Postprint: Effects and Mechanism of Optimized Kuijie Formula in Ulcerative Colitis Model Rats with Qi Stagnation and Blood Stasis

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Abstract

Background: Clinical practice has demonstrated that the optimized Kuijie Formula can effectively improve the quality of life of ulcerative colitis (UC) patients, promote intestinal mucosal healing and clinical remission, but its mechanism of action remains incompletely understood. Objective: To investigate the effects and mechanism of action of the optimized Kuijie Formula on UC rats with qi stagnation and blood stasis pattern. Methods: From September to October 2023, 70 SPF-grade male SD rats were selected and randomly divided into normal group, model group, sulfasalazine group, low-dose group, standard-dose group, yiqi (qi-boosting) group, and huoxue (blood-activating) group, with 10 rats in each group, using random number table method. The UC qi stagnation and blood stasis model was established using the TNBS/ethanol double inflammation method combined with restraint method. Normal group rats received 0.9% sodium chloride solution enema during modeling, and were synchronized with other groups for grasping and fixation; after successful modeling, they received equal volume of water gavage once daily for 14 days. Model group rats received equal volume of water gavage once daily for 14 days after successful modeling. Sulfasalazine group, low-dose group, standard-dose group, yiqi group, and huoxue group rats received sulfasalazine solution 0.54 g/kg, low-dose optimized Kuijie Formula solution 0.837 g/kg, standard-dose optimized Kuijie Formula solution 1.674 g/kg, Astragalus solution 1.8 g/kg, and Carthamus solution 0.9 g/kg respectively, all once daily for 14 days. High-precision transmission electron microscopy was used to observe ultrastructural changes in colon tissue after intervention, and expression levels of CXCR4, VEGFA, and TAK1 in colon tissue were compared among the 7 groups. Results: After intervention, colon tissue ultrastructure in low-dose and standard-dose groups tended to normalize. After intervention, protein grayscale ratios and relative mRNA expression levels of CXCR4, VEGFA, and TAK1 in colon tissue of model group

were higher than those of normal group; these values in sulfasalazine, low-dose, standard-dose, yiqi, and huoxue groups were lower than those of model group (P<0.05); protein grayscale ratios of CXCR4, VEGFA, and TAK1 in standard-dose group were lower than those of sulfasalazine group (P<0.05). Conclusion: The optimized Kuijie Formula and its yiqi and huoxue components can effectively reduce expression levels of CXCR4, VEGFA, and TAK1 in colon tissue of UC rats with qi stagnation and blood stasis pattern, and its therapeutic effect may be achieved through synergistic regulation of CXCR4, VEGFA, and TAK1 expression levels in colon tissue by yiqi and huoxue components.

Full Text

Effect and Mechanism of Optimized Kuijie Decoction in Ulcerative Colitis Rats with Qi Stagnation and Blood Stasis Syndrome

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Abstract

Background: The empirical formula Optimized Kuijie Decoction can effectively improve quality of life, promote intestinal mucosal healing, and induce clinical remission in ulcerative colitis (UC) patients, though its mechanism of action remains incompletely understood. **Objective:** To investigate the effects and mechanisms of Optimized Kuijie Decoction in a rat model of UC with Qi stagnation and blood stasis syndrome. **Methods:** Between September and October 2023, 70 SPF-grade male SD rats were randomly divided into seven groups (n=10 each): normal control, model, salicylazosulfapyridine, low-dose, standard-dose, Qi-enhancing, and blood-activating groups. A UC model with Qi stagnation and blood stasis was established using trinitrobenzenesulfonic acid (TNBS)/ethanol-induced colitis combined with restraint stress. The normal control group received 0.9% sodium chloride enema during modeling and equal-volume water gavage for 14 days post-modeling. The model group

received equal-volume water gavage for 14 days. Treatment groups received daily gavage for 14 days with: salicylazosulfapyridine (0.54 g/kg), low-dose Optimized Kuijie Decoction (0.837 g/kg), standard-dose Optimized Kuijie Decoction (1.674 g/kg), Astragalus suspension (1.8 g/kg), or Safflower suspension (0.9 g/kg). High-precision transmission electron microscopy examined colonic ultrastructural changes, and expression levels of CXCR4, VEGFA, and TAK1 were compared across groups. **Results:** Colonic ultrastructure in low-dose and standard-dose groups approached normal. Protein gray ratios and relative mRNA expression of CXCR4, VEGFA, and TAK1 were higher in the model group than the normal control ($P<0.05$). All treatment groups showed significantly lower expression than the model group ($P<0.05$), with the standard-dose group showing lower protein expression than the salicylazosulfapyridine group ($P<0.05$). **Conclusion:** Optimized Kuijie Decoction and its Qi-enhancing and blood-activating components effectively reduce CXCR4, VEGFA, and TAK1 expression in colonic tissue of UC rats with Qi stagnation and blood stasis, likely through synergistic regulation of these targets.

Keywords: Colitis, ulcerative; Syndrome of blood stasis and Qi stagnation; Rats; Optimized Kuijie decoction; Molecular mechanisms of pharmacological action (Traditional Chinese Medicine)

Introduction

Recent epidemiological data indicate that the incidence of ulcerative colitis (UC) in China continues to rise, with approximately 13.3 cases per 100,000 population [1]. Conventional treatments including aminosalicylates and corticosteroids demonstrate modest short-term efficacy but carry significant adverse effects and high recurrence rates. Optimized Kuijie Decoction, comprising Astragalus, fried Atractylodes macrocephala, Atractylodes lancea, Indigo naturalis, Patrinia, Pulsatilla, and Safflower, is an empirical formula developed by Professor Liu Yuedong for treating UC with spleen deficiency and damp-heat syndrome, demonstrating established efficacy and evidence-based validation [2-5]. Experimental studies have shown that Optimized Kuijie Decoction ameliorates symptoms in UC model rats by modulating extracellular signal-regulated kinase (ERK) and interleukin-1β pathways to improve intestinal inflammation [3], while network pharmacology research indicates its regulatory effects on intestinal immune responses involve IL-17 and Toll-like receptor signaling pathways [4-6]. Notably, the formula contains the classic Qi-tonifying and blood-activating herb pair Astragalus and Safflower. However, its mechanism in UC patients with Qi stagnation and blood stasis syndrome remains unclear. This study investigates the effects of Optimized Kuijie Decoction on a UC rat model with Qi stagnation and blood stasis, exploring its mechanism through analysis of colonic expression levels of chemokine receptor 4 (CXCR4), vascular endothelial growth factor A (VEGFA), and transforming growth factor kinase 1 (TAK1).

Methods

Animal Grouping and Treatment. Between September and October 2023, 70 SPF-grade male SD rats weighing 200-240 g (provided by the Laboratory Animal Center of Xi'an Jiaotong University, certificate No. 2018-001) were randomly divided into seven groups (n=10 each): normal control, model, salicylazosulfapyridine, low-dose, standard-dose, Qi-enhancing, and blood-activating groups. All rats were housed in a clean environment at 20$±$2°C with 50-60% relative humidity at the Experimental Center of Xianyang Central Hospital Affiliated to Shaanxi University of Chinese Medicine. The experimental protocol was approved by the Shaanxi University of Chinese Medicine Laboratory Animal Ethics Committee (Approval No. SUCMDL20231316003).

UC Model with Qi Stagnation and Blood Stasis. The model was established using TNBS/ethanol-induced colitis combined with restraint stress [2]. After one week of acclimatization, rats were restrained for approximately 8 hours daily. Following 24-hour fasting (with water ad libitum), rats were anesthetized with pentobarbital sodium (3 mL/kg) and administered 60 mg/kg TNBS/ethanol solution via intrarectal catheterization 8 cm from the anus to induce acute colitis. Fifteen days later, a second administration of 30 mg/kg TNBS/ethanol solution induced chronic relapsing colitis. After each enema, 0.5 mL air was injected, and rats were maintained in a head-down position for 3-5 minutes, then returned to cages in supine position. Successful establishment of the Qi stagnation and blood stasis model was verified through hemorheological parameters and disease activity index (DAI) scoring [2].

Drug Preparation and Administration. Salicylazosulfapyridine (Shanghai Fuda Pharmaceutical Company) was prepared as a 1 g/mL suspension. Optimized Kuijie Decoction (Astragalus 20 g, fried Atractylodes macrocephala 15 g, Atractylodes lancea 10 g, Indigo naturalis 3 g, Patrinia 20 g, Pulsatilla 15 g, Safflower 10 g) was decocted to a final concentration of 1 g/mL. Based on a 6.25:1 human-to-rat dose conversion, the standard dose was calculated as 1.674 $g \cdot kg^{-1} \cdot d^{-1}$ [6]. Astragalus (1.8 g/kg) and Safflower (0.9 g/kg) suspensions were prepared separately at 1 g/mL concentration.

The normal control group received 0.9% sodium chloride enema during modeling and equal-volume water gavage once daily for 14 days post-modeling. The model group received equal-volume water gavage for 14 days. Treatment groups received daily gavage for 14 days with their respective medications.

Colonic Ultrastructure Analysis. On day 15 post-modeling, 2-3 colonic tissue blocks (1 mm^3) were harvested from each rat, fixed with 2.5% glutaraldehyde and 1% osmium tetroxide, and examined using high-precision transmission electron microscopy.

Protein Expression Analysis. Western blotting detected CXCR4, VEGFA,

and TAK1 protein expression in colonic tissues. Tissues were homogenized in lysis buffer, centrifuged at 14,000×g for 10 minutes at 4°C, and protein concentrations were determined. Expression levels were quantified as gray ratios.

mRNA Expression Analysis. Real-time PCR measured relative mRNA expression of CXCR4, VEGFA, and TAK1 using the 2^(-ΔΔCt) method. Primer sequences are listed in .

Statistical Analysis. SPSS 26.0 software was used for statistical analysis. Measurement data are expressed as mean±standard deviation ($\bar{x}\pm s$). One-way ANOVA with homogeneity of variance test was performed; LSD-t test was used for pairwise comparisons when variances were equal, and non-parametric tests when variances were unequal. $P<0.05$ was considered statistically significant.

Results

Colonic Ultrastructure Changes. On day 15 post-modeling, normal control rats showed intact intestinal epithelial cells with uniform cytoplasmic matrix, abundant organelles, regularly arranged microvilli, and normal barrier structures. Model rats exhibited moderate-to-severe epithelial edema, swollen organelles, sparse and disordered microvilli, absent tight junctions and desmosomes, and widened intercellular spaces indicating abnormal barrier structure [Figure 1: see original paper]B. Salicylazosulfapyridine-treated rats showed near-normal ultrastructure with intact membranes and regularly arranged microvilli, though tight junctions appeared blurred [Figure 1: see original paper]C. Low-dose group rats showed mild epithelial swelling with relatively normal ultrastructure but compromised barrier integrity [Figure 1: see original paper]D. Standard-dose group rats demonstrated normalized ultrastructure with appropriately abundant mitochondria and intact rough endoplasmic reticulum [Figure 1: see original paper]E. Qi-enhancing group rats showed moderate edema with mitochondrial damage (cristae disruption and matrix dissolution) [Figure 1: see original paper]F. Blood-activating group rats exhibited normal organelle structure but widened intercellular spaces [Figure 1: see original paper]G.

Protein Expression. Protein gray ratios of CXCR4, VEGFA, and TAK1 differed significantly among groups ($P<0.05$). Model group rats showed higher expression than normal controls ($P<0.05$). All treatment groups exhibited significantly lower expression than the model group ($P<0.05$). The standard-dose group showed lower protein expression than the salicylazosulfapyridine group ($P<0.05$) [Figure 2: see original paper], .

mRNA Expression. Relative mRNA expression of CXCR4, VEGFA, and TAK1 also differed significantly among groups ($P<0.05$). Model group rats showed higher expression than normal controls ($P<0.05$). Low-dose, standard-dose, Qi-enhancing, and blood-activating groups demonstrated significantly lower expression than the model group ($P<0.05$) .

Discussion

UC is a chronic inflammatory bowel disease characterized by diarrhea, mucopurulent or bloody stools, tenesmus, and abdominal pain, significantly impairing quality of life. The exact pathogenesis remains unclear, and no curative therapy exists [3]. Current treatment focuses on improving quality of life, inducing and maintaining remission, promoting mucosal healing, and preventing complications.

Optimized Kuijie Decoction, developed by Professor Liu Yuedong based on UC pathogenesis [7-12], embodies therapeutic principles of strengthening the spleen, dispelling dampness, augmenting Qi, and activating blood circulation. In clinical practice, it effectively treats UC with spleen deficiency and damp-heat syndrome. The formula features Patrinia and Pulsatilla as sovereign drugs for clearing heat and detoxification; Astragalus as minister drug for augmenting Qi; Safflower and Indigo naturalis as assistant drugs for activating blood and cooling blood; and fried Atractylodes macrocephala and Atractylodes lancea as courier drugs for strengthening the spleen and drying dampness. This combination achieves the therapeutic effects of fortifying the spleen, dispelling dampness, moving Qi, activating blood, clearing heat, and relieving pain.

CXCR4, a chemokine receptor subfamily member widely expressed across cells and tissues, promotes cell migration and inflammatory cell activation via NF- B and JAK/STAT signaling pathways upon activation. The SDF-1/CXCR4 axis facilitates inflammatory cell recruitment to damaged colonic tissue. Studies show that UC patients exhibit elevated CD4+ T lymphocyte CXCR4 expression, and the specific CXCR4 antagonist T140 attenuates dextran sulfate sodium-induced colitis by blocking this axis [6]. VEGFA, a key angiogenic factor and pro-inflammatory cytokine in UC pathogenesis, is upregulated by activated platelet-derived angiogenic regulatory proteins, exacerbating inflammatory responses [4]. TAK1, a MAP3K family serine/threonine kinase, regulates NF- B nuclear translocation and inflammatory responses while activating JAK/STAT pathways involved in cell proliferation, macrophage activation, and inflammation [5]. The cross-regulation among these pathways enables VEGFA, TAK1, and CXCR4 to play crucial roles in UC development, though specific mechanisms may vary by cell type, disease state, and microenvironment [6,13-15].

Experimental studies demonstrate that Optimized Kuijie Decoction reduces pro-inflammatory cytokines (IL-1β, TNF-$ $1) and increases VEGF expression in TNBS/ethanol-induced UC rats, thereby inhibiting intestinal inflammation and promoting mucosal repair [16]. Network pharmacology predictions based on protein-protein interaction databases suggest the formula's therapeutic effects primarily target CXCR4, VEGFA, and TAK1, modulating inflammation and immune-related signaling pathways. Our results confirm that Optimized Kuijie Decoction and its individual Qi-enhancing and blood-activating components

significantly reduce colonic CXCR4, VEGFA, and TAK1 expression in UC rats with Qi stagnation and blood stasis.

The mechanism likely involves synergistic regulation by Astragalus and Safflower. Astragalus flavonoids, polysaccharides, and triterpenoids can inhibit VEGFA to reduce vascular supply and suppress TAK1 signaling to attenuate colonic injury. Safflower components (hydroxycoumarin, rutin, carotene, safflower flavonoids) regulate VEGF and VCAM-1 expression, inhibiting neovascularization and oxidative stress [17-21]. Notably, while Astragalus polysaccharides may induce mitochondrial damage, Safflower's antioxidant and anti-inflammatory properties protect cellular membranes. Their combined use in Optimized Kuijie Decoction ensures therapeutic efficacy while minimizing mitochondrial injury, representing a scientifically sound and safe formulation.

Traditional Chinese medicine emphasizes that Qi and blood constitute the foundation of vital activities. As stated in *Treatise on Blood Disorders*: "The human body is nothing beyond Yin and Yang; the terms Yin and Yang refer to water and fire; water and fire refer to Qi and blood." In treating gastrointestinal diseases like UC, TCM practitioners prioritize regulating Qi and blood flow, often adding Qi-tonifying herbs (Astragalus, Angelica, Codonopsis, Licorice, Atractylodes) to blood-activating formulas, or adding blood-activating herbs (Peach kernel, Safflower, Frankincense, Myrrh, Pollen typhae, Trogopterus, Musk, Red peony, Moutan) to Qi-tonifying formulas. Intestinal immunity constitutes a vital component of systemic immunity. Studies show Astragalus polysaccharides promote intestinal epithelial cell differentiation and IgA production, enhancing barrier function and protecting against harmful substances and bacteria [22]. Additionally, Astragalus polysaccharides increase intestinal prostaglandin E2 content, promoting immune cell growth and proliferation [23]. We hypothesize that the Qi-enhancing component strengthens the spleen-stomach and intestinal immunity/barrier function, while the blood-activating component improves intestinal microcirculation and regulates Qi-blood balance, with synergistic effects promoting repair of colonic injury and epithelial cells.

Ultrastructural changes in mitochondria and ribosome degranulation reflect cellular activity and viability. Reduced energy metabolism or apoptosis typically decreases mitochondrial number or disrupts structure, while decreased protein synthesis causes ribosome degranulation. Our ultrastructural analysis confirmed successful establishment of the UC Qi stagnation and blood stasis model. The low-dose and standard-dose groups showed normalized ultrastructure, while the Qi-enhancing group exhibited mitochondrial damage and the blood-activating group showed widened intercellular spaces, suggesting Astragalus may induce mitochondrial injury while Safflower protects cellular membranes. The combined formula demonstrates rational compatibility with high safety.

In summary, Optimized Kuijie Decoction and its Qi-enhancing and blood-activating components effectively reduce colonic CXCR4, VEGFA, and TAK1 expression in UC rats with Qi stagnation and blood stasis through synergistic regulation. While the specific chemical constituents remain to be fully charac-

terized, future research should explore the formula's modulation of intestinal flora and its relationship with intestinal inflammation and barrier function, potentially providing novel insights into its therapeutic mechanisms.

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Author Contributions

ZHANG Shuai and LI Na conceived the study design, collected data, and drafted the manuscript. SHEN Jiangli, LIU Yuedong, WU Xianshu, WANG Lei, and SHENG Tianjiao performed data entry and statistical analysis. XU Hongjun reviewed and edited the manuscript. ZHANG Shuai, LI Na, and AN Shengjun supervised quality control and take overall responsibility for the manuscript. All authors approved the final version.

Conflicts of Interest: None declared.

Note: Figure translations are in progress. See original paper for figures.