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Hedyotis Diffusa for the Treatment of Gastric Cancer

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Abstract. Under the backdrop of rapid social development in modern times, factors such as Helicobacter pylori infection, increased life pressure, and changes in dietary structure have become significant risk factors for gastric cancer (GC). In current research, Hedyotis diffusa contains a variety of anti-cancer active chemical components, and the mechanisms of action of these components are different. However, due to the complexity of its chemical composition, many active components and their mechanisms of action remain unclear. This article analyzes the pathogenesis of GC and the research on Hedyotis diffusa against GC cells, and concludes that Hedyotis diffusa can exert anti-cancer effects through multiple pathways such as anti-inflammation, regulation of oxidative stress levels, enhancement of the body's immunity, and inhibition of GC cell metastasis. It provides a reference for the multi-target anti-cancer mechanism of Hedyotis diffusa for future research. However, the effects of Hedyotis diffusa combined with different chemotherapy drugs and the problem of its complex chemical composition have not been solved. Future research can focus on clarifying and analyzing the effects of more chemical components of Hedyotis diffusa in combination with chemotherapy drugs.

Keywords: Hedyotis diffusa, Gastric cancer, Antitumor mechanism, Chinese herbal compound

1. Introduction

Gastric cancer (GC) is a highly prevalent malignant tumor worldwide, ranks among the top in terms of both incidence and mortality. In China, the incidence of GC is particularly prominent, ranking third. Against the backdrop of rapid social development today, factors such as increased life pressure, changes in dietary structure, and weak health awareness have significantly raised the risk of GC [1].

At present, the treatment of GC in Western medicine mainly relies on surgery, radiotherapy and chemotherapy. However, for patients in the advanced stage, the quality of life often declines due to the side effects of chemotherapy and chemotherapy resistance, and the treatment effect has not met expectations. In the theoretical system of traditional Chinese medicine (TCM), GC falls under the categories of "dysphagia", "nausea and vomiting", "mass accumulation" and "stomach pain". TCM has accumulated profound experience in this field and demonstrated unique advantages. However, the therapeutic effect has not reached the expected level. Among them, Hedyotis diffusa, as a relatively important anti-tumor TCM, is widely used in the adjuvant treatment of GC due to its

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functions of clearing heat, detoxifying, promoting diuresis and reducing swelling. Modern pharmacological studies have shown that its active components, such as flavonoids, terpenoids, anthraquinones and polysaccharides, exhibit significant potential advantages in anti-GC through multiple pathways including regulating the immune system, anti-inflammation, inducing apoptosis of tumor cells and antioxidation [2]. Flavonoids and terpenoids are quite important in the treatment of gastric malignancies, both exerting excellent anti-inflammatory effects. Among them, flavonoids can also play a role in immune regulation and promoting apoptosis of tumor cells [3].

Therefore, this study focuses on the pathogenesis of GC, mainly involving the transformation from inflammation to malignant tumors, the imbalance between cellular oxidation and antioxidation, and the infection process of Helicobacter pylori. During this process, Hedyotis diffusa has demonstrated multi-target anti-cancer advantages, highlighting the advantages of traditional Chinese herbal medicine in the treatment of malignant tumors. Under the sole chemotherapy of Western medicine, patients often experience adverse reactions after chemotherapy. However, Hedyotis diffusa can be used in combination with chemotherapy drugs to reduce these adverse reactions, thus providing a broader perspective for the integrated treatment of GC with both traditional Chinese and Western medicine. This review will systematically elaborate on the above content.

2. The pathogenesis of GC

According to the research on the burden of GC in China by Zhan Zhouwei et al., it was found that from 1990 to 2021, the burden of GC has been increasingly severe, mainly manifested in the rise of new cases and the increase in mortality rate [4]. With the rapid development of society, significant changes have occurred in lifestyle, including the increasing prevalence of factors such as rising obesity rates and reduced physical activity, which collectively contribute to a higher overall cancer risk among the population. Specific risk factors for GC include Helicobacter pylori infection, smoking, heavy drinking, and a high-salt diet [5]. However, the early symptoms of GC are insidious and lack specificity, which leads to most cases being diagnosed at the middle or advanced stage in clinical practice, significantly affecting the prognosis. For advanced GC, chemotherapy, as a core treatment approach, focuses more on tumor progression and extending the survival period of patients [6].

The key mechanism in the occurrence of GC is closely related to the imbalance of the cell's oxidation and antioxidant system, which is manifested as excessive accumulation of reactive oxygen species (ROS). Among them, the persistent infection of Helicobacter pylori is the key factor that triggers this imbalance [7]. The infection initially causes damage to the gastric mucosa and destruction of epithelial cells, which then triggers an abnormal inflammatory immune response. To eliminate the pathogen, neutrophils produce ROS through phagocytosis. However, the body usually has difficulty effectively eradicating Helicobacter pylori, leading to the persistence of chronic inflammation [8]. This persistent bacterial infection forms a vicious cycle, driving neutrophils to produce ROS through continuous stimulation of chronic inflammation. The body is unable to effectively eliminate the excessive ROS, and oxidative stress continuously intensifies the risk of malignant transformation of gastric mucosal cells. Studies have shown that the level of ROS in GC cells is significantly higher than that in normal gastric tissue cells, reflecting the oxidative stress state during tumorigenesis [9].

Helicobacter pylori infection, as a core driving factor in the pathogenesis of GC, induces inflammatory responses in the body, prompting the release of pro-inflammatory factors by macrophages and other cells, thereby creating a chronic inflammatory microenvironment and serving as a key pathological basis for the malignant transformation of gastric mucosa [10,11]. At

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the molecular level, Helicobacter pylori promotes tumor growth by enhancing glycolysis with hexokinase domain-containing 1 (HKDC1) and reprogramming lipid metabolism, and by regulating the TGF-β/Smad2/ pathway to activate the epithelial-mesenchymal transition (EMT) pathway. To verify the above mechanism, relevant studies used the C75BL/6J mouse model, dividing the mice into two groups, both of which were fed with Helicobacter pylori. The first group was euthanized after 12 weeks, while the second group was extended to 36 weeks after infection. Pathological analysis showed that the first group mainly presented chronic atrophic gastritis; the second group progressed to precancerous lesions. Western blot and immunohistochemical staining (IHC) results further confirmed that Helicobacter pylori was positively correlated with gastric mucosal damage [12].

The persistent damage caused by chronic inflammation is a core concept in the occurrence and development of cancer [13]. Inflammatory damage can be classified into systemic inflammation and local inflammation based on its extent. Systemic inflammation is triggered by external stimuli such as tobacco and alcohol, leading to the persistent presence of inflammatory mediators in the systemic circulation, which hinders the body's normal repair mechanisms and thereby increases the risk of cancer systemically. Local inflammation is caused by chronic inflammation in specific areas, such as the inflammation of the gastric mucosa resulting from persistent infection with Helicobacter pylori in the stomach, or irregular schedules affecting the microenvironment and promoting the initiation and progression of tumors in that area [7]. These two types of inflammatory responses together form an important basis for cancer risk [14].

3. The multi-target anti-cancer mechanism of hedyotis diffusa

Modern mass spectrometers and other technologies can be used to analyze that the anti-active ingredients of Hedyotis diffusa are mainly rich in flavonoids, terpenoids, anthraquinones, polysaccharides and other chemical components [2]. The two most important types of compounds for the intervention of GC are flavonoids and terpenoids. Flavonoids mainly play roles in anti-inflammation, immune regulation, and promoting apoptosis of tumor cells, while terpenoids mainly have anti-inflammatory and antioxidant effects. These active components can target and regulate multiple key pathological links in the occurrence and development of GC, including oxidative stress imbalance (excessive accumulation of ROS), immune homeostasis disorder, and chronic inflammation [15].

The active extract of Hedyotis diffusa has a significant regulatory effect on oxidative stress. In the research conducted by Nie Lihua et al., it was found that in the experimental group of mice given the extract of Hedyotis diffusa, the activities of key antioxidant enzymes such as superoxide dismutase (SOD) in their serum and liver tissues significantly increased, while the levels of serum peroxidation products significantly decreased [16]. The results suggest that Hedyotis diffusa can effectively enhance the body's oxidative defense capacity and correct the imbalance between oxidation and antioxidant systems.

Hedyotis diffusa also has the potential to inhibit the metastasis of GC cells. The study selected normal gastric mucosal epithelial cell line GES-1 and human GC cell lines AGS, HGC-27, MKN-1 and MKN-28 for the experiment. The Hedyotis diffusa formula was prepared, which included Hedyotis diffusa Willd, Smilax china L. and Solanum lyratum Thunb, and was extracted by water decoction. The test was conducted in BALB/c nude mice. The results demonstrated that Hedyotis diffusa formula could effectively inhibit the growth of GC cells, and the inhibitory effect was related to the concentration of Hedyotis diffusa formula. The higher the concentration, the more obvious the inhibitory effect on GC cells. The Transwell assay confirmed that Hedyotis diffusa could weaken the

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invasive ability of GC cells, and by regulating the Wnt/β-catenin pathway to block the binding of nuclear transcription factors, it could reduce the metastasis of GC cells [17].

In the research on the factors of chronic inflammation in the induction of GC, it was found that the main anti-inflammatory components of Hedyotis diffusa include quercetin in flavonoids and ursolic acid in triterpenoids, etc. [3]. These components can regulate immune cells in the body, such as stimulating lymphocytes and macrophages, etc., adjust the immune status of the body, gradually reduce the inflammatory response, and lower the risk of inflammation transforming into cancer [2,18].

In the treatment of advanced GC, although radiotherapy and chemotherapy are the main approaches, the problems of chemotherapy resistance and adverse reactions after chemotherapy often affect the therapeutic effect. Intervention with TCM is one of the coping strategies. In relevant research, the effect of Hedyotis diffusa injection on cisplatin chemotherapy resistance in human GC SGC-7901 cell lines was explored. It was found that after treatment with Hedyotis diffusa injection, the apoptosis rate of cells significantly increased, suggesting that it can intervene in the resistance after cisplatin chemotherapy [19].

4. Clinical efficacy and prospects

In clinical practice, the therapeutic effect of single Chinese herbal medicines (such as Hedyotis diffusa) is limited. However, TCM compound prescriptions follow the principle of "sovereign, minister, assistant and messenger" in their formulation, and through the synergistic effects of multiple drugs, significantly enhance the therapeutic effect. Compound decoctions containing Hedyotis diffusa (such as Tumor Formula, Fuzheng Huadu Decoction, and Yiqi Jiedu Huoxue Formula) have shown promising application prospects in the treatment of GC. The main ingredients of the Tumor Formula include Hedyotis diffusa, Scutellaria barbata, and Dioscorea opposita, etc. The main ingredients of Fuzheng Huadu Decoction include Hedyotis diffusa, Scutellaria barbata, Astragalus membranaceus, etc. The main ingredients of Yiqi Jiedu Huoxue Formula include Hedyotis diffusa, Astragalus membranaceus, Codonopsis pilosula, etc. An observation involving 20 patients showed that after taking "Tumor and Formula", 10 cases (50%) had marked improvement, 8 cases (40%) were effective, and only 2 cases (10%) were ineffective. This suggests that this formula can effectively promote the recovery of patients with GC. In terms of improving the survival period after GC surgery, a study involving 50 postoperative patients found that the application of "Fuzheng Huadu Decoction" containing 30g of Hedyotis diffusa resulted in a 3-year survival rate of 47.7% and a 5-year survival rate of 31.8% for the patients. This indicates the potential of extending the survival period. In terms of enhancing the efficacy and reducing the toxicity of combined chemotherapy. A controlled study involving 32 patients with gastric adenocarcinoma demonstrated that the " Yiqi Jiedu Huoxue Formula " in combination with the ELF chemotherapy regimen (a combination of etoposide, calcium folinate and fluorouracil, which is mainly used for treating GC) significantly increased the overall response rate compared to chemotherapy alone, and also reduced toxic reactions [20].

5. Conclusion

In conclusion, the various active components contained in Hedyotis diffusa have a significant intervention effect on GC cells. Its advantages in fighting GC mainly lie in regulating the balance of oxidative stress, activating immune cells, interfering with key biological processes of GC cells such as migration, transcription, metabolism and cell cycle, as well as exerting anti-inflammatory effects.

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However, the therapeutic effect of using Hedyotis diffusa alone is limited. It is necessary to combine it with other traditional Chinese medicine formulas or chemotherapy regimens to maximize the treatment effect. It is worth noting that there are many limitations to the treatment of GC with Western medicine chemotherapy alone, as it is often accompanied by drug resistance after chemotherapy and adverse reactions after chemotherapy. Therefore, integrating traditional Chinese medicine (such as Hedyotis diffusa) with Western chemotherapy to jointly achieve the maximum therapeutic effect is an important direction for the future clinical treatment of GC. Given the complexity of its chemical composition, future research could employ metabolomics technology to further analyze and identify more active components, enhance their bioavailability and target specificity, and develop precise treatment strategies, providing innovative ideas for the prevention and treatment of GC.

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