

Treatment of Digestive System Tumors with Hedyotis Diffusa Willd

Ye Zhou

*Department of Pharmacy, Inner Mongolia Medical University, Hohhot, China
zhouhua03@gmail.com*

Abstract. Hedyotis diffusa Willd (HDW) is a traditional Chinese medicine (TCM) with the functions of clearing heat, detoxifying, anti-inflammation and anti-cancer. In recent years, its potential in the treatment of digestive system tumors has attracted extensive attention. Studies have shown that its active components can exert anti-cancer effects through multiple pathways such as antioxidation, anti-inflammation, apoptosis induction, invasion and metastasis inhibition, and immune regulation. Moreover, when combined with chemotherapy and immunotherapy, it shows synergistic effects and advantages in reducing toxicity. However, systematic research on the mechanism of action of its active components and clinical application is still insufficient. This article reviews the main active components, molecular mechanisms of action, and combined strategies with modern treatment methods of HDW in digestive system tumors such as gastric cancer, colorectal cancer, and liver cancer. It also summarizes the preliminary exploration results of formulation optimization and targeted delivery, demonstrating its unique advantages in multi-target intervention of the tumor microenvironment, reversal of drug resistance, and enhancement of immune response. In the future, further clarification of the component-pharmacodynamic relationship, optimization of drug delivery systems, and large-scale clinical trials will help promote its clinical transformation in comprehensive tumor treatment and provide references for the development of new anti-cancer preparations of TCM. Meanwhile, the analysis of drug resistance mechanisms and long-term efficacy evaluation remain important directions for subsequent research.

Keywords: Hedyotis diffusa, Digestive system tumors, Anti-tumor mechanism, Immune regulation, Combined therapy

1. Introduction

Cancer is one of the main factors contributing to the global burden of disease, posing a significant threat to human life safety and quality of life. Global cancer statistics show that in 2022, there were 19.96 million new cancer cases and 9.74 million deaths worldwide [1]. Among them, the incidence and mortality rates of digestive system cancers ranked at the top. The incidence rates of colorectal cancer and gastric cancer were ranked 3rd and 5th among global malignant tumors respectively, and the death numbers of colorectal cancer, liver cancer and gastric cancer were ranked 2nd, 3rd and 5th respectively.

Although traditional chemotherapy is the main treatment method for various malignant tumors, it has problems such as significant toxic side effects, strong drug resistance, and high recurrence rate. Therefore, exploring safer, more effective, and long-term applicable anti-tumor treatment methods has become an important direction in current medical research. Chinese herbal medicine (CHM), as an important part of traditional Chinese medicine (TCM), has accumulated rich anti-tumor experience through thousands of years of practice. In recent years, with the development of modern pharmacology, molecular biology, and chemical technologies, more and more traditional CHMs have been proven to not only effectively inhibit the proliferation and metastasis of malignant tumor cells, but also improve the chemotherapy drug resistance and alleviate its adverse reactions by regulating the expression of drug transport proteins, multi-target improvement of the tumor microenvironment, and intervention in biological effects such as cell apoptosis, autophagy, pyroptosis, or ferroptosis [2]. Due to its "multi-target, multi-pathway, and individualized" characteristics, traditional CHM shows significant potential in anti-tumor treatment and becomes an important supplement or even alternative means in comprehensive tumor treatment.

Hedyotis diffusa Willd (HDW, baihuasheshecao), a plant of the Rubiaceae family, is the dried or fresh whole herb of HDW. It has the functions of clearing heat, detoxifying, promoting diuresis and relieving stranguria. It is clinically used for treating appendicitis, abscesses, sores and swellings, as well as snake bites and cancerous tumors [3]. In recent years, it has been found to have broad-spectrum anti-tumor activity, and shows significant efficacy in the treatment of digestive system tumors.

2. The pathogenesis of digestive system tumors

Digestive system tumors include gastric cancer, colorectal cancer and liver cancer, etc., which are types of malignant tumors with high incidence and mortality rates worldwide. Modern medical research indicates that their occurrence and development is a complex process involving multiple factors and multiple steps, and includes multiple molecular signaling pathways as well as pathological physiological mechanisms.

As one of the key driving factors, oxidative stress damage plays a significant role in the form of tumor. Abnormal tumor cell metabolism provokes a large accumulation of reactive oxygen species (ROS) within the cells. Excessive ROS can attack DNA, proteins, and lipids, causing gene mutations and chromosomal instability. These changes further activate signaling pathways such as phosphatidylinositol 3-kinase - protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), and nuclear factor κ B light chain-enhanced B cell (NF- κ B), which promote cell proliferation and anti-apoptosis, providing a favorable environment for tumor formation and progression.

In the PI3K/Akt pathway, PI3K catalyzes the conversion of phosphatidylinositol-4,5-bisphosphate (PIP₂) into PIP₃, which can recruit Akt to the membrane for activation. Akt then phosphorylates downstream targets such as mammalian target of rapamycin (mTOR) and Glycogen synthase kinase-3 β (GSK3 β), regulating cell cycle, metabolism and survival. As a result, this pathway often remains persistently activated due to the loss of gene of phosphate and tension homology deleted on chromosome ten (PTEN) inhibitory function or excessive activation of receptor tyrosine kinases.

Furthermore, chronic inflammation is regarded as the "soil" for tumors. Patients with digestive system tumors often have continuous high expression of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) in their bodies. These factors can activate the NF- κ B

pathway, promoting tumor cell proliferation, angiogenesis, and immune evasion, ultimately leading to a malignant cycle of inflammatory-cancer transformation.

The NF- κ B pathway is usually mediated by the I κ B kinase (IKK) complex. After phosphorylation of I κ B- α , the p65/p50 heterodimer is released into the nucleus, inducing the expression of genes such as COX-2, MMP-9, and Bcl-xL, thereby enhancing cell survival and migration. IL-6 can also phosphorylate and activate signal transducer and activator of transcription 3 (STAT3) through janus kinases (JAK), inducing the expression of Bcl-2 and Cyclin D1, which further promotes cell growth and inhibits the activity of immune cells.

Abnormal activation of signaling pathways, such as Wnt/ β -catenin, STAT3, and transforming growth factor- β (TGF- β), is also widespread. As a key molecular mechanism in the process of carcinogenesis, it not only disrupts the balance between cell proliferation and apoptosis, but also enhances the migration and invasion abilities of tumor cells. In addition, the inactivation of tumor suppressor genes (such as p53, PTEN), the activation of oncogenes (such as c-Myc, Ras), and tumor angiogenesis have a profound impact on the disease process.

In summary, the complexity of the pathological mechanism of digestive system tumors determines that the treatment methods need to have the ability of “multiple pathways and multiple targets” intervention, which is precisely the potential advantage of TCM treatment.

3. The active components of HDW and its anti-tumor effects

HDW is a TCM commonly used in clinical practice for clearing heat and detoxifying as well as eliminating abscesses and resolving lumps. It has a wide variety of chemical components, mainly including flavonoids, terpenoids, anthraquinones, sterols, polysaccharides, etc. [4]. Modern pharmacological research has found that it has broad-spectrum anti-tumor activity, especially showing outstanding performance in the treatment of digestive system tumors.

3.1. Flavonoid

Flavonoids are the main pharmacological components of HDW. Currently, more than ten types of flavonoids have been isolated from HDW. Among them, the derivatives of kaempferol and quercetin flavonoids are the main components of the flavonoids of *Oldenlandia diffusa* (FOD) in HDW [5]. Studies have found that they have strong free radical scavenging ability and antioxidant activity, and can significantly reduce the oxidative stress level in the tumor microenvironment. Zhang et al. discovered that FOD can reverse the epithelial-mesenchymal transition (EMT) of liver cancer cells MHCC97-H induced by TGF- β 1 and inhibit their invasion and metastasis [6]. Zhou et al. found that FOD can inhibit the proliferation of colon cancer cells at a certain concentration and play a promoting role in the apoptosis of human colorectal cancer cells by activating Caspase 3 and reducing the Bcl-2/Bax ratio [7].

3.2. Terpenoids

Terpenoids are important structural components of HDW, including triterpenoids and sesquiterpenoids. Triterpenoid compounds include santalol, isosantalol, ursolic acid (UA), and oleanolic acid (OA), etc. [8], and they have extensive anti-tumor activities. Triterpenoids, due to their unique pentacyclic triterpenoid structure, can penetrate the cell membrane and interfere with multiple signaling pathways, demonstrating the advantage of multi-target intervention. Among them, UA and OA are research hotspots. UA has been proven to induce apoptosis through the

mitochondrial pathway, and its mechanism mainly involves the regulation of Bcl-2 family proteins. Jia et al. found that UA can cause apoptosis of human colorectal cancer HT-29 cells by antagonizing Bcl-2. Meanwhile, OA has emerged in the research of ferroptosis [9]. Sun et al. discovered that OA can weaken the synthesis ability of glutathione (GSH) by down-regulating the expression of phosphoric acid serine transferase 1 (PSAT1), leading to accumulation of iron ions and increased lipid peroxidation levels, thereby inducing ferroptosis in colorectal cancer cells and achieving anti-tumor effects [10].

3.3. Polysaccharides

The polysaccharide components of HDW are mainly acidic heteropolysaccharides, with complex molecular structures. The main chains are composed of galactose, rhamnose, arabinose, etc. Studies have shown that the polysaccharide components can enhance immunity, have antioxidant effects, and inhibit the proliferation of tumor cells [4]. Bai et al. discovered that the hedyotis diffusa polysaccharid (HDP) activates the IL-2/IL-2R signaling pathway, promotes IL-2-dependent T cell proliferation, and increases the expression of local cytokines such as INF- γ and IL-12 [11]. In the immunotherapy model of colorectal cancer, the combined application of HDP and PD-1 inhibitors can significantly enhance the efficacy of immune checkpoint inhibitors in the treatment of colorectal cancer.

3.4. Other types

In addition to the aforementioned components, HDW is also rich in anthraquinones (such as 2-hydroxy-3-hydroxymethylanthraquinone, HMA) and sterols (such as stigmasterol, β -sitosterol). Jin et al. used the tandem mass tag (TMT) protein quantification technique combined with bioinformatics analysis to compare the protein expression profiles of the gallbladder cancer cell line (GBC-SD) before and after HMA treatment. They found that HMA could significantly regulate 217 differentially expressed proteins and inhibit the PI3K/Akt, Wnt, HIF-1, and mTOR pathways, exerting multi-target and all-round anti-cancer effects on gallbladder cancer [12]. Chai et al. conducted routine cultivation of mouse colon cancer cells CT-26 and intervened with stigmasterol (ST), using the cell counting kit-8 (CCK-8) method to detect and depict the cell growth curve. They confirmed that ST could inhibit the proliferation of CT-26 and induce cell apoptosis, demonstrating certain tissue-specific anti-tumor activity [13].

These components work together to target and inhibit the processes of tumor cell survival, division, migration and immune escape, thereby exerting a comprehensive anti-cancer effect.

4. The combined treatment strategy of HDW

Modern treatment concepts emphasize the use of combined medications and multi-mechanism intervention. HDW has extensive potential in this regard. Studies have found that the combination of HDW with cisplatin and 5-fluorouracil (5-FU) can enhance the efficacy of the drugs while reducing the toxic and side effects caused by chemotherapy. The mechanisms may include enhancing drug sensitivity, inhibiting drug resistance pathways, and synergistically inducing cell apoptosis, etc.

Chen et al. established a subcutaneous transplantation model of liver cancer in nude mice and found that HDW could enhance the inhibitory effect of low-dose 5-FU on vascular endothelial growth factors (VEGF) and TGF- β , significantly enhancing the anti-angiogenic effect [14]. Jin et al. established a subcutaneous transplantation tumor model of colorectal cancer and found that the

compound HDW could improve the intestinal damage caused by 5-FU chemotherapy. Histological analysis showed that this combined treatment could down-regulate the expression of inflammatory factors TNF- α and IL-1 β , reduce intestinal mucosal epithelial cell apoptosis, and maintain the integrity of the intestinal barrier [15].

With the widespread application of immune checkpoint inhibitors such as PD-1/PD-L1, HDW has shown potential synergistic effects in regulating the immune microenvironment. When combined with immunotherapy, HDW, by activating T cells and improving the polarization state of tumor-associated macrophages (TAM), works in synergy with PD-1/PD-L1 inhibitors to enhance the immune response rate. Zheng et al. discovered through network pharmacology and in vivo experiments in mice that HDW regulates key immune factors such as IL6 and TNF, and known that TAM transforms into the M2 type, improving the immune microenvironment of liver cancer [16]. Liu et al. found in the MFC gastric cancer tumor-bearing mouse model that FOD can inhibit the activity of PD-1/PD-L1 in tumors, promote the proliferation and activation of tumor-infiltrating CD8⁺ T cells, and thereby alleviate immune evasion [17].

Furthermore, the current research has initially attempted to develop HDW into water extract granules, oral liquids, or nano drug delivery systems to enhance bioavailability and targeting, laying the foundation for clinical translation. For instance, the PLGA nano-delivery system based on the active components of HDW significantly increased the cell uptake efficiency in vitro models and enhanced the inhibitory effect on colorectal cancer cells. In the future, optimizing the formulation forms and further analyzing the pharmacodynamic correlations of key components will further promote the application of HDW in clinical practice.

5. Conclusion

This article comprehensively reviews the chemical components, molecular mechanism of action, and combined treatment strategies of HDW in digestive system tumors, highlighting its multi-target intervention characteristics in diseases such as gastric cancer, colorectal cancer, and liver cancer. Studies have shown that HDW not only can achieve antioxidant, anti-inflammatory, apoptosis induction, and immune regulation through multiple signaling pathways, but also exhibits significant synergistic and toxicity-reducing effects when combined with chemotherapy and immunotherapy. The introduction of formulation optimization and targeted delivery technologies provides new solutions for improving its bioavailability and targeting.

These findings indicate that HDW has significant advantages in the multi-mechanism comprehensive intervention of tumors, providing a feasible approach for the application of TCM in modern tumor treatment. Compared with traditional single-target drugs, its ability to simultaneously regulate the tumor microenvironment through multiple pathways, inhibit drug resistance, and enhance immune response, demonstrates its potential important position in the comprehensive tumor treatment system. The summary and analysis model of this study can also provide a reference for other studies on anti-tumor effects of TCM.

However, at present, there is still a lack of in-depth verification regarding the precise correspondence between the components and therapeutic effects of HDW, as well as its long-term safety and clinical effectiveness. Future research should focus on the detailed analysis of the mechanism of action, the iteration of delivery technologies, and the optimization of combined treatment models, in order to lay a scientific foundation for its promotion in precision medicine and comprehensive treatment systems.

References

- [1] Wang, P., Huang, Q., Wang, S., Chen, X., Zhang, R., Zhao, J., ... Li, X. (2024). Interpretation of the key points of "Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries". *Chinese Journal of Clinical Thoracic and Cardiovascular Surgery*, 31(07), 933–954.
- [2] Huang, J., Liu, Y., Li, H., Mou, Q., Li, C., Liu, C., & Gao, Y. (2025). Traditional Chinese medicine ameliorates tumor chemotherapy resistance: A review. *Chinese Journal of Experimental Traditional Medical Formulae*, 31(10), 105–116.
- [3] Jiang, D., Zhong, C., Shao, P., Liu, B., Liu, D., Xu, G., ... Wu, M. (2025). Textual study of Baihuasheshecao (*Hedyotis diffusa*). *China Journal of Chinese Materia Medica*, 1–13.
- [4] Li, Z., Zhang, J., Li, F., Fu, L., Zhu, Z., & Wang, G. (2021). Research progress on chemical components and pharmacological action of *Hedyotis diffusa* in treating cancer. *Information on Traditional Chinese Medicine*, 38(02), 74–79.
- [5] Huang, L., Chen, B., & Luo, L. (2023). Research advances in chemical components, pharmacological activities, and clinical application of *Hedyotis diffusa*. *Chinese Pharmaceutical Affairs*, 37(12), 1451–1460.
- [6] Zhang, Y., Zhu, J., Xiao, J., Guo, Y., Liao, Z., & Xu, R. (2016). Effect and mechanism of total flavones of *Oldenlandia diffusa* Willd on epithelial-mesenchymal transition of MHCC97-H cell line induced by TGF- β 1. *Journal of Xi'an Jiaotong University (Medical Sciences)*, 37(02), 279–282, 306.
- [7] Zhou, J., & Chen, S. (2024). Effects of total flavonoids of Baihua Sheshecao on proliferation and apoptosis of human colorectal cancer cells. *Clinical Journal of Chinese Medicine*, 16(19), 49–54.
- [8] Li, B. (2016). Research progress on chemical components and pharmacological effects of *Hedyotis diffusa*. *Tianjin Pharmacy*, 28(05), 75–78.
- [9] Jia, P., Liu, J., Liu, Y., Wei, L., Zhang, L., & Lin, J. (2025). Ursolic acid induces apoptosis of human colorectal cancer HT-29 cells by antagonizing Bcl-2. *Journal of Guangdong Pharmaceutical University*, 41(03), 57–63.
- [10] Sun, Q., Sun, R., He, B., Meng, H., Jin, J., & He, J. (2025). Inhibition of glutathione pathway by oleanolic acid via PSAT1 leads to ferroptosis in colorectal cancer. *Drug Development Research*, 86(3), e70097.
- [11] Bai, L., Liu, X., Yuan, Z., Xu, G., Li, X., Wan, Z., ... Wei, G. (2025). Activation of IL-2/IL-2R pathway by *Hedyotis diffusa* polysaccharide improves immunotherapy in colorectal cancer. *International Journal of Biological Macromolecules*, 306(P4), 141013.
- [12] Jin, H., & Cui, M. (2021). Proteomics analysis on gallbladder carcinoma cells treated by 2-hydroxy-3-methylanthraquinone, the active component of *Herba Hedyotis*. *Military Medical Journal of South China*, 35(05), 315–322, 333.
- [13] Chai, X., Zhang, Z., Yin, P., He, L., Bai, Z., & Xiao, X. (2016). Comparative study on antitumor activity of active ingredients in *Oldenlandia diffusa*. *Journal of Logistics University of PAP (Medical Sciences)*, 25(05), 350–353.
- [14] Chen, X., Cao, Z., Zhang, Y., Liao, L., Liu, Z., & Du, J. (2012). Effect of *Hedyotis diffusa* Willd combined with low-dose 5-fluorouracil on antiangiogenesis in hepatocellular carcinoma. *Journal of Fujian University of Traditional Chinese Medicine*, 22(04), 20–23.
- [15] Jin, Y. (2018). Effect of *Hedyotis diffusa* Willd formula on alleviating 5-FU-induced intestinal damage in colorectal cancer (Master's thesis). Available from CNKI.
- [16] Zheng, Q., Wu, X., & Peng, S. (2024). The immunotherapy mechanism of *Hedyotis diffusa* Herba in treating liver cancer: A study based on network pharmacology, bioinformatics, and experimental validation. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 398(1), 1–15.
- [17] Liu, Q. (2024). Investigating the effects of total flavonoids of *Hedyotis diffusa* on immune function and on PD-1 and PD-L1 in MFC gastric cancer (Master's thesis). Available from CNKI.