lymphocytes Cell subpopulations and immunoglobulins thereby improve the body's immunity and further inhibit the growth of tumors in mice.

The above studies show that traditional Chinese medicine regulates intestinal flora, increases the diversity of beneficial bacteria, and reduces the level of harmful bacteria, thereby inhibiting the occurrence and development of tumors and achieving the purpose of treating colorectal cancer.

5.3. Treatment of gastric cancer

Gastric cancer is one of the common malignant tumors of the digestive system. Most clinical treatment is mainly based on comprehensive surgical treatment, and the prognosis is not good. Research confirmed that Lizard Powder Gel has a two-way effect on the regulation of intestinal flora in rats. High concentration of Lizard Powder Gel can increase the abundance of intestinal flora in rats and inhibit pathogenic bacteria in the gastrointestinal tract [36]. *Preoella* species, *Faecalibacterium* species, *Ruminococcus* species, and *Zurichella* species can promote the increase in the number of gastrointestinal probiotics such as *Akkermansia*, *Lactobacillus*, and *Bacteroides*, further balancing the intestinal flora structure, repair damaged gastric mucosa, thereby inhibiting the development of gastric precancerous lesions.

Studies have proven that Jianpi Fuzheng Jiedu Decoction can increase the number of bifidobacteria

and lactobacilli and reduce the number of harmful bacteria *Escherichia coli* and enterococci in patients with advanced gastric cancer undergoing chemotherapy [37]. This may increase the patient's immune function and reduce the risk of Adverse reactions and reduced tumor marker levels are important reasons. Research found that the species composition and richness of the intestinal flora of patients with mid-to-late gastric cancer with weak spleen and stomach are different from that of healthy people [38]. The flora is in a state of imbalance, with beneficial bacteria decreasing and pathogenic bacteria increasing, and chemotherapy further aggravates some of the intestinal flora. For flora imbalance, invigorating the spleen, nourishing the body, and eliminating the disease can increase the intestinal species composition and bacterial flora richness toward healthy people, further exerting its therapeutic effect. Buzhongyiqi modified formula can effectively improve the diversity of intestinal flora in gastric cancer tumor-bearing mice, recall 10 related bacterial genera such as *Streptococcus* and *Clostridium*, and maintain the balance of intestinal microbiota. Improving the body's immune ability can significantly inhibit the tumor mass of gastric cancer tumor-bearing mice, thereby exerting an anti-tumor effect [39].

Bai Xing et al have shown that the dense-spotted lizard may reduce the abundance of the carcinogen *Helicobacter pylori* and increase the abundance of Firmicutes that produce short-chain fatty acids (SCFAs) by regulating the homeostasis of intestinal flora [40]. Thereby regulating the abundance of SCFAs-related bacterial genera (*Bacteroidetes*, *Parabacteria*, *Clostridium*) and body immunity, thus exerting the effect of inhibiting gastric cancer.

The above-mentioned studies have shown that Chinese medicine alone or in combination can treat gastric cancer by regulating the homeostasis of the intestinal microbiota, improving the species composition and richness of the intestinal flora, reducing the abundance of pathogenic bacteria, and normalizing the intestinal flora, further increasing immunity, thereby inhibiting the progression of gastric cancer.

6. Conclusion and outlook

To sum up, traditional Chinese medicine monomers and compound formulas mainly increase the body's immune function by adjusting the proportion of beneficial bacteria and pathogenic bacteria in the intestine, and further inhibit the progression of digestive system tumors. Not only can it restore the homeostasis of intestinal microbiota and bring it back to normal, it can also intervene in the occurrence and development of digestive system tumors by regulating the "inflammatory-cancer" transformation signaling pathway. Based on the above research, traditional Chinese medicine can be added to the clinical application of radiotherapy and chemotherapy, and fecal analysis can be done. Probiotics can be targeted according to changes in intestinal flora.

At present, patients with clinical treatment of digestive system tumors are still led by surgical resection. Patients who cannot be treated in the middle and late stages are mostly clinically chemotherapy and Chinese medicine. However, while radiotherapy and chemotherapy drugs kill cancer cells, they also have toxic side effects on normal cells of the body. They are limited to disease differentiation and cannot be dialectical. Traditional Chinese medicine integrates holistic concept, syndrome differentiation and treatment, and harmony between nature and the people throughout the entire process of diseases, which is consistent with the theory of intestinal microecology. The components of traditional Chinese medicine monomers and traditional Chinese medicine compounds are complex, and the treatment targets are diverse. The dialectical treatment method produces few adverse reactions, which is one of the characteristics of traditional Chinese medicine in the treatment of tumors. However, the exact mechanism by which traditional Chinese medicine modulates intestinal flora to treat digestive system tumors has not yet been fully elucidated at the pharmacological level. The specific mechanism of action needs to be further confirmed by various *in vivo* and *in vitro*

experimental studies. Modern microbiology techniques, such as microbial metabolomics, can be used to further clarify this issue. Provide new treatment directions and ideas for the prevention and treatment of digestive system tumors.

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