

Clinical Experience

Patients with Metastatic Colorectal Cancer after Failure of Second-Line Treatment May Benefit from Low-Dose Apatinib and S-1 Combined with Jianpi Bushen Jiedu Decoction*

CHEN Yue¹, XU Yu-ying², JIANG Hai-jun³, WANG Lei², ZHAI Jia-wei¹, ZHANG Tong², and YANG Yu-fei²

ABSTRACT **Objective:** To evaluate the effect and safety of low-dose of apatinib and S-1 combined with Jianpi Bushen Jiedu Decoction (JBJD) in patients with metastatic colorectal cancer (mCRC) who have failed second or above lines treatment, in order to provide more treatment option for mCRC patients by integrated medicine. **Methods:** Thirteen patients were selected from a single-arm, open-label clinical study from April 2019 to September 2020. The patients were treated with low-dose apatinib (250 mg, once a day) and S-1 (20 mg, twice a day) combined with JBJD for at least one cycle and were followed up to August 2021. The primary endpoint was disease progression-free survival (PFS). Disease control rate (DCR), objective response rate (ORR), and overall survival (OS) of patients were observed as the secondary endpoints. Adverse events were recorded as well. **Results:** The average age of the 13 patients was 56.5 ± 13.0 years and 76.9% were male. The median PFS and median OS were 4.6 and 8.3 months, respectively. The ORR was 7.7% (1/13) while the DCR was 61.5% (8/13). The common adverse events were hypertension, proteinuria, elevated transaminase, and thrombocytopenia. One patient experienced thrombocytopenia of grade 3. **Conclusions:** Patients with mCRC after failure of the second or above lines of treatment may potentially benefit from the treatment of low-dose apatinib and S-1 combined with JBJD because of its similar effect as the standard dose of target therapy and relatively better safety. (Registration No. ChiCTR1900022673)

KEYWORDS metastatic colorectal cancer, apatinib, S-1, Jianpi Bushen Jiedu Decoction, Chinese medicine, progression-free survival, clinical trial

Colorectal cancer is one of the most common types of gastrointestinal tumors, accounting for about 10% of the total number of new cancer cases and cancer-related deaths worldwide.⁽¹⁾ In China, the incidence of colorectal cancer has increased in recent years, 28.2 per 100,000, ranking the third highest incidence among all kinds of cancer, while the mortality rate is 13.62 per 100,000, ranking the fifth.⁽²⁻⁴⁾ The symptoms of colorectal cancer are insidious and difficult to be diagnosed early.^(5,6) About 25% of colorectal cancer patients have metastases when diagnosed,⁽⁷⁾ and more than 50% of patients will eventually develop metastatic colorectal cancer (mCRC).⁽⁸⁾

Most patients with mCRC cannot be cured, and the main purpose of treatment is to improve their quality of life and prolong survival time to some extent. By far, regorafenib, fruquintinib, and trifluridine-tipiracil are recommended as the third-line treatment for patients with mCRC refractory to standard first- and second-line therapy. However, there is no definitive therapeutic

regimen in patients who failed third-line treatment. In daily clinical practice, it was found that some mCRC patients cannot receive standard targeted drugs or combined with chemotherapeutics drugs. Recently, several studies have shown that apatinib either alone or in combination with chemotherapy has good efficacy and safety for mCRC.⁽⁹⁻¹¹⁾ Among them, the combination of apatinib and S-1 has a good application prospect.^(12,13) However, these trials enrolled patients with good

©The Chinese Journal of Integrated Traditional and Western Medicine Press and Springer-Verlag GmbH Germany, part of Springer Nature 2022

*Supported by National Administration of Traditional Chinese Medicine: Qihuang Scholar (No. 02045004) and Collaborative Pilot Project of Clinical Traditional Chinese and Western Medicine for Major and Difficult Diseases in 2019 (No. 070030003)

1. Graduate School, Beijing University of Chinese Medicine, Beijing (100029), China; 2. Department of Oncology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing (100091), China; 3. Department of Oncology, Central Hospital of Ankang City, Ankang, Shaanxi Province (725000), China

Correspondence to: Prof. YANG Yu-fei, E-mail: yuf93@vip.sina.com

DOI: <https://doi.org/10.1007/s11655-022-3676-7>

performance status only and the incidence of adverse events (AEs) remained high. How to reduce the risk of that AE occurring without compromising clinical effectiveness? A number of studies have shown that Chinese medicine (CM) has unique advantages in the treatment of mCRC, such as relieving clinical symptoms, improving quality of life, and prolonging survival of patients.⁽¹⁴⁻¹⁶⁾ Prof. YANG Yu-fei has focused on CM treatment in patients with mCRC for many years. Prof. Yang put forward the concept of Jianpi Bushen Jiedu [invigorating Pi (Spleen), tonifying Shen (Kidney), and detoxifying] treatment for mCRC, which has been proven to have good clinical effects.⁽¹⁷⁾ In light of this, the treatment that low-dose apatinib (250 mg, once a day) and S-1 (20 mg, twice a day) combined with Jianpi Bushen Jiedu Decoction (健脾补肾解毒方, JBJD) was proposed for patients with mCRC who have failed in the second or above lines of treatment and were unwilling or intolerant to the standard treatment. This prospective interventional study in patients with mCRC aimed to confirm the efficacy and safety of JBJD combined with apatinib and S-1.

METHODS

Inclusion Criteria

The inclusion criteria were as follows: (1) patients were ≥ 18 and ≤ 80 years of age, either gender; (2) all were histologically diagnosed and staged as clinically metastatic (stage IV) CRC;⁽¹⁸⁾ (3) previous administration of first- and second-line treatment for mCRC (patients who received prior two or more chemotherapy regimens with or without targeted therapy were eligible); (4) all treated patients were either ineligible for or had refused conventional therapy that are recommended by the National Comprehensive Cancer Network (NCCN)⁽¹⁹⁾ and the Chinese Society of Clinical Oncology (CSCO) guidelines,⁽²⁰⁾ such as surgery, chemotherapy and radiotherapy; (5) Eastern Cooperative Oncology Group Performance Status (ECOG) of 0–2; (6) life expectancy of at least 3 months; (7) measurable lesions based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (8) adequate heart, lung, liver and renal functions; (9) adequate coagulation function and no history of abnormal bleeding, thrombosis, or active inflammatory disease; (10) the investigator considered the patients would be benefited clinically.

Exclusion Criteria

Patients with any of the following conditions

were excluded: (1) presence of other cancers; (2) uncontrollable hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, even when taking oral antihypertensives); (3) patients with uncontrolled or symptomatic cardiovascular diseases; (4) any factors affecting absorption of oral medications, such as unable to take oral medication and intestinal obstruction; (5) patients experienced major surgical procedure, open biopsy or significant traumatic injury within 28 days.

Patients

Patients were selected from a prospective, open, one-arm clinical study, which was carried out in the Department of Oncology, Xiyuan Hospital, China Academy of Chinese Medical Sciences from April 2019 to August 2021. This study has been approved by the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (No. 2019XLA011-2) and registered at the Chinese Clinical Trial Registry (No. ChiCTR1900022673). The patients were enrolled consecutively and all patients provided signed informed consent before enrollment in the study.

Intervention

JBJD is composed of *Radix pseudostellariae* 30 g, *Atractylodes macrocephalae* Rhizoma 10 g, *Poria cocos* 10 g, *Radix glycyrrhizae* 6 g, *Ligustrum lucidum* Ait 10 g, *Eclipta prostrata* L. 10 g, *Gastrodia elata* Blume 10 g, *Uncaria rhynchophylla* (Miq.) Jacks. 10 g, *Hedyotis diffusa* Willd 15 g, and *Rhizoma Smilacis glabrae* 15 g. JBJD were manufactured by the Department of Pharmaceutics of Xiyuan Hospital, China Academy of Chinese Medical Sciences. The decoction was administered orally twice daily, in the morning and evening after meal. All eligible patients were also scheduled to receive oral treatment of apatinib, 250 mg, once a day and S-1, 20 mg, twice a day (both from Jiangsu HengRui Medicine Co., Ltd., China). Interruption happened until objective disease progression, intolerable toxicity, or occurrence of another discontinuation criterion.

Outcome Assessments

Objective response criteria of the tumors, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated according to the RECIST version 1.1 criteria. The primary endpoint was progression-free survival (PFS). Disease control rate (DCR), objective

response rate (ORR), and overall survival (OS) of patients were observed as the secondary endpoints. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade treatment-emergent AEs. AEs were recorded from enrollment to 30 days following the end of therapy.

Statistical Analysis

Data entry was double entered by members of the study team, and the data entered were then reconciled. Descriptive statistics were used to summarize the clinical characteristics of the patients. The OS and PFS were reported as medians and 2-sided 95% confidence intervals (CI), which were estimated using the Kaplan-Meier method. The proportions of patients with CR, PR, SD and PD were calculated. The ORR was calculated as CR + PR, while DCR as CR+PR+SD. GraphPad Prism software (version 7, LaJolla, CA) and SPSS version 20.0 (IBM Corp., Armonk, USA) were used for the statistical analysis. *P*<0.05 was considered statistical significance.

RESULTS

Patients' Characteristics

From April 2019 to September 2020, a total of 150 patients were screened and 13 patients were enrolled in the study (Appendix 1). All patients received at least one cycle of JBJD combined with low-dose apatinib and S-1 and were followed up to August 30th, 2021. The demographic and clinical characteristics of the patients are shown in Table 1.

Treatment Administration

The profile of treatment administration and dose modification is shown in Appendix 2. All patients were treated with JBJD combined with low-dose apatinib and S-1. Among them, one patient discontinued all medications due to the pandemic of COVID-19. One patient suspended all medications due to external infections and received treatment again after 6 days. And the other patient due to personal reasons discontinued apatinib and S-1 and received treatment again after 1 month. The rest were due to side effects. Overall, the median time of treatment was 4.6 months.

Efficacy

Among the 13 available patients, only 1 (7.7%) achieved PR. The tumor responses of the 13 patients are shown in Figure 1. The patients who achieved SD and PD were 7 (53.8%) and 5 (38.5%), respectively, with an

Table 1. Baseline Characteristics of Patients with Metastatic Colorectal Cancer (13 cases)

Characteristic	Case (%)	Characteristic	Case (%)
Age (Year)		KRAS status	
$\bar{x} \pm s$	56.5 ± 13.0	Wild	6 (46.2)
Range	35–78	Mutated	7 (53.8)
Sex		NRAS status	
Male	10 (76.9)	Wild	12 (92.3)
Female	3 (23.1)	Mutated	1 (7.7)
ECOG PS		BRAF status	
0	2 (15.4)	Wild	12 (92.3)
1	9 (69.2)	Mutated	1 (7.7)
2	2 (15.4)	Monoclonal antibodies	
Metastatic site		Bevacizumab*	11 (84.6)
Liver	6 (46.2)	Cetuximab	6 (46.2)
Lung	8 (61.5)	Regofinil	3 (23.1)
Lymph node	1 (7.7)	PD-1/PD-L1	3 (23.1)
Pelvic	2 (15.4)	Others	4 (30.8)
Brain	1 (7.7)	Treatment state	
Bone	1 (7.7)	3rd-line	8 (61.5)
Others	2 (15.4)	4th-line and above	5 (38.5)

Notes: ECOG PS: Eastern Cooperative Oncology Group Performance Status performance score; *2 patients refused to undergo bevacizumab for financial reasons

ORR of 7.7% (95% CI, 0%–24.5%) and DCR of 61.5% (95% CI, 30.9%–92.1%). The median PFS and median OS were 4.6 and 8.3 months, respectively (Figure 2).

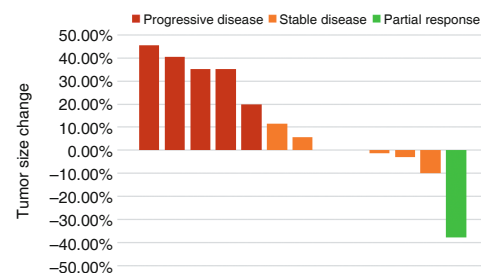


Figure 1. Waterfall Plot for Tumor Size Changes from Baseline of mCRC Patients after Treatment of Low-Dose Apatinib and S-1 Combined with JBJD

Notes: mCRC: metastatic colorectal cancer; JBJD: Jianpi Bushen Jiedu Decoction; the same below

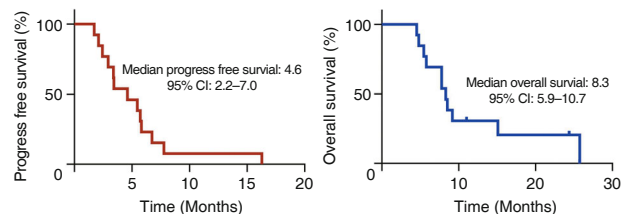


Figure 2. Kaplan-Meier Curves of Progression-Free and Overall Survivals of mCRC Patients after Treatment of Low-Dose Apatinib and S-1 Combined with JBJD

AEs

The incidence of AEs is summarized in Table 2. There were no treatment-related deaths. The most common AEs were hypertension with an incidence of more than 60% (8 cases), followed by proteinuria, elevated transaminase, and thrombocytopenia, with incidences of 38.5%, 30.8%, and 30.8%, respectively. Only 1 patient experienced thrombocytopenia of grade 3. The most common causes for dose reduction were thrombocytopenia, neutropenia, and proteinuria.

Table 2. Adverse Events of mCRC Patients after Treatment of Low-Dose Apatinib and S-1 Combined with JBJD

Adverse events	Any grade	Grade 3 or 4
Nonhematologic		
Hand-foot syndrome	1 (7.7)	0
Hypertension	8 (61.5)	0
Proteinuria	5 (38.5)	0
Elevated transaminase	4 (30.8)	0
Fatigue	3 (23.1)	0
Bleeding	2 (15.4)	0
Diarrhea	2 (15.4)	0
Hematologic		
Leukopenia	1 (7.7)	0
Thrombocytopenia	4 (30.8)	1 (7.7)

DISCUSSION

In China, regorafenib, fruquintinib, and trifluridine-tipiracil were approved for patients with mCRC in the third-line setting, which showed that the median PFS of patients with mCRC treated by third-line and above was only 2.0–3.7 months, and the median OS was 7.8–9.0 months.^(21,22) The results of the ALTER0703 trial recently published showed that the median PFS of patients with mCRC treated with anlotinib was 4.1 months, but it has not been approved for third-line treatment of mCRC.^(23,24) Meanwhile, some patients cannot receive standard treatment for various reasons, such as intolerable side effects, poor physical condition, and old age. In all, the efficacy of later-line treatment of mCRC patients still faces big challenges. Thus, our study fully respected for the patients' willingness and took the advantages of CM. Patients who had failed second-line treatment and were either ineligible for or had refused the standard treatments were enrolled. Our study adopted a treatment model of integrated Chinese and Western medicine to provide mCRC patients with a treatment option of CM combined with low-dose antiangiogenic drugs and chemotherapeutic drugs.

Apatinib is a new type of tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor 2. Clinical studies showed that the median PFS and OS of mCRC who failed the second-line treatment treated with apatinib 500 mg were 4.8 and 9.1 months, respectively. The common grade 3–4 AEs were hypertension (12.5%), hand-foot syndrome (10.4%), thrombocytopenia (10.4%) and proteinuria (8.3%).^(25,26) Among 167 patients with refractory mCRC treated with apatinib and S-1, thrombocytopenia (37.93%), leukopenia (27.59%) and elevated transaminase (27.59%) were the most frequent severe AE according to Li, et al⁽¹²⁾ and a total of 10 cases with grade 3 AEs were reported as well.⁽¹²⁾ Dai, et al⁽¹³⁾ retrospectively analyzed patients of mCRC treated with apatinib and S-1. The median PFS and median OS were 3.93 and 7.77 months, respectively. The major AEs and the incidences were fatigue (52.3%), hypertension (45.0%), hand-foot syndrome (22.7%), leukopenia (15.9%), neutropenia (15.9%), thrombocytopenia (22.7%), elevated transaminase levels (13.6%), and diarrhea (15.9%).

JBJD is a prescription for strengthening the body resistance to eliminate pathogenic factors. In this prescription, *Radix pseudostellaria*, *Atractylodis macrocephalae Rhizoma*, *Poria cocos*, *Radix glycyrrhizae* can invigorate Pi and replenish qi. They were useful for treating hypofunction of Pi, a symptom that is partially equivalent to that of gastrointestinal motility disorders, such as fatigue, diarrhea, and nausea.^(27,28) *Ligustrum lucidum* Ait, *Eclipta prostrata* L. can nourish Gan and Shen, which have an impact on promoting hematopoiesis, and prevents myelosuppression in patients treated with chemotherapy and targeted therapy.⁽²⁹⁾ *Gastrodia elata* Blume and *Uncaria rhynchophylla* (Miq.) Jacks. can calm Gan and suppress yang, and experimental studies show that they have blood pressure-lowering activity.⁽³⁰⁻³²⁾ *Hedyotis diffusa* Willd and *Rhizoma smilacis glabrae* could enhance host anti-tumor immunity and anti-tumor effects.^(33,34)

The results of this study showed that the combination of JBJD with low-dose apatinib and S-1 had comparable efficacy with better tolerability in mCRC patients after second-line treatment. However, patients enrolled in this study demonstrated worse ECOG-PS and fewer AEs of grade 3 and 4. On the basis of symptomatic treatment, drug reduction, or short-term withdrawal, most of the AEs would be tolerated, predictable, controllable, and reversible. Therefore, the combination of JBJD with

apatinib and S-1 might be safe and effective for mCRC patients in the third-line or higher setting. Patients with mCRC who are elderly, poor in physical and economic conditions, or unable to tolerate conventional therapy are likely to benefit from the treatment. However, this study was an open-label, single-arm clinical trial. The limitation of our study included the small sample size without a control group, the efficacy was lack of comparison, and the description of clinical characteristics is statistically weak. Because of the epidemic of COVID-19, it was difficult to enroll as many participants as originally planned, although we had already extended the enrollment period. Thus, the duration of the study reported in this article was longer than that in the trial registration and the protocol, and the sample was smaller. And it was also a significant reason for treatment interruption. Therefore, further prospective randomized controlled clinical trials are urgently needed to verify the efficacy and safety of this treatment.

The treatment of integrated Chinese and Western medicine in this study was not simply CM plus Western medicine. It is a treatment for the patient who is unable or unwilling to receive conventional Western medicine and difficult to benefit from pure CM treatment. On the basis of understanding the principles and programs of Western medicine, medicinal properties and drugs were used as sharp tools for removing pathogens in CM and increasing the treatment efficacy. This treatment in this study has many strengths. Firstly, all drugs were taken orally, and patients did not need to be hospitalized. They could be treated in outpatient clinics, which was convenient for patients and relieved hospitalization pressure. Secondly, the dosage of drugs can be adjusted flexibly, and can be increased or decreased in time according to the patient's responses, side effects, clinical symptoms, etc. moreover, the risk of AEs was low. The control of side effects can significantly extension of the frontiers of the treatment, thereby enhancing the efficacy of mCRC patients. It is hoped that this study could provide new horizons for the clinical trials of integrated Chinese and Western medicine in treating mCRC, so as to explore a way of integrated treatment suitable for mCRC patients.

In conclusion, this clinical trial demonstrated that the combination of JBJD with low-dose apatinib and S-1 may have similar efficacy and comparably better safety profile for use after failure of the second line for patients with mCRC, especially for patients who were at advanced age, poor in physical and economic conditions, or unable to tolerate conventional therapy. Our study was a single-

center open-label, single-arm clinical trial with small number of patients and more prospective randomized controlled clinical trials are urgently needed.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Author Contributions

Chen Y wrote the manuscript and was involved in the extraction of data, the statistical analysis of data and the follow-up of the patients. This project was initiated and developed by Yang YF, Xu YY and Jiang HJ. Yang YF was involved in the design of the study and manuscript revision and review. Xu YY and Jiang HJ were involved in the design of the study, literature research and the follow-up of the patients. Wang L was responsible for the follow-up of the patients. Zhai JW was responsible for the follow-up of the patients and data checking. Zhang T was involved in manuscript revision and review. All authors read and approved the final manuscripts.

Electronic Supplementary Material: Supplementary material (Appendices 1–2) is available in the online version of this article at <https://doi.org/10.1007/s11655-022-3676-7>.

REFERENCES

1. Dekker E, Tanis PJ, Vleugels J, Kasi P, Wallace M. Colorectal cancer. *Lancet* 2019;394:1467-1480.
2. Zheng R, Sun K, Zhang S, Zeng H, Zou X, Chen R, et al. Report of cancer epidemiology in China, 2015. *China J Oncol (Chin)* 2019;41:19-28.
3. Feng R, Zong Y, Cao S, Xu R. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? *Cancer Commun* 2019;39:12-22.
4. Chen H, Zheng R, Wang L, Lv Z, Du L, Wei W, et al. Progress in cancer epidemiology research in China in 2019. *Chin J Dis Control Prev (Chin)* 2020;24:373-379.
5. Chen WQ, Li N, Lan P, Chen HD, Du LB, Sun F, et al. Expert consensus on national early diagnosis and early treatment of colorectal cancer. *Nat Med J China (Chin)* 2020;100:1691-1698.
6. Brouwer NPM, van der Kruijssen DEW, Hugen N, de Hingh IHJT, Nagtegaal ID, Verhoeven RHA, et al. The impact of primary tumor location in synchronous metastatic colorectal cancer: differences in metastatic sites and survival. *Ann Surg Oncol* 2020;27:1580-1588.
7. Cheng L, Eng C, Nieman LZ, Kapadia AS, Du XL. Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. *Am J Clin Oncol* 2011;34:573-580.
8. Shao C, Zuo Q, Lin J, Yu RJ, Fu Y, Xiao M, et al. Effect of Chinese herbal medicine on the survival of colorectal cancer

- patients with liver-limited metastases: a retrospective cohort study, 2008 to 2017. *Integr Cancer Ther* 2019;18:1871102119.
9. Li NN, Zhou JF, Zhao L, Ying HY, Jia N. Efficacy and safety of apatinib in treating advanced colorectal cancer. *Acta Acad Med Sin (Chin)* 2019;41:170-174.
 10. Bao JM, Gao YM, Qiu HL, Zhou XM. Clinical trial of apatinib mesylate tablets combined with capecitabine tablets and oxaliplatin injection in the treatment of advanced colorectal cancer. *Chin J Clin Pharm (Chin)* 2019;35:1565-1567.
 11. Gu JY, Ye JH, Zhao Q, Zhang ZW. Apatinib combined with chemotherapy for advanced colon cancer: one case report and literature review. *J Modern Oncol (Chin)* 2020;28:3596-3599.
 12. Li N, Deng W, Zhang G, Du Y, Guo Y, Ma Y, et al. Low-dose apatinib combined with S-1 in refractory metastatic colorectal cancer: a phase 2, multicenter, single-arm, prospective study. *Front Oncol* 2021;11:728854.
 13. Dai YH, Sun L, Huang TT, Qiu H. Clinical analysis of third-line combination therapy with S-1 plus apatinib for advanced colorectal cancer. *Chin J Clin Oncol (Chin)* 2019;46:945-948.
 14. Zhang T, Yang YF, He B, Yi DH, Hao J, Zhang D. Efficacy and safety of Quxie Capsule in metastatic colorectal cancer: a double-blind randomized placebo controlled trial. *Chin J Integr Med* 2018;24:171-177.
 15. Zhang T, He WT, Zi MJ, Song G, Yi DH, Yang YF. Cohort study on prognosis of patients with metastatic colorectal cancer treated with integrated Chinese and Western medicine. *Chin J Integr Med* 2018;24:573-578.
 16. Miao WR, Liu NN, Zhu HR, Li Q. Traditional Chinese medicine combined with chemotherapy in treatment of advanced colorectal cancer: a systematic review. *Chin Arch Tradit Chin Med (Chin)* 2018;36:1119-1124.
 17. Jiang HJ, He B, Zhang T, Yang YF. Yang Yufei's experience in the treatment of advanced colorectal cancer. *Guid J Tradit Chin Med Pharm (Chin)* 2020;26:187-189.
 18. Hospital Administration, National Health Commission of the People's Republic of China; Oncology Branch of Chinese Medical Association. Chinese protocol of diagnosis and treatment of colorectal cancer (2017 ed). *Chin J Pract Surg (Chin)* 2018;38:1089-1103.
 19. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, et al. Colon cancer, Version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2021;19:329-359
 20. Dong CX, Ding YW, Weng SS, Li CC, Huang YQ, Hu HG, et al. Update in version 2021 of CSCO guidelines for colorectal cancer from version 2020. *Chin J Cancer Res (Chin)* 2021;33:302-307.
 21. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015;16:619-629.
 22. Li J, Qin S, Xu RH, Shen L, Xu J, Bai Y, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial. *JAMA* 2018;319:2486-2496.
 23. Chi Y, Shu Y, Ba Y, Bai Y, Qin B, Wang X, et al. Anlotinib monotherapy for refractory metastatic colorectal cancer: a double-blinded, placebo-controlled, randomized phase III trial (ALTER0703). *Oncologist* 2021;26:e1693-e1703.
 24. Cheng Y, Du FC, Fang FQ, Duan ZJ, Lei W, Shi KG. Third-line treatment for metastatic colorectal cancer: anlotinib is superior to chemotherapy and similar to fruquintinib or regorafenib. *Neoplasma* 2020;67:1384-1390.
 25. Wang F, Yuan X, Jia J, Bi X, Zhou Z, Zhou Q, et al. Apatinib monotherapy for chemotherapy-refractory metastatic colorectal cancer: a multi-centre, single-arm, prospective study. *Sci Rep* 2020;10:6058.
 26. Chen X, Qiu T, Zhu Y, Sun J, Li P, Wang B, et al. A single-arm, phase II study of apatinib in refractory metastatic colorectal cancer. *Oncologist* 2019;24:407-883.
 27. Dai LL, Chen DM, Zhou SM, Zhao N, Si WT, Cao Y, et al. Two-stage three-step method" assists in the prevention and treatment of adverse reactions of colorectal cancer chemotherapy. *J Tradit Chin Med (Chin)* 2019;60:982-985.
 28. Xu L, Huang SP. Effect of the ginsenoside Rb1 on the spontaneous contraction of intestinal smooth muscle in mice. *World J Gastroenterol* 2012;18:5462-5469.
 29. Li X, Lu X, Fan D, Li L, Lu C, Tan Y, et al. Synergistic effects of Erzhi Pill combined with methotrexate on osteoblasts mediated via the Wnt1/LRP5/ β -catenin signaling pathway in collagen-induced arthritis rats. *Front Pharmacol* 2020;11:228.
 30. Gao J, Wang T, Wang C, Wang S, Wang W, Ma D, et al. Effects of Tianshu Capsule on spontaneously hypertensive rats as revealed by $^1\text{H-NMR}$ -based metabolic profiling. *Front Pharmacol* 2019;10:989.
 31. Tian Z, Zhang S, Wang H, Wang S, Wang W, Ma D, et al. Intervention of uncaria and its components on liver lipid metabolism in spontaneously hypertensive rats. *Front Pharmacol* 2020;11:910.
 32. Pei Y, Wang R, Zhou H. Network pharmacology mechanism in treating hypertension with apocynum venetum. *Central South Pharm (Chin)* 2019;17:1997-2001.
 33. Pu F, Chen F, Lin S, Chen S, Zhang Z, Wang B, et al. The synergistic anticancer effect of cisplatin combined with *Oldenlandia diffusa* in osteosarcoma MG-63 cell line *in vitro*. *OncoTargets Ther* 2016;9:255-263.
 34. Wu Y, Xu J, Liu Y, Zeng Y, Wu G. A review on anti-tumor mechanisms of coumarins. *Front Oncol* 2020;10:592853.