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# Traditional Chinese medicine-induced treatment in colitis-associated colorectal cancer

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*To the Editor*: Colorectal cancer is one of the most common cancers worldwide, and chronic inflammation caused by colitis, especially ulcerative colitis, increases the risk of colorectal cancer. Compared with sporadic colorectal cancer whose hallmark is constitutive activation of Wingless/β-catenin signaling and the adenoma-carcinoma sequence, *P53* and *K-Ras* mutations, which occur earlier, adenomatous polyposis coli occurs later during the progression of colitis-associated colorectal cancer (CAC). Surgery and chemotherapy are the preferred treatments of CAC, but long-term use of first-line chemotherapy agents such as 5-fluorouracil or irinotecan is limited by drug resistance or adverse reactions. Therefore, it is necessary for us to identify "green" drugs. Traditional Chinese medicines (TCMs) are complex and diverse and are found in nature. The anti-inflammatory, antibacterial, antiviral, antioxidant, antitumor, antiradiation, and immunomodulatory activity of TCMs have been extensively studied. TCMs are more able than synthesized drugs to prevent inflammation from progressing to cancer. This review summarizes the advantages of TCMs for treating CAC.

With increase of the severity of the inflammation, the risk of cancer development increases. Nuclear factor kappa-B (NF-κB), P53, and the cyclooxygenase-2/prostaglandin E2 signaling pathways are known to be involved in the pathogenesis of CAC. Accumulation of reactive oxygen species causes oxidative stress and destroys DNA, proteins, and lipids, leading to tumors. Most TCMs have anti-inflammatory activity that participates in the prevention or treatment of CAC. Wogonoside administration leads to the return of downstream inflammatory factors such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) levels close to normal. Wogonoside also reduces neutrophil and macrophage infiltration in CAC.[1] Betaine administration inhibited inflammatory-related cytokines such as TNF-α, IL-6, inducible nitric oxide (NO) synthase, reactive oxygen species, and cyclooxygenase-2. Apple polysaccharide extract is effective as chemoprevention by inhibiting NF-κB-mediated inflammation pathways in colorectal cancer. Inhibition of inflammation in cancer may be key in treating CAC with TCMs.

Activation of NF-κB and its signal pathways regulate cell proliferation and apoptosis by up-regulating the expression of cyclins and *Bcl-2* family members. Honokiol, a biphenolic compound found in *Magnolia grandiflora*, induces ferroptosis in colon cancer cells by reducing glutathione peroxidase 4 activity. An ethanol extract of *Aster glehni*, reduced nuclear factor NF-κB activation by phosphorylation and degradation of inhibitor of kappa Bα, leading to inhibition of NF-κB p65 nuclear translocation. The evidence indicated that *A. glehni* may have promise as a protective agent against CAC by suppression of the NF-κB signaling pathway. Oral administration of an ethanol extract of *Tuber aestivum sprouts* significantly decreased the expression of the β-catenin-related *cyclin D1* and *c-Myc* genes in colon tissue from mice with azoxymethane (AOM)/dextran sulfate sodium (DSS)-induced CAC. Low-dose bufalin effectively suppressed tumorigenesis in colorectal cancer models, accompanied by attenuated epithelial cell proliferation (i.e., lower cyclin A, cyclin D1, and cyclin E levels, and higher p21 and p27 levels) and promoted apoptosis (i.e., lower Bcl-2, Bcl-xL, and survivin levels, and higher Bax and Bak levels).[2] TCMs such as wogonoside and *Rhizopus nigricans* may have superior effectiveness against CAC because they inhibit cell proliferation and promote apoptosis.

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The host intestinal immune system restrains bacteria, and under normal conditions limits the entry of bacteria into the intestinal epithelium. The gut microbiota interacts with immune cells in the intestinal mucosa to promote the development and maintenance of the immune system. Microbial overstimulation may lead to inappropriate activation of intestinal immune cells and the development of intestinal inflammation. In an AOM/DSS-induced CAC mouse model, the probiotics *Alloprevotella*, *Bacteroides,* and *Lactobacillus* were decreased and the pathogenic bacteria *Muribaculaceae*, *Proteobacteria*, *Citrobacter*, *Akkermansia,* and *Klebsiella* were increased. The imbalance led to inflammation and weakening of intestinal barrier function.[3] Enriching probiotics and reducing the abundance of pathogenic bacteria are considered to be useful in the treatment of CAC. For example, isoliquiritigenin reduces the abundance of genera including *Escherichia* and *Enterococcus,* which are opportunistic pathogens and increased the levels of probiotics like *Butyricicoccus*, *Clostridium*, and *Ruminococcus* to protect mice from AOM/DSS-induced CAC.[4] *Lactobacillus bulgaricus* is a widely used probiotic bacterium, was found to inhibit tumor progression and intestinal inflammation in an AOM/DSS-induced CAC mouse model, with reduction of IL-6, TNF-α, IL-17, IL-23, and IL-1β. Recent studies have identified potentially effective CAC treatments that act by improving the intestinal microenvironment, including antibiotics, probiotics, prebiotics, and fecal microbiota transplantation. TNF-α induces a variety of cellular responses by interacting with transmembrane receptors. TNF-α antagonists inhibit CAC growth in AOM/DSS-treated mice. The IL-23/T-helper 17 pathway is involved in the pathophysiology of CAC. Previous studies have shown reduced tumor development in AOM/DSS-treated IL-17A-deficient mice with CAC. The IL-6/IL-6R axis is active in immune cell recruitment and T cell survival and differentiation. Silibinin, dietary cocoa, and *Rhizoma Paridis* total saponins protected against CAC in mice by inhibiting the IL-6/signal transducer and activator of the transcription 3 protein signaling pathway.

Synergistic combinations of TCMs with chemotherapy agents are seen as promising methods to treat CAC by overcoming the weaknesses of single-target drugs.[5] Curcumin combined with resveratrol inhibited the growth of CAC cells more strongly than either agent alone, which was attributed to the enhancement of anti-proliferation and pro-apoptosis activity. Other studies investigated the effects of TCMs as modulators for chemotherapy. Ursolic acid, a pentacyclic triterpenoid found in holy basil, was found to enhance the anticancer effects of capecitabine through inhibition of NF-κB. Curcumin combined with FOLFOX had superior anticancer effectiveness by downregulating epidermal growth factor receptors and insulin-like growth factor-1R signaling.

Recent advances in TCMs-induced prevention and therapy of CAC are discussed here and the comprehensive information are shown in Supplementary Table 1, http://links.lww.com/CM9/B515. We aimed to supply new approaches in CAC treatment using TCMs, and TCMs can block the progress from inflammation to cancer, not only inhibits cancer cell growth. This correspondence may uncover the tip of the iceberg of mechanisms underlying TCMs for treating CAC that have not been extensively studied. The huge potential of TCMs may provide new insights into drug design and CAC therapy, especially in preventing the progression from inflammation to cancer.

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### Conflicts of interest

None.

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