

Protective Effect from Ulcerative Colitis to Colitis- associated Cancer in Experimental Models with Huangqin Decoction

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Summary

We demonstrated the therapeutic potential of Huangquin Decocotion-1 (HQD-1) for acute/chronic ulcerative colitis. Furthermore, HQD-1 was effective for colitis-associated cancer prevention. The mechanism of HQD-1 may involve the inhibition of inflammation

and oxidative stress in mice. All these data confirm the effects of the clinical application of HQD-1 for ulcerative colitis patients. HQD-1 can also be used as a preventive agent against colitis-associated cancer in chronic ulcerative colitis patients.

Background and Justification

Colorectal cancer (CRC) ranks as the neoplasm with the third highest incidence and death rate in humans. Evidence is accumulating that inflammatory bowel disease (IBD) is strongly associated with CRC, with ulcerative colitis and Crohn's disease being the two main forms of IBD in humans. Indeed, the natural pathology of IBD sufferers, and particularly ulcerative colitis patients, may be marked by the development of CRC. During the course of IBD, inflammatory cytokines contribute to the formation of a tumour-supportive microenvironment. In addition, the production of large amounts of reactive oxygen species (ROS) in inflamed tissue by inflammatory cells, neutrophils and macrophages results in oxidative stress and impairment of antioxidant defences. Increased levels of ROS lead to protein damage, lipid peroxidation and DNA damage, all leading to genetic and epigenetic alterations, which promote the occurrence of carcinoma. However, progression from IBD to CRC is a long process, so it may prove feasible to prevent CRC through IBD treatment.

Aminosalicylates have been extensively used to treat patients with IBD with several studies demonstrating their potential in the prevention of colitis-associated cancer. However, some groups were not able to reproduce the findings when these drugs were used. Corticosteroids play an important role in the treatment of IBD, and some studies have found beneficial effects in the prevention of CRC with corticosteroids, although the adverse effects of their long-term use are considerable. Treatment with herbal products represents a novel approach to IBD. However, although the development of new drugs for IBD and IBD-associated CRC is an urgent necessity, there is insufficient data on the preventive role of herbal products in CRC development in IBD patients.

Description

Colitis sufferers are at high risk of developing CRC. Huangqin Decoction (HQD), one of the traditional Chinese formulae chronicled in *Shang Han Lun* (the Treatise on Cold Damage Disorders), was commonly used to treat a range of gastrointestinal symptoms. In our study, we used current biomedical approaches to investigate the protective/preventive efficacy and possible mechanism of HQD in mice models with dextran sulphate sodium (DSS)-induced acute/chronic ulcerative colitis and azoxymethane (AOM)/DSS-induced colitis-associated cancer. Four herbs of HQD were extracted using four processes named HQD-1, HQD-2, HQD-3 and HQD-4. Acute/chronic ulcerative colitis was induced in mice by adding DSS to drinking water, while AOM and DSS in combination were used to induce colitis-associated cancer. The mice were administered at a dose of 9.1 g/kg HQD via oral gavage per day. Body weight, stool characteristics and haematochezia were observed daily. Measurements of survival rate, length of the colorectum, tumour numbers and tumour size were conducted. The colorectal tissues were used to detect levels of inflammatory cytokines using quantitative reverse transcription PCR (qRT-PCR). The expression of 8-oxoguanine, nitrotyrosine and proliferating cell nuclear antigen (PCNA) were examined using immunohistochemistry. The activity of superoxide dismutase (SOD), which prevents damage from ROS, the levels of other chemical markers, and the apoptosis (cell death) rate of colorectal tissues were measured using respective kits.

HQD-1 may significantly inhibit acute DSS-induced ulcerative colitis. HQD-3 and HQD-4 exhibited a mild ameliorative effect. However, HQD-2 had almost no protective effect and resulted in a higher mortality rate than DSS. The high mortality rate of HQD-2 may have resulted from the higher content of baicalein, wogonin and oroxylin A or their combination. Furthermore, HQD-1 possessed the ability to protect against DSS-induced chronic ulcerative colitis in mice, to inhibit the production of inflammatory cytokines and to improve anti-oxidative activity. The preventive effect of HQD-1 on AOM/DSS-induced CAC in mice was notable. HQD-1 also evidently inhibited the expression of inflammatory cytokines and oxidative damage in mice. The four herbs in the HQD extract mix (HQD-1) could perhaps be used to cure acute/chronic colitis and, furthermore, prevent colitis-associated cancer. The protective/preventive mechanism of HQD-1 may involve the inhibition of inflammation and oxidative stress.

Partnerships

Partnerships were undertaken with Qiang Yu of the Department of Pharmacology, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, and with Chung S. Yang of the Department of Chemical Biology at the Center for Cancer Prevention Research and Rutgers Cancer Institute of New Jersey, Rutgers University in the USA.

Replicability

There is no patent and Huangqin Decoction (HQD) is one of the traditional Chinese formulas chronicled in Shang Han Lun.

Lessons Learned

The unit of measurement in Shang Han Lun is different from that of modern units. Therefore, the confirmation of the dosage is difficult. After consulting specialist books, we solved this issue.

The results showed the content of baicalein, wogonin and oroxylin A were higher in HQD-2 than in HQD-1.

The high mortality rate of HQD-2 might have resulted from the higher content of these three compounds or their combination. Whether the three compounds or their combination result in a higher death rate will be confirmed in future in vivo experiments.