

## Therapeutic targets of Traditional Chinese Medicine for colorectal cancer

Li Weidong, Li Chunsheng, Zheng Honggang, Chen Guohong, Hua Baojin

**Li Weidong, Zheng Honggang, Hua Baojin**, Oncology Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

**Li Chunsheng**, Nephrology department, Taizhou Central Hospital, Taizhou 318000, China

**Chen Guohong**, Urinary surgery Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

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**Correspondence to:** **Dr. Hua Baojin**, Oncology Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China. [dr.huabaojin@hotmail.com](mailto:dr.huabaojin@hotmail.com); **Dr. Chen Guohong**, Urinary surgery Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China. [cghdoctor@sina.com](mailto:cghdoctor@sina.com)

**Telephone:** +86-10-88001221.

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### Abstract

**OBJECTIVE:** To explore the role of Traditional Chinese Medicine (TCM) in the prevention and treatment of colorectal cancer and identify possible therapeutic targets of TCM to provide clues for the use of TCM for colorectal cancer prevention and treatment in the clinic and to find novel directions for new drug discovery for colorectal cancer.

**METHODS:** We used PubMed and Google to search for and collect scientific publications for a full evaluation of current evidence in the literature indicating the potential role of Chinese herbal medicines

and their respective ingredients as effective candidates for colorectal cancer prevention and treatment.

**RESULTS:** We extracted a detailed description of potential therapeutic Chinese herbal medicines and their constituent ingredients that target different mechanisms in colorectal cancer such as gene mutation, dysregulation of signaling pathways, metabolism disorders, and the inflammatory microenvironment, including both conventional and non-conventional approaches.

**CONCLUSION:** TCM may be a promising complementary and alternative therapy for the treatment of colorectal cancer.

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**Key words:** Colorectal neoplasms; Medicine, Chinese traditional; Prevention and control; Therapeutics; Drug delivery systems

### INTRODUCTION

Colorectal cancer is a serious and fatal disease. Although the specific pathogenetic mechanism is not fully proven, it is generally accepted that the risk factors for colorectal cancer include a genetic component, such as gene mutations, and an environmental component, such as a high-fat diet.<sup>1</sup> Current clinical treatment of colorectal cancer mainly focuses on the use of radiation therapy and chemotherapy. However, as long-term use of these therapies causes serious side effects there is a need to find alternative therapies with high efficacy but few side effects. Use of Traditional Chinese Medicine (TCM) is an attractive approach for the prevention and treatment of colorectal cancer worldwide.<sup>2</sup>

This paper focuses on the pathogenesis of colorectal cancer and the efficacy of Chinese medicine in preventing and treating cancer with the aim of identifying possible therapeutic targets of Chinese herbal medicine that might be beneficial in the prevention and treatment of colorectal cancer.

## METHODS

We searched PubMed and Google online up to July 2014 to find papers focusing on colorectal cancer prevention and treatment to evaluate current evidence in the literature indicating the potential role of Chinese herbal medicines and their respective ingredients as effective candidates for colorectal cancer prevention and treatment. The search terms used were: "Traditional Chinese Medicine" or "Chinese Herbal Medicine" and "Colon Cancer". Reference lists of the retrieved articles were also reviewed for additional relevant studies.

## RESULTS

### *Targeting kras and apc mutation in colorectal cancer with TCM*

Sporadic colorectal cancer in humans is caused by long-term accumulation of multiple somatic mutations in various genes, including oncogenes, tumor suppressor genes, and epigenetic genes. The three routes of cancer associated with genomic instability are chromosomal genomic instability (CIN), microsatellite instability, and a CpG island methylation phenotype (CIMP). CIN is one of the main causative factors of colon cancer (present in 80%-85% of cases), and is closely related to the malignant progression of colorectal cancer.<sup>3</sup> CIN combined with mutation or inactivation of the adenomatous polyposis coli (APC) gene and functional mutations in the  $\beta$ -catenin gene (CTNNB1) can lead to the formation of early intestinal adenocarcinoma. Somatic APC mutation is present in approximately 90% of sporadic colorectal cancer tumor tissues and can lead to constitutive  $\beta$ -catenin activation and the subsequent activation of many genes involved in the induction of tumorigenesis, such as c-myc.

Kras mutations in colorectal cancer patients are linked to the patient's life span, tumor progression, and chemotherapy resistance.<sup>4</sup> In addition, Kras mutation combined with APC loss synergistically increases Wnt signaling, thus contributing to tumor growth and invasion.<sup>5</sup> The presence of a Kras mutation in a patient with colorectal cancer therefore makes the disease harder to treat.

Numerous studies have shown that Chinese herbal medicine has a definite effect on colorectal cancer through the regulation of gene expression. Resveratrol, a major ingredient of Huzhanggen (*Radix Polygoni Cuspidati*), can induce colorectal cancer cell apoptosis,<sup>6</sup> inhibit cell proliferation,<sup>7,8</sup> and inhibit APC<sup>min</sup> intestinal

tumor formation in mice.<sup>9</sup> These chemopreventive roles of resveratrol and other active ingredients in herbal medicines can be partially reflected by post-transcriptional regulation and epigenetic modifications.<sup>10,11</sup> For example, resveratrol has been shown to increase the expression of miRNA-622 in colorectal cancer cells while inhibiting the expression of Kras.<sup>12</sup>

Berberine, a main ingredient in Huanglian (*Rhizoma Coptidis*), downregulates c-myc expression and increases APC gene expression, thus interfering with  $\beta$ -catenin nuclear translocation; in addition, berberine intervention in APC<sup>Min/+</sup> mice leads to smaller intestinal tumor size and a decreased number of tumors through inhibition of the Wnt /  $\beta$ -catenin signal.<sup>13</sup>

Colorectal cancer gene mutations are mainly concentrated in APC, Kras, and certain other genes, and such mutations are considered the ultimate targets for blocking tumor angiogenesis and tumor cell proliferation through the Wnt /  $\beta$ -catenin signal pathway. If TCM or its single constituents could regulate downstream targets of  $\beta$ -catenin, it might be a perfect candidate for inhibition of the progression of colorectal cancer.

### *Targeting metabolism disorders in colorectal cancer with TCM*

Colorectal cancer is known to be associated with a high-fat diet and colorectal metabolism disorders. Epidemiologic studies found that the incidence of colorectal cancer and mortality rates vary geographically.<sup>14-16</sup> There is evidence that diet and nutritional factors play key roles in the onset and progression of colorectal cancer;<sup>17-20</sup> consumption of a high-fat diet and genetic risk factors can induce an energy imbalance and increase the incidence of colorectal cancer.<sup>21-25</sup> In Apc<sup>Min/+</sup> mice, a spontaneous increase in the number of intestinal tumors is associated with a high-fat diet.<sup>26</sup>

AMP-activated protein kinase (AMPK) is one of the key sensors for regulation of energy metabolism and is also a key factor in the regulation of cell growth and apoptosis.<sup>27-29</sup> Once activated, AMPK can phosphorylate many metabolic enzymes, inhibit the signaling pathways of ATP consumption, and increase fatty acid oxidation.<sup>30,31</sup>

Many flavonoids extracted from Chinese herbal medicines, such as wogonin,<sup>32</sup> tanshinone II A,<sup>33</sup> quercetin,<sup>34,35</sup> and cryptotanshinone,<sup>36</sup> can induce AMPK activation, which then inhibits proliferation and induces apoptosis of cancer cells.<sup>37</sup> Therefore, selected pharmaceutical ingredients from TCM that target the activation of AMPK may be helpful for colorectal cancer prevention and treatment. There are more than 20 types of Chinese herbal medicine that can be used for metabolic disorders, and their main mechanisms of action are regulation of mitochondrial function and glucose metabolism and stimulation of AMPK activation.<sup>38-40</sup> Berberine, an alkaloid from TCM, can significantly inhibit colorectal cancer proliferation and tumor formation through activation of AMPK.<sup>41</sup>

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