DOI: 10.66069/ojspub.27450746

Research Progress on the Treatment of Colorectal Cancer Based on Collateral Disease Theory

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Abstract: ***Colorectal cancer (CRC) is a common malignant tumor of the digestive system, with persistently high incidence and mortality rates worldwide. Its treatment is challenged by critical issues such as recurrence, metastasis, and chemoresistance. In recent years, traditional Chinese medicine (TCM) has demonstrated unique advantages in the treatment of malignant tumors. As an important component of the TCM theoretical system, collateral disease theory has shown significant potential value in the treatment of CRC and provides novel perspectives for elucidating its pathogenesis and developing therapeutic strategies. This article systematically reviews the core concepts of collateral disease theory and its relevance to CRC, summarizes CRC treatment strategies based on collateral disease theory—including the application of therapeutic principles, herbal prescriptions, and external treatment methods—and discusses their clinical advantages and existing limitations. By integrating findings from modern medical research with TCM syndrome differentiation and treatment experience, this review aims to provide a theoretical basis and practical reference for the integrated treatment of CRC with traditional Chinese and Western medicine.***

Keywords: Collateral disease theory, Colorectal cancer, Traditional Chinese medicine treatment, Yangzheng Xiaoji Capsules, Lipid metabolism.

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide and the second leading cause of cancer-related death [1]. Among gastrointestinal malignancies, CRC has the highest incidence and mortality rates, accounting for 38.5% and 28.2% of the morbidity and mortality risk of gastrointestinal cancers, respectively [2]. The incidence of CRC continues to rise [3], posing a serious threat to human health; however, its etiology and pathogenesis have not yet been fully elucidated. CRC development is closely associated with genetic factors, living environment, and lifestyle. Major risk factors include high-fat [4], high-sugar [5], and low-fiber diets [6], as well as unhealthy lifestyle habits such as alcohol consumption [7] and smoking [8]. Studies [9,10] have shown that dysregulated lipid metabolism is an important hallmark of malignancy and is closely related to the occurrence and progression of CRC [11]. Regulation of lipid metabolic reprogramming may inhibit the proliferation and migration of CRC cells, thereby exerting antitumor effects. Lipid metabolic reprogramming is one of the major mechanisms by which tumor cells adapt to the tumor microenvironment, evade apoptosis, and promote metastasis [9,11].

At present, conventional Western medical treatment for CRC mainly includes surgery, chemotherapy, radiotherapy, and cryotherapy [12]. Chemotherapy, as one of the principal treatment modalities for CRC, may cause adverse effects to varying degrees, including neutropenia, vomiting, diarrhea, and neurotoxicity, thereby compromising patients' quality of life. In recent years, Chinese herbal medicine has become an important approach in anti-CRC treatment because of its advantages of multitarget and multipathway actions, relatively low toxicity, and fewer adverse reactions [13]. According to the collateral disease theory of traditional Chinese medicine (TCM), the occurrence of CRC is associated with functional impairment and structural damage of the collaterals. Theories such as the "cancer collateral theory" [14], the "theory of latent stasis-toxin in the collaterals" [15], and "intertwined phlegm and blood stasis" provide new perspectives and therapeutic approaches for the TCM treatment of CRC.

2. Connotation and Development of Collateral Disease Theory

Collateral disease theory has been widely applied to internal medicine and the treatment of difficult and complicated diseases for more than 2,000 years and represents an important component of traditional Chinese culture. The theory can be traced back to the Huangdi Neijing (The Yellow Emperor's Inner Canon). The chapter "Miu Ci Lun" in the Su Wen states: "When pathogenic factors invade the skin and body hair, they enter and lodge in the sun collaterals… then overflow into the major collaterals, giving rise to unusual diseases." The chapter "Bai Bing Shi Sheng" in the Ling Shu states: "When retained without resolution, pathogenic factors are transmitted and lodge in the collateral vessels… when they remain for a prolonged period, they accumulate and form masses, which may adhere to the sun collaterals or the collateral vessels." These passages suggest that pathogenic factors may lodge in the collaterals and, when retained for a prolonged period, form accumulations or masses that are considered analogous to tumors; such pathological changes may also spread along the course of the collateral vessels. The Ling Shu: Ben Shu states: "The sites where collateral vessels branch, where the five Shu points remain, where the six Fu organs connect, where the four seasons enter and exit, where the five Zang organs flow, as well as their breadth, number, depth, and distribution," laying a foundation for the development of collateral disease theory.

The Clinical Guide Medical Records (Linzheng Zhinan Yian)

emphasizes that "early-stage disease affects the channels, whereas longstanding disease enters the collaterals; channels govern qi, while collaterals govern blood." It holds that collateral vessels, as pathways for the circulation of qi and blood, are susceptible to obstruction by blood stasis as a result of prolonged stagnation of pathogenic factors or deficiency of healthy qi. Accordingly, treatment should follow the principle that "collaterals function through unobstruction," employing methods that promote collateral circulation, such as acrid medicinals and insect-derived medicinals with collateral-unblocking and obstruction-dispersing properties. As a branch of the TCM theoretical system, collateral disease theory may be divided into the qi-collateral system, which regulates qi movement, and the blood-collateral system, which facilitates blood circulation [16].

In the modern development of collateral disease theory, Academician Wang Yongyan and colleagues proposed new interpretations of the theory, shifting research from the study of collateral diseases to the investigation of dynamic disease changes. They introduced the concept of "diseased collaterals" (bingluo) and explored dynamic changes in disease location on the basis of pathological alterations in collaterals. They proposed that collaterals possess extensive, complex, and multidimensional characteristics [17]. Based on the dimensions of time, space, and function, Academician Wu Yiling established a research framework centered on a "three-dimensional network system" of collaterals. His research suggests that tumor formation is consistent with the concept of "collateral stagnation forming masses" in collateral disease theory. He incorporated collateral disease concepts into tumor treatment and proposed the regulation and balancing of nutrient qi and defensive qi [18], thereby forming the therapeutic principle of "unblocking as the primary therapeutic strategy." This principle is consistent with the concept of "unblocking the collaterals" advocated by physicians such as Zhang Zhongjing. Modern researchers [19] have further revealed that collaterals may influence tumor development by regulating angiogenesis and improving microcirculatory disturbances.

3. Alignment Between CRC Pathogenesis and Collateral Disease Theory

There is no specific corresponding disease name for colorectal cancer (CRC) in classical Chinese medical literature. In traditional Chinese medicine (TCM), malignant tumors may generally be categorized under the concept of "cancerous masses" (aiji). The concept of cancer was recorded in the Song Dynasty text Renzhai Zhizhi Fuyifang (Supplementary Prescriptions from the Direct Guidance of Renzhai): "Cancer is elevated superficially and deeply sunken beneath, resembling a rock, with toxic roots deeply concealed." In TCM theory, the formation and transmission of "masses" (ji) are closely related to the occurrence, progression, invasion, metastasis, and dissemination of tumors in modern medicine.

The chapter "Bai Bing Shi Sheng" in the Ling Shu states: "When deficient pathogenic factors invade the body, they begin at the skin… If they remain without resolution, they are transmitted and lodge outside the intestines and stomach, between the thoracic and abdominal membranes, adhere to the vessels, and persist without dispersing. They then accumulate and form masses, attaching either to the sun collaterals or to the collateral vessels." In addition, the chapter "Ci Jie Zhen Xie" in the Huangdi Neijing: Ling Shu states: "When there is already a knot or aggregation, qi converges there, body fluids are retained there, and pathogenic qi invades it. The condensation becomes progressively more severe day by day, connecting and gathering together to form masses and tumors." These descriptions further indicate that tumors result from the prolonged stagnation of pathogenic factors and the formation of masses due to retained pathological substances in the collaterals. They established a theoretical basis for the application of collateral vessel and collateral disease concepts in tumor treatment.

On this basis, Zhang Zhongjing developed therapeutic approaches involving the promotion of blood circulation, removal of blood stasis, and unblocking of the collaterals, as well as the use of insect-derived medicinals to search through and unblock the collaterals. He proposed methods such as using insect medicinals to unblock collaterals and resolving phlegm to unblock collaterals, thereby treating abdominal masses and accumulations from the perspective of collateral disease. Representative prescriptions include Dahuang Zhechong Pill and Biejiajian Pill [20]. In summary, collateral disease theory enables the pathological process of collateral vessel lesions to be closely associated with tumor invasion, metastasis, and other stages of tumor progression. This is also consistent with Ye Tianshi's proposition that "in the early stage, disease involves qi stagnation in the channels; with prolonged duration, blood is damaged and the disease enters the collaterals."

Modern studies suggest that the collaterals are associated with qi and blood and serve as sites for body fluid and blood metabolism, possessing nutritional and metabolic functions. Therefore, the collateral system may be closely related to microcirculation and extracellular matrix (ECM) metabolism. The occurrence and progression of CRC are often accompanied by abnormal ECM deposition [21], which is highly consistent with the pathogenesis of "collateral retention forming masses" (luoxi chengji) in collateral disease theory. The deposition of large amounts of ECM proteins promotes fibrosis within tumor tissue. Alterations in ECM composition can also affect cell proliferation and migration, resulting in abnormal ECM dynamics and thereby facilitating the formation of a cancer-associated tumor microenvironment characterized by invasiveness [22].

Tumor growth, dissemination, and metastasis are closely associated with angiogenesis. In modern medicine, the structure and function of microvessels and the microcirculation are similar to the morphology and functions attributed to collaterals in collateral disease theory. Tumor neovascularization differs from normal vasculature in its mode of formation, structure, and function. From the perspective of collateral disease theory, excessive tumor angiogenesis may correspond to "excessive proliferation of collaterals"; its disorganized and tortuous structural features may be regarded as "collateral obstruction due to blood stasis"; and its high permeability may be associated with "insecurity of collateral qi."

Based on the correspondence between collateral disease

theory and the structural and functional characteristics of tumor neovascularization, researchers have proposed therapeutic approaches including "suppressing hyperactivity and inhibiting the collaterals," "acrid dispersion and collateral unblocking," and "tonifying qi and stabilizing the collaterals." Their respective mechanisms involve eliminating pathogenic factors within the collaterals, directly unblocking the collaterals, and repairing damaged collateral vessels. Studies have indicated that collateral disease theory may play a positive role in tumor treatment by inhibiting tumor angiogenesis, effectively improving the tumor microenvironment, and reducing the permeability of tumor neovessels [19].

Clinical observations have shown that patients with CRC commonly exhibit pathological manifestations such as microcirculatory disturbances and hypercoagulability, often accompanied by signs of collateral blood stasis, including a dark-purple tongue and a choppy pulse. In TCM, these manifestations are considered to result from qi stagnation, blood stasis, and the intermingling of phlegm and blood stasis [23]. As qi is regarded as the commander of blood, qi deficiency fails to promote blood circulation, leading to blood stasis. Collateral vessel disorders are often complicated by stasis and stagnation, which may further result in obstruction of the vessels and impaired blood flow. Consequently, a choppy pulse is commonly observed, while the tongue is often dark purple and may present with petechiae or ecchymoses.

Phlegm-dampness is generally considered a substantial pathogenic factor with heavy, turbid, and viscous characteristics. These properties readily obstruct qi movement and block the vessels and collaterals, thereby impairing collateral patency and hindering blood circulation. Therefore, the formation of blood stasis is often accompanied by the generation of phlegm-dampness, and the two frequently coexist as pathogenic factors. When phlegm and blood stasis obstruct each other, manifestations may include a deep-slippery pulse, a dark tongue, and a white, greasy tongue coating [24]. This is also supported by Selected Clinical Experiences of Guan Youbo, which states: "A white greasy coating, dark tongue body, and deep-slippery pulse are all signs of phlegm-dampness obstructing the collaterals." From a TCM perspective, tumor development may be attributed to "internal deficiency of healthy qi and the mutual binding of toxin and blood stasis" [25-27]. This is consistent with the pathological evolution of "collateral deficiency-collateral stasis-collateral mass formation" and reflects the continuous progression of disease stages described in collateral disease theory.

4. CRC Treatment Strategies Guided by Collateral Disease Theory

According to modern pathological, pharmacological, and molecular studies, the principal mechanisms by which TCM prevents and treats tumors include the following [28]:

Direct antitumor effects, including direct killing of tumor cells; induction of cell death, such as apoptosis, autophagy, and ferroptosis; induction of cellular differentiation; and inhibition of tumor cell invasion and migration [29].

Regulation of the tumor microenvironment, including modulation of protein expression in cells within the tumor microenvironment and inhibition of epithelial-mesenchymal transition (EMT), thereby indirectly suppressing tumor cell growth and metastasis [30].

Improvement of immune dysregulation, including enhancement of cytotoxic T-cell activity, inhibition of regulatory T-cell activity, and suppression of tumor-associated immune remodeling, thereby contributing to antitumor therapeutic effects [31].

Regulation of gut microbiota dysbiosis, including increasing the abundance of beneficial intestinal bacteria, reducing the abundance of pathogenic bacteria, increasing beneficial microbial metabolites, and improving intestinal barrier function [32].

4.1 Representative Prescriptions and Modern Pharmacological Research

Biejiajian Pill (Biejiajian Wan) was first recorded in the chapter "Treatment of Malaria According to Pulse Conditions and Symptoms" in the Jingui Yaolue (Essential Prescriptions of the Golden Chamber): "In malaria occurring once a month, recovery should occur within fifteen days; if recovery does not occur, it should resolve by the end of the month. If it still does not resolve, what should be done? The physician said: 'This is the formation of abdominal masses, known as malaria mother; it should be treated urgently with Biejiajian Pill.'"

Biejiajian Pill was initially prescribed for "malaria mother," a condition characterized by prolonged, unresolved malaria that damages qi and blood, impairs their circulation, and leads to the accumulation of phlegm-turbidity and blood stasis beneath the hypochondrium, thus forming palpable masses. Its major therapeutic actions include promoting blood circulation and unblocking collaterals, transforming dampness and resolving phlegm, as well as dispersing accumulations and eliminating abdominal masses. As a classical prescription developed by Zhang Zhongjing that extensively employs insect-derived medicinals for collateral unblocking, it is regarded as a representative formula for the treatment of collateral diseases.

Some scholars [33] have suggested that Biejiajian Pill has comprehensive advantages in tumor treatment. On the one hand, it employs insect-derived medicinals that enter the blood collaterals to search through and unblock the collaterals, expel pathogenic factors, promote channel and collateral circulation, break blood stasis, and remove stasis, thereby establishing a foundation for early therapeutic intervention. On the other hand, it regulates the spleen and stomach and nourishes qi and blood, achieving both pathogen elimination and reinforcement of healthy qi. Biejiajian Pill may also regulate the biological behavior of tumor cells, improve the tumor microenvironment [34], and inhibit tumor angiogenesis. It has been reported to significantly reduce microvessel density in tumors of tumor-bearing mice. Its antiangiogenic effect may be mediated through inhibition of tumor vascular endothelial growth factor (VEGF) [35]. A murine study [36] indicated that Biejiajian Pill may regulate ferroptosis in hepatocellular carcinoma cells by inhibiting the p62/Keap1/NRF2 signaling pathway. Clinical studies have also suggested

that Biejiajian Pill may be used alone for the treatment of cancerous masses [37].

Gexia Zhuyu Decoction (Gexia Zhuyu Tang) was recorded in Yilin Gaicuo (Correcting the Errors in Medical Works) by Wang Qingren of the Qing Dynasty. It is primarily indicated for abdominal accumulations and masses, fixed pain, and related conditions. It is a principal prescription for CRC with the TCM syndrome pattern of internal binding of toxin and blood stasis. Its therapeutic approach focuses on activating blood circulation, eliminating blood stasis, breaking up masses, and dissipating nodules, which is consistent with the treatment principles of collateral disease theory.

Modern studies have shown that Gexia Zhuyu Decoction may regulate the gut microbiota. Gut microbiota dysbiosis plays an important role in the occurrence and progression of CRC [38]. Following treatment with Gexia Zhuyu Decoction, the diversity and richness of intestinal microbiota may be improved to a certain extent, which may represent one mechanism through which TCM intervenes in gut microbiota regulation [39]. Studies have shown that Gexia Zhuyu Decoction can reverse multidrug resistance in xenograft tumors in nude mice [40]. Its potential mechanism may involve downregulation of multidrug resistance gene 1 (MDR-1) expression. The formula may also reduce MDR-1 expression in patients with recurrent or metastatic colorectal cancer. When combined with chemotherapy, it may further improve chemotherapy response rates.

Yangzheng Xiaoji Formula is an anticancer Chinese patent medicine developed on the basis of collateral disease theory. Its core therapeutic actions are to remove blood stasis and resolve toxins, strengthen the spleen and tonify the kidneys, and combat cancer and disperse accumulations. The formula is rigorously composed according to the principles of chief, deputy, assistant, and envoy medicinals. Astragalus (Huangqi) tonifies the spleen and replenishes qi, whereas glossy privet fruit (Nüzhenzi) nourishes the liver and tonifies the kidneys. Used in substantial doses as chief medicinals, they act synergistically to strengthen the spleen, tonify the kidneys, and nourish the liver.

At the level of deputy medicinals, ginseng strongly replenishes primordial qi, while Ganoderma (Lingzhi) nourishes true yin and replenishes essence and qi. Together, they enhance the chief medicinals' effects in replenishing and nourishing spleen- and kidney-derived essence and qi. Curcuma rhizome (Ezhu) promotes blood circulation and eliminates masses, whereas Gynostemma pentaphyllum (Jiaogulan) clears heat, resolves toxins, promotes diuresis, reduces swelling, replenishes qi, and strengthens the spleen. These medicinals act as deputies to support the chief medicinals and enhance the therapeutic effect.

Among the assistant medicinals, Atractylodes macrocephala (Baizhu) and Poria (Fuling) strengthen the spleen, replenish qi, promote diuresis, and reduce swelling. Hedyotis diffusa (Baihuasheshecao) and Scutellaria barbata (Banzhilian) clear heat, resolve toxins, disperse masses, and dissipate nodules. Endothelium corneum gigeriae galli (Jineijin) strengthens the spleen and resolves food accumulation; Eupolyphaga (Tubiechong) breaks blood stasis and removes stasis; and Artemisia capillaris (Yinchen) soothes the liver, regulates qi, clears heat, and eliminates dampness. Cynanchum paniculatum (Xuchangqing) promotes collateral circulation and activates blood circulation and is used as the envoy medicinal.

The entire formula emphasizes both reinforcement of healthy qi and elimination of pathogenic factors, thereby addressing both root causes and manifestations and integrating tonification with purgation. By strengthening the spleen and tonifying the kidneys, it regulates the fundamental pathogenesis, enhances spleen and kidney function, and achieves the therapeutic effect of "when healthy qi is nourished, accumulations resolve spontaneously." Simultaneously, the use of blood-activating, toxin-resolving, collateral-unblocking, and mass-dispersing medicinals targets the manifestations, promotes unobstructed circulation in the channels and collaterals, and eliminates stasis and toxins.

The combination of Yangzheng Xiaoji Capsules with chemotherapy for advanced colon cancer may improve therapeutic efficacy and quality of life, enhance antitumor immune responses, and reduce tumor burden. Zhang Lishuang et al. [41] analyzed 15 controlled trials and found that, compared with chemotherapy alone, the addition of Yangzheng Xiaoji Capsules to conventional chemotherapy for digestive tract malignancies effectively improved disease control, TCM syndrome outcomes, quality of life, and immune function.

Wang Mingxing et al. [42] conducted a systematic analysis of randomized controlled trials indexed in the China National Knowledge Infrastructure (CNKI), Wanfang Data, PubMed, and other databases from their inception to October 20, 2023, concerning Chinese patent medicines combined with FOLFOX chemotherapy for intermediate- and advanced-stage CRC. The findings indicated that, on the basis of conventional chemotherapy, Yangzheng Xiaoji Capsules were superior to nine other Chinese patent medicines, including Xiaoaiping, in improving the objective response rate (ORR), disease control rate (DCR), quality of life (QOL), and immune function.

Song Yuanyuan et al. [43] obtained favorable outcomes using Yangzheng Xiaoji Capsules in a clinical study of cancer-related fatigue (CRF). A total of 84 patients with CRF were enrolled and assigned to treatment groups. Following intervention, the treatment group demonstrated significant improvements in Karnofsky Performance Status (KPS) scores, emotional dimension scores, and overall fatigue scores. Statistical analysis showed that the differences in these three indicators between the treatment and control groups were statistically significant ($P < 0.05$), confirming the beneficial effects of Yangzheng Xiaoji Capsules on clinical outcomes related to CRF.

In an orthotopic colon cancer transplantation model in mice, Zhang et al. [44] found that Yangzheng Xiaoji Formula effectively enhanced the anti-fatigue capacity of tumor-bearing mice. Further analysis demonstrated that the formula significantly downregulated the expression of interleukin-13 (IL-13) and interleukin-6 (IL-6). As IL-13 and IL-6 are important inflammatory mediators, their reduced

expression may alleviate inflammatory responses in tumor-bearing mice, providing mechanistic support for the ability of Yangzheng Xiaoji Formula to improve the physiological status of tumor-bearing animals.

4.2 Principles of Stage-Based Treatment

Studies have shown that collateral disease theory may guide stage-based treatment of CRC according to the course of disease development [45]. Surgery is one of the core treatment modalities for CRC, and the pathogenesis differs substantially among the preoperative, perioperative, and postoperative stages. Before surgery, the predominant pathogenesis involves qi stagnation, blood stasis, and the intermingling of cancer toxin, resulting in obstruction and blockage of the collaterals. During the perioperative period, surgical procedures lead to considerable depletion of qi and blood and obstruction of qi movement, causing deficiency and stagnation of the collaterals. After surgery, spleen and kidney deficiency is aggravated, the collaterals become deficient and depleted, and residual cancer toxin may remain, creating the potential for disease recurrence.

For the preoperative stage, treatment should focus on resolving phlegm and removing blood stasis, detoxifying and unblocking the collaterals, and searching out and eliminating pathogenic factors lodged in the collaterals. On the basis of fundamental TCM treatment for CRC, the effects of detoxification and collateral unblocking should be further strengthened, with modifications made according to individual symptoms. For example, Hedyotis diffusa (Baihuasheshecao) and Scutellaria barbata (Banzhilian) may be selected for their heat-clearing and detoxifying properties to eliminate cancer-related toxins. In addition, insect-derived medicinals, such as scorpion (Quanxie), earthworm (Dilong), stiff silkworm (Jiangcan), and centipede (Wugong), may be combined. Owing to their dispersing and penetrating properties, these medicinals can reach deep pathological sites, search out pathogenic toxins concealed in the collaterals, and eliminate accumulated pathogenic factors, thereby inhibiting tumor progression.

During the perioperative stage, treatment should primarily focus on replenishing qi and nourishing blood, strengthening the spleen and promoting bowel function, and warming and unblocking the nutritive collaterals. CRC is inherently a chronic consumptive disease. Prolonged invasion by cancer toxin results in deficiency of healthy qi, while surgical intervention further impairs gastrointestinal function, severely affecting the generation and circulation of qi and blood and exacerbating their depletion. Therefore, perioperative treatment should prioritize the replenishment of qi and blood and the warming and unblocking of the collaterals. By improving qi and blood deficiency, such treatment may mitigate the traumatic impact of surgery and establish a foundation for postoperative recovery.

Postoperative treatment should focus on strengthening the spleen and tonifying the kidneys, replenishing deficiency and harmonizing the collaterals, and eliminating residual toxins. Following surgery, surgical trauma and the adverse effects of postoperative chemotherapy may further aggravate spleen and kidney deficiency. Due to inadequate nourishment by qi and blood, the collaterals become deficient and depleted. Meanwhile, residual cancer toxins that have not been thoroughly eliminated may continue to consume healthy qi. When healthy qi is weak, it is unable to restrain pathogenic toxins effectively; consequently, residual cancer toxins may contribute to tumor recurrence or metastasis.

At this stage, the disease is characterized by a mixture of deficiency and excess. The deficiency aspect is primarily spleen and kidney deficiency, whereas the excess aspect includes pathogenic factors such as phlegm-turbidity, blood stasis, and residual cancer toxins concealed in the collaterals. Therefore, postoperative treatment should address both deficiency and excess. On the one hand, emphasis should be placed on strengthening the spleen and tonifying the kidneys, cultivating primordial qi, and consolidating the constitutional foundation, thereby improving overall bodily function and enhancing resistance to pathogenic factors. On the other hand, resolving phlegm, removing blood stasis, unblocking the collaterals, and eliminating toxins should also be emphasized. As stated in the Weisheng Baojian (Precious Mirror of Health), “When healthy qi is nourished, accumulations will resolve spontaneously,” highlighting the importance of strengthening healthy qi and consolidating the root.

5. Clinical Advantages and Existing Challenges

5.1 Clinical Advantages

1) Holistic regulation: Collateral disease theory emphasizes both strengthening healthy qi and eliminating pathogenic factors. It may inhibit tumor angiogenesis, regulate lipid metabolism in tumor cells, suppress tumor metastasis, alleviate tumor-associated pathological injury, enhance immune function, restore vitality, and improve the functional status of the zang-fu organs. These effects may positively contribute to improving the quality of life of patients with cancer. Moreover, based on TCM syndrome differentiation and stage-based treatment, individualized therapeutic regimens can be developed according to each patient’s specific condition, potentially improving therapeutic efficacy.

2) Multi-target intervention: Chinese herbal compound prescriptions may exert therapeutic effects through multiple pathways, including regulation of abnormal ECM metabolism and deposition, inhibition of angiogenesis, improvement of the tumor immune microenvironment, and modulation of the gut microbiota. Such multi-target interventions may influence the occurrence and progression of tumors.

3) Toxicity reduction and efficacy enhancement: TCM treatment may reduce gastrointestinal and hematological toxicities associated with chemotherapy, alleviate chemotherapy resistance, and decrease the incidence of adverse reactions such as myelosuppression and hepatotoxicity or nephrotoxicity.

5.2 Existing Challenges

1) Insufficient mechanistic research: The specific molecular mechanisms underlying the treatment of CRC with Chinese herbal medicines and prescriptions guided by collateral disease theory have not yet been fully elucidated. Further

refinement and in-depth investigation of collateral disease theory are still needed. Although existing studies have confirmed that certain Chinese herbal medicines exert definite effects in regulating the CRC tumor microenvironment, the specific active constituents responsible for these key regulatory effects remain unclear. This limitation considerably restricts the in-depth development and broader clinical application of Chinese herbal medicines. Future studies should deepen mechanistic research, further interpret collateral disease theory, and reveal its molecular basis in the occurrence and progression of CRC.

2) Lack of high-quality evidence-based medical evidence: There is a lack of high-quality evidence, particularly multicenter randomized controlled trials. Large-scale clinical trial data supporting the efficacy and safety of collateral disease-based treatment strategies for CRC are still insufficient.

3) Challenges in individualized treatment: A major challenge is how to develop individualized treatment regimens according to patients' genetic profiles, immunohistochemical characteristics, pathological classifications, and other clinical features. New strategies should be developed by integrating these modern medical indicators with collateral disease theory.

4) Lack of standardization: Insufficient standardization is a prominent issue in the field of TCM. The core of TCM treatment lies in developing individualized regimens based on patient-specific differences. Although this model fully reflects the unique advantages of personalized diagnosis and treatment, it also results in a lack of unified treatment standards, substantially increasing the complexity of efficacy evaluation and validation of Chinese herbal therapies. Therefore, standardized syndrome differentiation and classification criteria based on collateral disease theory should be established. An objective syndrome differentiation system may be developed by integrating tongue manifestations, pulse characteristics, immune biomarkers, pathological classifications, immunohistochemical findings, and other relevant indicators.

6. Summary and Prospects

In summary, the application of collateral disease theory in the treatment of CRC offers advantages including holistic regulation, individualized treatment, toxicity reduction, and efficacy enhancement. Collateral disease theory provides new therapeutic concepts and approaches for the clinical management of CRC. It may not only improve therapeutic outcomes and help prevent CRC recurrence and metastasis, but also alleviate the adverse effects of conventional therapies such as chemotherapy and improve patients' quality of life.

Nevertheless, its modernization and broader application still require overcoming challenges such as weak mechanistic evidence and insufficient clinical data. In the future, through the integration of advanced technologies, implementation of multicenter clinical studies, and collaborative innovation between TCM and Western medicine, collateral disease theory may open new avenues for precision treatment of CRC. Potential future research directions include investigating the effects of collateral disease-based treatment on CRC lipid metabolism. For example, lipid metabolism may be used as an entry point to examine the effects and underlying mechanisms of Yangzheng Xiaoji Capsules on lipid metabolism in CRC under the guidance of the theory of phlegm-blood stasis intermingling and collateral disease. Further exploration may also focus on novel acupuncture-based collateral-unblocking approaches. Acupoints such as Taichong (LR3), Qimen (LR14), and Baihui (GV20), which are considered to promote qi circulation and unblock the collaterals, as well as Xuehai (SP10), Hegu (LI4), and Zusanli (ST36), which promote qi circulation and activate blood circulation, may be selected. Based on collateral disease theory, acupuncture may regulate zang-fu organ function, alleviate post-chemotherapy myelosuppression, and enhance the effects of promoting qi circulation, activating blood circulation, removing blood stasis, and dispersing masses.

With further research and interpretation of collateral disease theory, together with the continued accumulation of clinical trial evidence, the prospects for applying collateral disease-based therapies to CRC will become increasingly broad. In the future, more collateral disease-based therapeutic approaches are expected to be developed and incorporated into the clinical management of CRC, providing greater benefits for patients. At the same time, interdisciplinary collaboration and academic exchange should be strengthened to continuously advance research and development on collateral disease-based treatment strategies for CRC.

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