

Traditional Chinese Medicinal Syndromes and Treatment in Colorectal Cancer

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ABSTRACT

Colorectal cancer remains the third most common malignancy worldwide. According to the principles of Traditional Chinese Medicine (TCM), colorectal cancer is related to spleen-deficiency, damp-heat, and toxicity accumulation. Traditional Chinese medicine has been confirmed to effectively reduce toxic side effects and enhance curative effects of chemotherapy, palliate clinical syndrome, prevent recurrence and metastasis, improve quality of life and immune function, and prolong survival time in colorectal cancer. However, TCM theoretical and syndrome differentiation study has lagged far behind due to progression of therapy model in colorectal cancer. As a type of drug treatment, there are some common biological basis between chemotherapy, targeted therapy and anti-cancer herb therapy in colorectal cancer, such as apoptosis, cell senescence and autophagy. There are growing needs to explore the effect mechanism and compatibility of anti-cancer herbs, to further enhance the efficacy of TCM treatment in colorectal cancer.

Keywords: Colorectal Cancer; Syndrome Differentiation; Traditional Chinese Medicinal Treatment; Anti-Cancer Herb

1. Introduction

Colorectal cancer remains the third most commonly diagnosed cancer in males and the second in females worldwide. The incidence of colorectal cancer is increasing due to smoking, lack physical activities, overweight and obesity, red and processed meat consumption, and excessive alcohol consumption [1]. The current treatment of colorectal cancer mainly depends on surgery, chemotherapy, radiotherapy and targeted therapy. In China, Traditional Chinese Medicine (TCM) plays an important role in the treatment of colorectal cancer. The description of colorectal cancer in TCM can be traced back to the era of Huang-Di's Canon of Internal Medicine (400 B.C.). From TCM perspective, the carcinogenesis of colorectal cancer is related to the Pi-Xu (spleen-Qi deficiency), Shi-Re (damp-heat) and Du-Ju (toxicity accumulation). Accumulated studies have showed that TCM may help to reduce the side effects and enhance the curative effects of chemotherapy, palliate clinical syndrome, prevent recurrence and metastasis, prolong survival time and improve the quality of life in colorectal cancer.

2. Syndrome Differentiation in Colorectal Cancer

TCM syndrome (ZHENG) is a kind of pathological

status that integrated the information of TCM pathogenesis and clinical manifestation. Syndrome is the basis of individualized TCM treatment (Syndrome Based Differential Treatment). The clinical manifestation of colorectal cancer is complex and different patients may present different TCM syndromes. Based on clinical epidemiology study, Wang *et al.* reported that the Shi-Re (damp-heat) is the most frequent observed syndrome in colorectal cancer, followed by Pi-Wei-Qi-Xu (spleen and stomach deficiency), Qi-Xue-LiangXu (both Qi and blood deficiency), and Gan-Shen-Yin-Xu (liver and kidney deficiency). Shi-Re (Damp-heat), the most common basic syndrome, always accompanied by other syndromes [2]. Lin *et al.* found that the descending order of appearance frequency of TCM syndromes in colorectal cancer is Pi-Xu (spleen deficiency), Qi-Xu (Qi deficiency), Yin-Xu (Yin deficiency), Xue-Xu (blood deficiency), Tan-Shi (phlegm dampness), Re-Du (heat-toxicity), Qi-Zhi (Qi stagnation), Yang-Xu (Yang deficiency) and Xue-Yu (blood stasis). In addition, the survival time of Yin-Xu (Yin deficiency) patients is shorter than that of non-Yin deficiency patients, and the survival time of simple Qi deficiency syndrome patients is longer than that of non-simple Qi deficiency syndrome patients. However, the survival time of pure spleen deficiency syndrome patients has no difference from that of non-pure spleen deficiency syndrome patients. Yin deficiency

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and simple Qi deficiency could be considered as predictors of colorectal cancer prognosis [3].

By analyzing literature published in the past decade, Zhao *et al.* found that the common syndromes in colorectal cancer, including Pi-Shen-Yang-Xu (spleen-kidney Yang deficiency), Shi-Re (damp-heat), Gan-Shen-Yin-Xu (liver-kidney Yin deficiency), Qi-Xue-Liang-Kui (Qi and blood deficiency), Yu-Du (stasis-toxin), Pi-Xu (spleen deficiency), Qi-Zhi-Xue-Yi (Qi stagnation and blood stasis) and Shi-Re-Yun-Du (damp-heat and accumulated toxin). Among them, spleen deficiency plays an important role in the pathogenesis of colorectal cancer [4]. By statistics relevant literatures about TCM syndromes of colorectal cancer in the past 30 years, Deng *et al.* found that among the deficiency syndromes of colorectal cancer, Pi-Shen-Yang-Xu (spleen-kidney Yang deficiency) and Qi-Xue-Liang-Xu (Qi-blood deficiency) are the most common syndromes. For sthenia syndromes, Shi-Re (damp-heat) and Yu-Du (stasis-toxin) are frequently observed. The top five syndromes are Pi-Shen-Yang-Xu (spleen-kidney Yang deficiency), Qi-Xue-Liang-Xu (Qi-blood deficiency), Gan-Shen-Yin-Xu (liver-kidney Yin deficiency), Shi-Re (damp-heat syndrome) and Yu-Du (stasis-toxin) [5].

In different stages of colorectal cancer, the syndromes may be different. Jia *et al.* reported that TCM syndromes of colorectal cancer mainly include Qi-Zhi-Xue-Yu (Qi stagnation and blood stasis), Gan-Shen-Yin-Xu (liver-kidney Yin deficiency), Shi-Du (damp-heat and toxicity accumulation), Qi-Xue-Liang-Xu (Qi and blood deficiency) and Pi-Shen-Yang-Xu (spleen-kidney Yang deficiency). Among them, Shi-Du (damp-heat and toxicity accumulation) is commonly observed in Dukes A and B stage, Qi-Xue-Liang-Xu (Qi and blood deficiency) is common in Dukes B stage, Qi-Zhi-Xue-Yu (Qi stagnation and blood stasis) and Gan-Shen-Yin-Xu (liver-kidney Yin deficiency) are frequently observed in Dukes C stages. Compared with other syndromes, Qi-Zhi-Xue-Yu (stagnation and blood stasis) and Gan-Shen-Yin-Xu (liver-kidney Yin deficiency) are relatively late than Shi-Du (damp-heat and toxicity accumulation) and Qi-Xue-Liang-Xu (Qi and blood deficiency) [6]. Zhao *et al.* showed that TCM syndromes of colorectal cancer in adjuvant therapy period includes Pi-Xu-Shi-Zu (spleen deficiency and retention of dampness), Qi-Xue-Liang-Xu (Qi-blood deficiency), Gan-Shen-Yin-Xu (liver-kidney Yin deficiency), Shi-Re (damp-heat) and Xue-Yu (blood stasis) [7].

Different treatments may influence the clinical syndromes of colorectal cancer. Wang *et al.* reported that the major syndrome of colorectal cancer before operation is Yu-Du (stasis-toxin). With the development of colorectal cancer, the proportion of Shi-Re (damp-heat) gradually increases and the deficiency syndrome gradually occurs.

The major syndrome of colorectal cancer after operation is mixed sthenia and asthenia syndrome, but in 3 months after operation, the principal syndrome is mainly sthenia syndrome. In the early stage, Shi-Re (damp-heat) is the most frequently observed sthenia syndrome. One week after operation, Yu-Du (stasis-toxin) gradually becomes the dominant syndrome. The accompanied syndrome in the early stage of post-operation is asthenia syndrome especially Qi deficiency, but decreases after one week [8]. In addition, chemotherapy can cause the deficiency of Zheng Qi (the vital energy) and asthenia syndromes increases after chemotherapy in colorectal cancer [9]. At the same time, syndromes are also related to the side effects of chemotherapy. Xu *et al.* found, in advanced colorectal cancer, severe side effects of chemotherapy frequently occurred in patients with Pi-Shen-Yang-Xu (spleen-kidney Yang deficiency) and Qi-Xue-Liang-Xu (Qi-blood deficiency) syndrome, and suggested that TCM treatment should give priority to strengthen healthy energy during chemotherapy in advanced colorectal cancer [10].

Although the result of different reports is not consistent with each other, but they all indicate that colorectal cancer is closely related to Pi-Xu (spleen deficiency), Shi-Re (heat-damp), and Du-Ju (toxicity accumulation). The syndrome differentiation of colorectal cancer still needs further studies in consideration of clinical manifestation, different disease and treatment stage, and clinical curative effect.

3. Clinical Study of TCM Treatment in Colorectal Cancer

Accumulated clinical studies showed that TCM is effective in colorectal cancer in certain respects, such as reducing side effects and enhancing curative effects of chemotherapy, ameliorating clinical syndromes, preventing recurrence and metastasis, improving quality of life and immune function, and prolonging survival time in colorectal cancer patients (**Table 1**).

In reducing side effects and enhancing curative effect of chemotherapy, Liu *et al.* showed that Pi-Shen Decoction may decrease the systemic reaction and digestive tract reaction caused by MFA regiment chemotherapy, and prolong survival time in patients with colorectal cancer [11]. Mok *et al.* indicated that TCM can significantly ameliorate chemotherapy caused nausea [12]. Through 3-year observation on 120 cases of metastatic colorectal cancer patients, Cao *et al.* found that the combined treatment of Yi-Qi-Zhu-Yu Decoction and FOLFOX-4 regiment can effectively prolong the overall survival time and decrease the side effects of chemotherapy [13]. The studies by Tao *et al.* showed that treatment based on TCM syndrome differentiation can extend the long-term

Table 1. Clinical study on TCM treatment in colorectal cancer.

Name	Herbs	Effects	Ref.
Pi-Shen Decoction	<i>Astragalus memranaceus</i> (Huang-Qi), <i>Codonopsis pilosula</i> (Dang-Shen), <i>Atractylodes macrocephala</i> Koidz. (Bai-Shu), etc.	Reduce the side effects of chemotherapy, prolong survival	[11]
CHM	<i>Scrophularia ningpoensis</i> Hemsf. (Xuan-Shen), <i>Plantago asiatica</i> L. (Che-Qian-Zi), <i>Lysimachia christinae</i> Hance (Jin-Qian-Cao), <i>Lygodium japonicum</i> (Thunb.) Sw. (Hai-Jin-Sha), <i>Kochia scoparia</i> (L.) Schrad. (Di-Fu-Zi), <i>Dianthus superbus</i> L. (Qu-Mai), <i>Areca catechu</i> L. (Da-Fu-Pi), <i>Aconitum carmichaeli</i> Debx. (Chuan-Wu), <i>Zingiber officinale</i> (Gan-Jiang), etc.	Alleviate chemotherapy induced nausea	[12]
Yi-Qi-Zhu-Yu Decoction	<i>Panax ginseng</i> (Ren-Shen), <i>Sophora flavescens</i> Ait. (Ku-Shen), <i>Ligusticum chuanxiong</i> (Chuan-Xiong), <i>Stephania tetrandra</i> (Fang-Ji), <i>Curcuma phaeocalis</i> Val. (Er-Shu), <i>Astragalus memranaceus</i> (Fisch.) Bge. (Huang-Qi), <i>Codonopsis pilosula</i> (Franch.) Nannf. (Dang-Shen), <i>Atractylodes lancea</i> (Cang-Shu), etc.	Reduce the side effects of chemotherapy, improve overall survival	[13]
TCM Syndrome Differential Treatment	<i>Panax ginseng</i> (Ren-Shen), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), <i>Citrus reticulata</i> Blanco (Chen-Pi), <i>Glycyrrhiza uralensis</i> (Gan-Cao), <i>Smilax China</i> L. (Ba-Qia), the roots of <i>Actinidia arguta</i> (Teng-Li-Gen), etc.	Improve the prognosis, reduce recurrence and metastasis, prolong disease-free survival	[14]
Jian-Pi-Jie-Du Decoction	<i>Astragalus memranaceus</i> (Huang-Qi), <i>Codonopsis pilosula</i> (Dang-Shen), Coix Seed (Yi-Yi-Ren), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), <i>Citrus reticulata</i> Blanco (Chen-Pi), <i>Aucklandia lappa</i> Decne. (Mu-Xiang), <i>Oldenlandia diffusa</i> (Bai-Hua-She-She-Cao), <i>Scutellaria barbata</i> (Ban-Zhi-Lian), <i>Taraxacum mongolicum</i> (Pu-Gong-Yin), <i>Cynanchum paniculatum</i> (Xu-Chang-Qin).	Improve quality of life	[15]
Jian-Pi-Yi-Qi Decoction	<i>Codonopsis pilosula</i> (Dang-Shen), <i>Astragalus memranaceus</i> (Huang-Qi), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), Coix Seed (Yi-Yi-Ren), <i>Amomum villosum</i> Lour. (Sha-Ren), <i>Pinellia ternate</i> (Ban-Xia), <i>Sparganium stoloniferum</i> (San-Leng), <i>Curcuma phaeocalis</i> Val. (Er-Shu).	Improve the quality of life, reduce the side effects of chemotherapy	[16]
Fu-Pi-Yi-Wei Decoction	<i>Dendrobium</i> (Shi-Hu), <i>Atractylodes lancea</i> (Cang-Shu), Coix Seed (Yi-Yi-Ren), <i>Pinellia ternate</i> (Ban-Xia), <i>Dioscorea opposita</i> Thunb. (Shan-Yao), <i>Poria cocos</i> (Fu-Ling), <i>Amomum compactum</i> Soland. Ex Maton (Dou-Kou), <i>Gynostemma pentaphyllum</i> (Jiao-Gu-Lan), <i>Paeonia lactiflora</i> (Bai-Shao), <i>Agastache rugosa</i> (Huo-Xiang).	Reduce the side effects of chemotherapy, improve quality of life and immune function of patients, increase the effective of chemotherapy	[17]
Jian-Pi-Xiao-Liu Decoction	<i>Astragalus memranaceus</i> (Huang-Qi), <i>Codonopsis pilosula</i> (Dang-Shen), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), Coix Seed (Yi-Yi-Ren), <i>Smilax China</i> L. (Ba-Qia), <i>Curcuma phaeocalis</i> Val. (Er-Shu), <i>Curcuma wenyujin</i> (Yu-Jin), <i>Smilax glabra</i> Roxb. (Tu-Fu-Ling), <i>Scolopendra</i> (Wu-Gong), <i>Arca subcrenata</i> Lischke (Wa-Leng-Zi), <i>Polygonatum sibiricum</i> (Huang-Jin), <i>Cornus officinalis</i> (Shan-Yu-Rou), <i>Epimedium brevicornum</i> (Xian-Lin-Pi), <i>Cuscuta chinensis</i> . (Tu-Si-Zi).	Reduce recurrence and metastasis	[18]
Fu-Zheng Capsule	<i>Panax ginseng</i> (Ren-Shen), <i>Poria cocos</i> (Fu-Ling), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Glycyrrhiza uralensis</i> (Gan-Cao), <i>Myristica fragrans</i> (Rou-Dou-Kou), <i>Citrus reticulata</i> Blanco (Chen-Pi), <i>Aucklandia lappa</i> Decne. (Mu-Xiang), <i>Hordeum vulgare</i> L. (Mai-Ya), <i>Gallus gallus domesticus</i> Brisson (Ji-Nei-Jin), etc.	Reduce recurrence and metastasis, improve the quality of life	[19]
Qu-Xie Capsule	<i>Croton tiglium</i> L. (Ba-Dou), <i>Evodia rutaecarpa</i> (Wu-Zhu-Yu), <i>Zingiber officinale</i> (Gan-Jiang), <i>Cinnamomum cassia</i> (Rou-Gui), <i>Aconitum carmichaeli</i> Debx. (Chuan-Wu), <i>Pinellia ternate</i> (Ban-Xia), <i>Citrus reticulata</i> Blanco (Chen-Pi), etc.	Reduce recurrence and metastasis, improve the quality of life	[19]
Si-Jun-Zi Decoction, Chai-Hu-Shu-Gan Decoction, Ba-Zhen Decoction	<i>Panax ginseng</i> (Ren-Shen), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), <i>Citrus reticulata</i> Blanco (Chen-Pi), <i>Glycyrrhiza uralensis</i> (Gan-Cao), <i>Bupleurum chinensis</i> (Chai-Hu), <i>Rehmannia glutinosa</i> . (Shu-Di), etc.	Decrease the relapse or metastasis rate	[20]

Continued

Yi-Qi -Jie-Du Decoction	<i>Codonopsis pilosula</i> (Dang-Shen), <i>Astragalus memranaceus</i> (Huang-Qi), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), <i>Glycyrrhiza uralensis</i> (Gan-Cao), <i>Citrus aurantium</i> L. (Zhi-Ke), <i>Citrus reticulata</i> Blanco (Chen-Pi), <i>Curcuma phaeocaulis</i> Val. (Er-Shu), <i>Oldenlandia diffusa</i> (Bai-Hua-She-She-Cao), <i>Scutellaria barbata</i> (Ban-Zhi-Lian), the roots of <i>Actinidia arguta</i> (Teng Li-Gen), <i>Sarcandra glabra</i> . (Zhong-Jie-Feng), <i>Angelica Sinensis</i> (Dang-Gui).	Control the progression of the disease, improve quality of life	[21]
Zhao's No. three Decoction	<i>Codonopsis pilosula</i> (Dang-Shen), <i>Polyporus umbellatus</i> (Zhu-Ling), Coix Seed (Yi-Yi-Ren), <i>Atractylodes macrocephala</i> (Bai-Shu), <i>Poria cocos</i> (Fu-Ling), <i>Pinellia ternate</i> (Ban-Xia), <i>Citrus reticulata</i> Blanco (Chen-Pi), the leaves of <i>Eriobotrya japonica</i> (Pi-Pa-Ye), etc.	Control the progression of the disease, improve quality of life and survival	[22]
Jian-Pi Decoction	<i>Poria cocos</i> (Fu-Ling), <i>Glycyrrhiza uralensis</i> (Gan-Cao), <i>Fritillaria thunbergii</i> Miq. (Zhe-Bei-Mu), <i>Platycodon grandiflorus</i> (Jie-Geng), Coix Seed (Yi-Yi-Ren), <i>Curcuma phaeocaulis</i> Val. (Er-Shu), <i>Ficus pumila</i> L. (Mu-Man-Tou).	Stable tumor focus, enhance immune function, improve quality of life	[23]
Ai-Di injection	<i>Panax ginseng</i> (Ren-Shen), <i>Astragalus memranaceus</i> . (Huang Qi), <i>Acanthopanax senticosus</i> (Ci-Wu-Jia), <i>Mylabris phalerata</i> Pallas (Ban-Mao), etc.	Enhance immune function, reduce the side effects of chemotherapy, improve quality of life and survival	[24-26]
Kang-Ai injection	<i>Astragalus memranaceus</i> (Fisch.) Bge. (Huang-Qi), <i>Panax ginseng</i> (Ren-Shen), Oxymatrine.	Improve quality of life, reduce the side effects of chemotherapy	[30]
Shen-Qi-Fu-Zheng injection	<i>Astragalus memranaceus</i> (Huang-Qi), <i>Codonopsis pilosula</i> (Dang-Shen).	Enhance immune function, improve quality of life and survival, reduce the side effects of chemotherapy, improve the efficacy of chemotherapy	[31,32]
Huai-Er Granule	<i>Huaier mycoplasm</i> .	Enhance immune function, reduce the side effects of chemotherapy, improve hematopoietic function	[33,34]
Kang-Lai-Te	Coix Seed (Yi-Yi-Ren) Extract.	Enhance immune function, improve quality of life, reduce the side effects of chemotherapy, improve the efficacy of chemotherapy	[35,36]
Astragalus injection	<i>Astragalus memranaceus</i> (Fisch.) Bge. (Huang-Qi).	Enhance immune function, improve the quality of life, reduce the side effects of chemotherapy	[37]

survival time in postoperative patients with colorectal cancer [14].

In improving quality of life, Huang *et al.* reported that the combined treatment of Jian-Qi-Jie-Du Decoction and FOLFOX-4 regimen can effectively improve clinical syndromes and quality of life in patients with colorectal cancer [15]. Liu *et al.* demonstrated that combined treatment with Jian-Pi-Yi-Qi herbs may improve quality of life and reduce the side effects of chemotherapy in patients with advanced colorectal cancer [16]. Wu *et al.* found that Fu-Pi-Yi-Wei Decoction can effectively improve quality of life and enhance immune function in postoperative patients with colorectal cancer [17].

In preventing recurrence and metastasis, Ma *et al.* showed that Jian-Pi-Xiao-Liu Decoction may effectively decrease the recurrence and metastasis of colorectal cancer [18]. Luo *et al.* found that Fu-Zheng Capsule and Qu-Xie Capsule have a better performance in the reduction of recurrence and metastasis, and improvement of

quality of life in the subsequent consolidation therapy in stage II and III colorectal cancer after radical resection [19]. In 222 elder patients with stage II and III colorectal cancer, Yang found that TCM treatment can greatly reduce the possibility of recurrence on the basis of conventional chemotherapy [20].

For advanced colorectal cancer treatment, Xiong *et al.* reported Yi-Qi-Qing-Du Decoction combined with Cinobufacini injection and sodium cantharidinate can improve quality of life and control tumor focus in advanced colorectal cancer [21]. You *et al.* found that Zhao's No. Three Decoction may alleviate clinical syndromes, improve quality of life, stabilize tumor focus, control cancer progression and prolong survival time in patients with advanced colorectal cancer [22]. Yin *et al.* showed that the combined treatment of spleen-strengthening herbs and chemotherapy has obvious effects on stabilizing tumor focus, improving quality of life and immune function in advanced colorectal cancer [23].

In addition to herb decoction therapy, Chinese patent drug also plays an important role in colorectal cancer treatment. The common Chinese patent drugs used in colorectal cancer include Ai-Di injection, Matrine injection, Kang-Ai injection, Shen-Qi-Fu-Zheng injection, Huai-Er granule, Kang-Lai-Te injection, Astragalus injection and others. These Chinese patent drugs have been proved to have a sound adjuvant therapeutic effect in the colorectal cancer.

Ai-Di injection can enhance the curative effect of chemotherapy, reduce side effects of chemotherapy to a certain extent, improve the quality of life and immune function, and extend survival time in colorectal cancer patients [24-26]. Matrine injection can reduce the side effects of chemotherapy, strengthen immune function and improve quality of life in colorectal cancer patients. In improving quality of life, Matrine injection has a better performance in colorectal cancer patients with Shi-Re (damp-heat) and Qi-Zhi-Xue-Yu (Qi stagnation and blood stasis) syndrome [27-29]. Kang-Ai injection may obviously improve quality of life and reduce the side effects of chemotherapy in patients with advanced colorectal cancer [30].

Shen-Qi-Fu-Zheng injection can reduce the toxic and side effects and improve the curative effect of chemotherapy, reduce the chemotherapy influence on the immune function, improve quality of life and prolong the survival time in colorectal cancer patients [31,32]. Huai-Er granule can reduce the toxicity of chemotherapy and improve hemopoietic function as well as the immune function in colorectal cancer patients [33,34]. Kang-Lai-Te combined with chemotherapy can improve the efficiency and reduce the side effect of chemotherapy, and improve quality of life and immune function in colorectal cancer patients [35,36]. Astragalus injection may relieve clinical syndromes, improve quality of life, and synergize with Interleukin-2 to improve immune function in post-operative colorectal cancer patients [37]. Astragalus polysaccharide can effectively reduce the incidence and decline degree of leukocytopenia caused by chemotherapy [38].

4. Therapeutic Mechanisms of TCM against Colorectal Cancer

Current pharmacotherapy, such as chemotherapy, targeted therapy act on cancer cells mainly through cell apoptosis, cell senescence and autophagy and other mechanisms [39-41].

Apoptosis has been recognized as major anti-cancer mechanism of pharmacotherapy. It has been confirmed that *Curcuma aromatica* and Cantharidin promoted apoptosis and G2/M cell cycle arrest in colorectal cancer cells, and related to caspases activation and cell cycle regulatory

protein [42,43]. *Spatholobus suberectus* promoted apoptosis and G2/M cell cycle arrest in colon cancer, and associated with DNA damage and Chk1/Chk2 phosphorylation [44]. *Houttuynia cordata* Thunb and *Hedyotis diffusa* Willd extract induced cell apoptosis in colon cancer cells [45,46]. Curcumin decreased colon cancer growth, associated with proteasome inhibition, proliferation suppression, and apoptosis induction in tumor tissues [47]. Other herbs or herbal components, such as *Melia toosendan* fruit, *Hedyotis diffusa* Willd, DYZ-2-90, and 4,7-Dimethoxy-5-Methyl-1,3-Benzodioxole also showed apoptosis inducing effects in colorectal cancer cells [48-51].

Autophagy, Type II programmed cell death, an evolutionarily conserved self-defense mechanism in which organelles and proteins are sequestered and subsequently degraded through fusion with lysosomes, has been recognized as a target for cancer treatment [41,52]. Bufalin, a component from *Venenum Bufonis*, induced autophagy-mediated cell death in human colon cancer cells through reactive oxygen species generation and JNK activation [53]. Triterpenes, an ingredient from *Ganoderma Lucidum*, may inhibit cell proliferation, cell cycle arrest in G0/G1 phase, and autophagy by downregulation of expression and phosphorylation of p38 MAPK, upregulation Beclin-1 and LC-3 expression in HT-29 colon cancer [54].

Cell senescence, a state of stable irreversible cell cycle arrest provoked by a variety of stimuli, also contributes to herbal therapeutic response [40,55,56]. We have demonstrated that Teng-Long-Bu-Zhong Decoction, a Chinese herb formula, may induce LS-174-T colon cancer cell senescence as indicated by typical large and flatten senescent morphology, positive senescence-associated β -galactosidase staining and G0/G1 phase cell cycle arrest, and associated with upregulation of p21 and p16 expression and downregulation RB phosphorylation [57].

In prevention cancer metastasis, Norcantharidin may downregulate MMP-9 expression by inhibiting Sp1 transcriptional activity in colorectal cancer CT26 cells [58]. Berberine can inhibit colon cancer cell migration via AMP-activated protein kinase-mediated downregulation of integrin β 1 signaling [59]. Dauricine inhibited cell invasion in colon cancer cells and related to NF- κ B signaling pathway [60]. Triptolide may inhibit colon cancer cells migration by downregulating VEGF, COX-2, thrombin receptor, CXCR4, TNF receptors, and TGF- β receptors [61].

Some herbs can also enhance therapeutic effects of chemotherapy or other therapy. In mismatch repair defect cells, He *et al.* found that Honokiol can enhance the anti-cancer effect of γ -irradiation treatment, activate caspase-3, promote cell apoptosis and may relevant to expression of cyclin A1 and D1 and increased phosphory-

lated p53 [62]. *Taiwanofungus camphoratus* (*Antrodia camphorata*) may enhance the cytotoxic effects of Amphotericin B [63]. Tetrandrine and Notoginseng may enhance anti-cancer effects of 5-Fu in colon cancer cells [64,65].

In prevention pathogenesis of colorectal cancer, adlay bran ethanol extract and residue may inhibit the number of crypt foci premalignant lesion, modify their mucin composition and present a dose-dependent manner [55]. *Cistanche deserticola* significantly reduced the number of mucosal hyperplasia in Tgfb1Rag2 null mice and correlated with significant stimulation of the immune system,

suggested the potential to prevent intestinal inflammation disorders including colorectal cancer [56]. Triptolide may inhibit the colitis-related carcinogenesis of colorectal cancer through downregulation of Rac1 and the JAK/STAT3 pathway [57].

Current studies suggested, besides conventionally improving clinical syndromes, anti-cancer effects of TCM against colorectal cancer and the conventional chemotherapy drugs share common biological basis (**Table 2**). Related explores will provide new insight into integrated treatment with TCM and western medicine for colorectal cancer.

Table 2. Effects and target of Chinese herb against colorectal cancer.

Herb/Compound	Effects	Molecular targets	Ref.
<i>Curcuma aromatica</i>	Apoptosis, G2/M arrest	Caspases, Cyclin B1, CDK1	[42]
Cantharidin	Apoptosis, G2/M arrest	Caspases, Cyclin A, Cyclin B, CDK1, CHK1, p21, Fas/CD95, Bax/Bcl-2	[43]
<i>Spatholobus suberectus</i>	Apoptosis, G2/M arrest	Chk1, Chk2	[44]
<i>Houttuynia cordata</i> Thunb	Apoptosis	Reactive oxygen species, Caspases, Bax/Bcl-2	[45]
<i>Hedyotis diffusa</i> Willd	Apoptosis	Caspases, Bax/Bcl-2	[46]
Curcumin	Apoptosis	Proteasome	[47]
<i>Melia toosendan</i> fruit	Apoptosis	Caspase-9, Caspase-3	[48]
<i>Hedyotis diffusa</i> Willd	Apoptosis	STAT3, Cyclin D1, CDK4 and Bcl-2/Bax, p21	[49]
DYZ-2-90	Apoptosis	ERK, JNK	[50]
4,7-Dimethoxy-5-Methyl-1,3-Benzodioxole	Anchorage-independent proliferation, G0/G1 arrest, apoptosis	p53, p21/Cip1, p27/Kip1, cyclins D1, D3 and A	[51]
Bufalin	Autophagy	Reactive oxygen species, JNK, ATG5, Beclin-1	[53]
Triterpenes	G0/G1 arrest, apoptosis, autophagy	p38 MAPK	[54]
TLBZD formula	Cell senescence	p16, p21, RB	[57]
Norcantharidin	Metastasis	MMP-9, Sp1, NF- κ B, STAT1	[58]
Berberine	cell migration	AMP-activated protein kinase, integrin β 1	[59]
Dauricine	apoptosis, inhibits proliferation and invasion	NF- κ B	[60]
Triptolide	Proliferation and migration	c-myc, and A, B, C, and D-type cyclins, VEGF, COX-2, thrombin receptor, CXCR4, TNF receptors, and TGF- β receptors	[61]
Honokiol	Radiosensitizes, Apoptosis	Caspase 3, Bax/Bcl2, p53, Cyclin A1 and D1	[62]
<i>Taiwanofungus camphoratus</i>	Apoptosis, enhances cytotoxic effects of amphotericin B		[63]
Tetrandrine	Apoptosis, synergize 5-Fu	β -catenin	[64]
Notoginseng	Enhances anti-cancer effect of 5-Fu, Apoptosis		[65]
Adlay bran	Carcinogenesis		[66]
<i>Cistanche deserticola</i>	Carcinogenesis	Splenic macrophage and natural killer cells, Nitric oxide synthase II	[67]
Triptolide	Carcinogenesis, proliferation, migration, colony formation, G0/G1 arrest	IL6, JAK1, IL6R, STAT3, Rac1, cyclin D1, CDK4	[68]

5. Conclusion

TCM has certain advantages in aspects of reducing side effects and enhancing the curative effects of chemotherapy, palliating clinical syndrome, preventing recurrence and metastasis, improving quality of life and immune function, and prolonging survival time in colorectal cancer. However, with the progress of colorectal cancer treatment mode, TCM theories and studies on typing of syndrome differentiation are obviously lagging behind. TCM study on colorectal cancer should fit with the actual clinical practice to give full play to TCM advantages so as to improve clinical curative effects. Anti-cancer herb studies on colorectal cancer indicate that anti-cancer effects of TCM and chemotherapy, targeted therapy and other drug treatments share common biological basis, such as cell apoptosis, cell senescence and autophagy, etc. Current studies still cannot reveal the TCM property of anti-cancer herbs. We need to further study the action basis and compatibility of anti-cancer herbs so as to improve the curative effect of TCM treatment for colorectal cancer.

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