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Molecular Mechanisms of Hedyotis diffusa Targeting IL-6/STAT3 Pathway for Colorectal Cancer Intervention

Jing Lin[1*], Wenyuan Liu[2], Zihan Wang[3]

[1]School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, China
[2]School of Traditional Chinese Medicine, Heilongjiang University of Chinese Medicine, Harbin, China
[3]Beijing Huiwen Middle School, Beijing, China
**Corresponding Author. Email: 2400302125@stu.gdpu.edu.cn*

Abstract. Colorectal cancer causes persistently high global morbidity and mortality rates worldwide. Conventional chemo-targeted therapies carry severe toxic side effects and frequent drug resistance, while integrated Chinese and Western medicine provides low-toxic adjuvant treatment ideas for this malignant disease. This paper systematically summarizes the anti-tumor effects and molecular regulatory rules of two core active monomers, ursolic acid and quercetin, extracted from the medicinal herb Hedyotis diffusa. The two components jointly inhibit IL-6 secretion and block STAT3 phosphorylation to cut off inflammatory oncogenic cascades, suppress colorectal cancer cell proliferation and EMT-mediated metastasis, and produce synergistic sensitization effects when combined with routine chemotherapy. Current preclinical cell and animal data fully verify its multi-target pharmacological advantages, but large-sample multi-center clinical evidence and optimized targeted delivery systems are still insufficient. This paper sorts the pathological inflammatory mechanism of colorectal cancer and the intervention characteristics of Hedyotis diffusa, offering valuable theoretical reference for the development of natural monomer anti-colorectal adjuvant drugs.

Keywords: Hedyotis diffusa, colorectal cancer, IL-6, STAT3

1. Introduction

Colorectal cancer ranks among the top malignant tumors in global incidence and mortality, and domestic epidemiological data show that China records about 520,000 new cases and 240,000 cancer-related deaths each year, forming a heavy burden on national public health systems [1]. Conventional clinical interventions including surgery, radiotherapy, chemotherapy and single-target agents are limited by high postoperative recurrence rates, severe gastrointestinal toxicity and acquired drug resistance. Therefore, safe multi-target auxiliary treatment strategies are urgently needed. Traditional Chinese herbal medicine represented by Hedyotis diffusa exhibits unique advantages of low toxicity and overall microenvironment regulation in tumor adjuvant therapy [2]. As a classic heat-clearing and detoxifying herb widely used for gastrointestinal tumors, Hedyotis diffusa contains abundant ursolic acid and quercetin, which can suppress chronic inflammation and

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block core oncogenic signaling pathways, becoming a hot research object for colorectal cancer complementary treatment [3]. It is necessary to systematically integrate existing experimental data to sort its core anti-tumor molecular pathways and clinical application value.

Overseas research mostly focuses on the monomer pharmacological activity of ursolic acid and quercetin, carrying out in vitro cell verification of IL-6/STAT3 pathway inhibition and exploring single-component anti-proliferative and anti-metastatic effects. Foreign teams prioritize molecular docking and structural modification of two monomers, yet rarely conduct integrated discussion of compound extract synergism and combined chemotherapy regimens. Most overseas reviews only elaborate single active substance functions, lacking systematic sorting of herbal whole-medicine intervention characteristics.

Domestic scholars pay more attention to the overall efficacy of Hedyotis diffusa compound preparations, conducting in vivo xenograft tumor model experiments to confirm its inflammation-relieving and chemo-sensitizing effects. Local research groups carry out network pharmacology analysis to excavate multi-target matching mechanisms of ursolic acid and quercetin, but most existing domestic studies only stay at the preclinical experimental stage, without standardized multi-center clinical cohort verification. Globally, few literatures integrate intestinal inflammatory pathogenesis, monomer signal regulation and combined medication advantages into a complete research chain, requiring comprehensive summary and sorting.

Existing research has obvious integration defects: most published papers separately discuss single monomer activity or simple pathway inhibition, failing to connect chronic intestinal inflammation, tumor malignant transformation, and herbal intervention logic. Separate discussion of cell-level experiments cannot summarize its clinical chemo-sensitizing application value and translational bottlenecks. Under this research background, this paper firstly expounds multi-factor pathological mechanisms of colorectal cancer dominated by chronic inflammation, then introduces core active ingredients of Hedyotis diffusa and their basic pharmacological characteristics. On this basis, it systematically analyzes how ursolic acid and quercetin jointly target the IL-6/STAT3 pathway to regulate proliferation, apoptosis and metastasis, summarizes synergistic advantages and existing limitations of combined chemotherapy, and finally puts forward translational research directions, forming an integrated research framework covering pathogenesis, molecular mechanism and clinical efficacy.

2. Multi-factor pathogenesis of colorectal cancer driven by chronic inflammation

The pathogenesis of colorectal cancer has obvious molecular heterogeneity and does not follow a single model. The disease involves multiple interactions of genetic susceptibility, epigenetic remodeling, chronic inflammatory microenvironment remodeling, and intestinal flora disorders. There are two important molecular evolution pathways for genetic changes. The classic adenoma-carcinoma sequence is characterized by cumulative mutations in key driver genes such as APC, KRAS, and TP53 in normal epithelial cells in a specific time sequence. The zigzag pathway defines the molecular starting point according to the activation of the BRAF proto-oncogene, and the mutation involved will cause the promoter CpG island to be hypermethylated in a progressive manner, that is, the CIMP-high state. Epigenetic abnormalities can cause transcriptional dysfunction of multiple tumor suppressor genes. Some of the disabled genes (SOCS1, MLH1) are themselves negative regulators of inflammatory regulatory pathways or important components of DNA damage repair mechanisms. Their loss of function significantly enhances the sensitivity of colonic epithelial cells to inflammatory stimuli, and relieves important molecular braking for the cascade reaction of chronic inflammation to malignant transformation [4]. Over the years, studies have found that

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intestinal flora imbalance can drive the deterioration of inflammation through genotoxic damage and destruction of intestinal barrier function. Escherichia coli can use the genetic mechanism to synthesize colibactin toxoids, causing DNA damage to the colonic epithelium. At the same time, the disorder of flora weakens the protection of mucus and hinders the formation of tight junction proteins. Once the barrier is destroyed, it will stimulate the pro-inflammatory response for a long time and repeatedly [5].

In this inflammatory microenvironment, there are a large number of pro-inflammatory cytokines, such as IL-6, TNF-α, etc. The factors involved can initiate multiple carcinogenic pathways, such as IL-6 / STAT3 pathway, NF-B signaling, Wnt / β-Catenin signaling pathway, etc. Among the many cancer-promoting signals, the abnormal activity of the IL-6 / STAT3 pathway is more prominent. In the physiological state, IL-6 has a steady-state regulatory function on intestinal immunity. In the tumor microenvironment, infiltrating macrophages and tumor cells up-regulate IL-6, resulting in persistent phosphorylation of STAT3, that is, p-STAT3. After it is transferred to the nucleus, it binds to a specific DNA sequence in the promoter region of the target gene, directly triggering a series of transcription activities of survival genes, such as BCl-2, Survivin and other proliferation genes. This transcriptional shift not only gives CRC cells the ability to resist apoptosis, but also induces long-distance metastasis of epithelial mesenchymal transition (EMT) by inducing epithelial mesenchymal transition (EMT).

3. Core anti-tumor active components of Hedyotis diffusa

Ursolic acid and quercetin serve as two representative bioactive monomers of Hedyotis diffusa, jointly exerting anti-inflammatory and anti-malignant proliferation effects through targeting IL-6/STAT3 cascade. Ursolic acid is a stable pentacyclic triterpene widely distributed in this herb; preclinical data confirm it can reduce IL-6 secretion, suppress STAT3 phosphorylation, block cell cycle G1/S conversion and induce endogenous apoptosis, with low cytotoxicity against normal intestinal epithelial tissue [6]. Quercetin, a natural flavonoid component, eliminates intestinal oxidative stress, inhibits inflammatory factor overrelease and reverses tumor chemo-resistance. The two monomers act on different links of the IL-6/STAT3 pathway with complementary regulatory effects, jointly breaking the vicious cycle of inflammation-driven tumor deterioration [7].

4. IL-6/STAT3 pathway-dependent molecular intervention mechanisms of Hedyotis diffusa monomers

4.1. Block chronic inflammation-mediated tumor initiation

Persistent IL-6 overexpression in the tumor microenvironment continuously activates cytoplasmic STAT3 phosphorylation and nuclear translocation, initiating transcription of multiple oncogenic genes to form an inflammatory-tumor vicious cycle. Hedyotis diffusa total extract, purified ursolic acid and quercetin can simultaneously reduce IL-6 protein abundance in cell supernatant and lesion tissue, and suppress STAT3 phosphorylation level to hinder its nuclear entry, thereby silencing downstream proliferative and inflammatory signal transduction and cutting off the source of inflammation-induced malignant transformation [6, 8].

Apart from direct regulation on tumor cells, the two monomers also act on stromal macrophages and intestinal epithelial cells to interrupt the generation of pro-inflammatory signals at the source. Under chronic inflammatory stimulation, tissue-resident macrophages will polarize to an immunosuppressive M2 phenotype and continuously secrete IL-6 to sustain STAT3 overactivation.

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Ursolic acid and quercetin can reverse M2 polarization of intestinal macrophages, elevate the secretion of anti-inflammatory IL-10 and reduce the release of IL-6, TNF-α and other pro-inflammatory cytokines, forming a double-layer blocking effect on the inflammatory pathway from both parenchymal tumor cells and stromal immune cells. Related co-culture experiments of macrophages and colon cancer cells prove that after monomer intervention, the IL-6 concentration in co-culture medium decreases by more than 60%, and the phosphorylation level of STAT3 in co-cultured tumor cells drops sharply compared with the model group, which further verifies the dual regulatory mode of the two monomers on the inflammatory microenvironment.

4.2. Arrest tumor cell cycle and activate apoptosis

Sustained STAT3 activation upregulates Cyclin D1 and CDK4 to accelerate G1/S phase transition and inhibit Bax-mediated apoptotic signals. Ursolic acid and quercetin jointly restrain STAT3 activity, downregulate proliferation-related proteins and increase the Bax/Bcl-2 ratio, further activating the Caspase-3/Caspase-9 cascade to trigger programmed death of colorectal cancer cells and restrain clone formation capacity [6, 9].

In terms of dosage-dependent efficacy difference, a medium-concentration combination of ursolic acid and quercetin presents the strongest cycle-blocking and pro-apoptotic effects. Low-concentration single monomer only produces mild inhibitory activity, while ultra-high concentration will cause mild oxidative damage to normal colon epithelial cells due to excessive clearance of intracellular reactive oxygen species. Combined administration at matching medium doses can maximize anti-tumor efficacy while avoiding off-target toxicity, which provides an important reference for the setting of intervention concentration in subsequent animal and clinical trials.

4.3. Inhibition of invasion and metastasis and epithelial-mesenchymal transition (EMT)

Hyperactivated STAT3 promotes MMP2/MMP9 secretion and downregulates E-cadherin, inducing EMT to strengthen tumor migration. Ursolic acid and quercetin block IL-6/STAT3 signal transmission, lower matrix metalloproteinase expression, restore epithelial phenotype and weaken tumor invasive capacity [10].

In vivo orthotopic colon cancer mouse models further validate the anti-metastatic synergism of the two monomers. After continuous oral intervention with Hedyotis diffusa extract containing equivalent doses of ursolic acid and quercetin, the number of liver and lung metastatic lesions in model mice is significantly reduced, and immunohistochemical detection of tumor tissues shows obvious downregulation of p-STAT3, MMP9 and Vimentin proteins. In contrast, single-component administration only achieves partial suppression of metastatic lesions, which fully reflects the complementary advantages of the two active ingredients in jointly inhibiting the EMT process mediated by IL-6/STAT3 pathway.

5. Synergistic value and translational deficiencies of Hedyotis diffusa combined chemotherapy

In the treatment system of integrated traditional Chinese and Western medicine for colorectal cancer, the application of Hedyotis diffusa combined with chemotherapeutic drugs has significant clinical advantages. One is the advantage of a multi-target synergistic effect, which is different from the mode of single-target killing of tumor cells by chemotherapy drugs. Hedyotis diffusa can simultaneously exhibit anti-inflammatory, anti-tumor and regulate immunity, and form a synergistic anti-tumor effect with chemotherapy to improve the overall therapeutic effect. The second is the

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advantage of low toxicity and toxicity reduction. The toxicity of traditional Chinese medicine components is low, which can significantly alleviate the gastrointestinal reaction, bone marrow suppression, body immunity decline and other toxic and side effects caused by chemotherapeutic drugs such as 5-fluorouracil and oxaliplatin, and protect the normal tissue of the body. The third is to improve the prognostic advantages, which can improve the intestinal microenvironment and body state of patients, reduce the risk of postoperative recurrence and metastasis, and improve the quality of life of patients.

At the same time, there are still obvious research and application limitations in this therapy. First, the bioavailability in vivo is insufficient. Ursolic acid and quercetin have poor natural water solubility, limited fat solubility, low oral absorption and utilization rate, and poor targeted enrichment effect in vivo, which limits the full play of the efficacy. Second, clinical evidence is weak. Most of the existing studies are basic cell and animal experiments. There are few large-sample, multi-center, randomized controlled clinical studies, and a lack of high-level evidence-based medical support. Third, the medication standards are not uniform. At present, there is no clear optimal intervention dose, administration cycle, optimal monomer ratio and compound compatibility standard, and there is a lack of a standardized basis for clinical application.

The intervention of colorectal cancer with Hedyotis diffusa extract or active monomer alone can effectively inhibit the basic growth of the tumor, reduce chronic intestinal inflammation and delay tumor progression. It is suitable for early inflammatory intervention of colorectal cancer, adjuvant conditioning in the postoperative recovery period and advanced palliative treatment of intolerance to chemotherapy. The overall effect is mild and safe, but the strong anti-tumor effect on advanced tumors is limited.

When combined with clinical first-line chemotherapy drugs, it can produce significant synergistic and attenuated reversal of drug resistance. Studies have shown that the tumor inhibition rate of Hedyotis diffusa combined with 5-fluorouracil, oxaliplatin and other conventional chemotherapy regimens in the treatment of colorectal cancer was significantly higher than that of the chemotherapy group and traditional Chinese medicine group. On the one hand, it can reverse the chemoresistance of tumor cells by regulating the IL-6 / STAT3 pathway and restore the sensitivity of tumor cells to chemotherapeutic drugs. On the other hand, it can significantly reduce the side effects of chemotherapy-induced leukopenia, nausea and vomiting, intestinal mucosal injury, etc., protect the body's immune function, and effectively compensate for the limited efficacy of chemotherapy alone, large side effects, and drug resistance. It is an ideal compatibility regimen for comprehensive treatment of colorectal cancer [11].

The dose gradient study of existing pharmacological experiments confirmed that Hedyotis diffusa and its monomers have the optimal pharmacodynamic dose window. The low-dose efficacy is insufficient; the high-dose has no obvious synergistic effect and may increase the metabolic burden. The medium-dose interval can achieve the balance effect of maximizing efficacy and minimizing toxicity, which is the optimal dose range for basic experiments and clinical interventions.

6. Limitations & future outlooks

6.1. Existing research limitations

Current relevant research mainly relies on preclinical cell and xenograft animal models, lacking long-term human cohort safety and efficacy data. The synergistic compatibility rules of ursolic acid and quercetin have not been quantitatively clarified, and unified clinical administration specifications are absent. Besides, poor water solubility restricts intratumoral enrichment of

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monomers, and systematic research on novel nano-delivery carriers is insufficient. The internal interaction between herbal monomers and intestinal flora under IL-6/STAT3 pathway regulation also needs further in-depth exploration.

6.2. Follow-up research directions

Subsequent research can carry out multi-center randomized controlled clinical trials to supplement high-level evidence for combined medication. Novel liposome and polymer nano preparations should be developed to improve monomer solubility and tumor targeting. Multi-omics technologies can be adopted to excavate the interaction network of two monomers on inflammatory signaling and intestinal flora, and standardized compatibility and dosage schemes can be formulated to promote the clinical transformation of Hedyotis diffusa adjuvant therapy for colorectal cancer.

7. Conclusion

This paper systematically elaborates the core regulatory effects of Hedyotis diffusa's ursolic acid and quercetin on the IL-6/STAT3 inflammatory oncogenic pathway in colorectal cancer. Chronic intestinal inflammation mediated by overexpressed IL-6 and persistent STAT3 activation drives colorectal cancer proliferation, apoptosis escape and distant metastasis. The two active monomers can simultaneously reduce IL-6 secretion and block STAT3 phosphorylation to cut off inflammatory oncogenic cascades, arrest tumor cell cycle and reverse EMT phenotype, and generate synergistic chemo-sensitizing and toxicity-reducing effects when combined with first-line chemotherapy drugs. Current research is limited by insufficient clinical evidence and low monomer bioavailability, and targeted nano preparations and standardized clinical trials are the key directions for future transformation. The integrated summary of multi-layer inflammatory intervention mechanisms in this paper provides systematic theoretical support for developing natural monomer adjuvant therapeutic agents for colorectal cancer.

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These authors contributed equally to this work.

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