The Anti-Gastric Cancer Mechanisms of Major Flavonoid Components from Scutellarin Barbata

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Abstract. Gastric cancer is a highly prevalent malignancy of the digestive system worldwide, posing a serious threat to human health, particularly in East Asia where the burden is substantial. With advances in traditional Chinese medicine research, Scutellaria barbata has attracted considerable attention due to its heat-clearing, detoxifying, and antitumor properties, with flavonoid constituents recognized as the primary bioactive compounds responsible for its anticancer effects. Current studies indicate that flavonoids from S. barbata can inhibit gastric cancer cell proliferation, induce apoptosis and autophagy, and suppress metastasis and angiogenesis by modulating multiple signaling pathways at both cellular and animal levels. Although research on this topic is increasing, the mechanisms of individual flavonoid components and their clinical validation remain relatively limited. This review systematically summarizes the progress of major flavonoid compounds from S. barbata, including luteolin, apigenin, naringenin, and wogonoside, in gastric cancer research, analyzing their effects and mechanisms in cellular experiments, animal models, and clinical applications, while also delineating the regulatory patterns of different signaling pathways involved in their anticancer activity. The results suggest that S. barbata flavonoids exert multi-targeted synergistic effects with potential clinical value. This study provides a reference for further exploration of the pharmacological mechanisms of S. barbata flavonoids and their development as novel anticancer agents, while highlighting current limitations such as unclear targets of individual constituents and insufficient clinical evidence. Future research should integrate multi-omics approaches with clinical trials to investigate the crosstalk among signaling pathways and advance translational applications.

Keywords: Gastric cancer, Scutellaria barbata, Flavonoid Components.

1. Introduction

Gastric cancer remains one of the most prevalent and lethal malignancies of the digestive system worldwide, consistently ranking among the highest in both incidence and mortality. According to the GLOBOCAN 2020 statistics, over one million new cases of gastric cancer are diagnosed annually, with more than 700,000 deaths reported globally. This disease poses a serious threat to human health, with particularly high incidence rates in East Asian countries [1]. China is among the countries most severely affected, ranking at the forefront in both incidence and mortality. The pathogenesis of gastric cancer is a multifactorial and multistep process, involving genetic susceptibility, environmental influences, dietary habits, infections, and other risk factors. Because the early symptoms are often nonspecific, many patients are diagnosed only at advanced stages, when treatment is more challenging and survival rates are significantly reduced. As a result, identifying more effective strategies for prevention and therapy has become a pressing priority in oncological research.

In recent years, traditional Chinese medicine (TCM) has gained increasing attention as an adjuvant approach to cancer treatment due to its mild pharmacological effects, relatively low toxicity, and multi-target regulatory potential. Scutellaria barbata (Ban-Zhi-Lian), a widely used medicinal herb in TCM, has long been applied for its properties in clearing heat and toxins, promoting blood circulation, and exerting antitumor activities [2]. Among its phytochemicals, flavonoids are considered to be the key bioactive constituents responsible for anticancer effects. Previous studies have demonstrated that flavonoids from Scutellaria barbata can suppress the proliferation of gastric cancer cells, induce apoptosis, inhibit angiogenesis, and impede tumor metastasis in both in vitro and in vivo models [3]. Nevertheless, systematic and in-depth investigations into the specific flavonoid compounds, their

precise anti-gastric cancer activities, and molecular mechanisms remain insufficient. Most available studies have primarily focused on crude extracts, with relatively limited research on the isolation, structural characterization, and target-specific mechanisms of individual flavonoid components [4].

Against this background, the present review aims to systematically summarize the current progress on flavonoid compounds derived from Scutellaria barbata in the treatment of gastric cancer. Specifically, it provides a comprehensive overview of the major active constituents, their anticancer mechanisms, and related pharmacological studies. By consolidating existing evidence, this review intends to offer a theoretical foundation and research direction for future investigations on Scutellaria barbata flavonoids, and to facilitate the development of novel therapeutic agents for gastric cancer.

2. Phytochemical Analysis of Scutellaria Barbata

2.1. Overview of Scutellaria Barbata

Scutellaria barbata, a perennial herb belonging to the genus Scutellaria in the family Lamiaceae, is widely distributed in Zhejiang, Jiangsu, Anhui, and other regions of China. Its medicinal use has been recorded in ancient Chinese medical texts. For instance, in Yaojing Shiyi Fu, it was described as the "immortal herb for treating snakebites," and Waike Zhengzong also documented its therapeutic properties. According to TCM theory, it is pungent and bitter in taste, cold in nature, and enters the lung, liver, and kidney meridians. It is believed to possess the effects of clearing heat and detoxification, promoting blood circulation and removing blood stasis, as well as alleviating pain [5]. Modern pharmacological studies have demonstrated that S. barbata exhibits a wide range of biological activities, including antitumor, anti-inflammatory, antioxidant, antibacterial, antiviral, hypoglycemic, and lipid-lowering effects. Clinically, it has been applied in the treatment of lung cancer, ovarian cancer, and breast cancer. Among its bioactive constituents, flavonoids represent the primary material basis and play a central role in its pharmacological activities.

2.2. Analysis of Flavonoid Constituents in Scutellaria Barbata

In studies on the chemical constituents of Scutellaria barbata, flavonoids represent the most characteristic and representative group of compounds. Liu Xinyang et al. investigated these constituents from multiple perspectives, emphasizing their pharmacological significance. From a pharmacological standpoint, their research primarily focused on the preparation processes of flavonoids, including solvent extraction, microwave-assisted extraction, supercritical fluid extraction, and alcohol extraction–acid precipitation. By optimizing process parameters and comparing extraction yields, their work provided valuable references for subsequent pharmacological studies and clinical development [6]. In contrast, Wang Chenyuan et al. concentrated on the analysis of chemical constituents. Using whole S. barbata herbs sourced from the Bozhou herbal medicine market in Anhui, they carried out ethanol extraction and solvent partitioning, followed by separation with silica gel column chromatography and Sephadex LH-20 (GE Healthcare, Sweden) gel chromatography. Structural identification was then performed through nuclear magnetic resonance (NMR) and mass spectrometry (MS) [7]. Their results revealed that S. barbata is highly enriched in flavonoids, including both aglycones (such as scutellarein, luteolin, and apigenin) and glycosides (such as baicalin and cosmosiin). Liu et al. further summarized that more than 50 flavonoid compounds have been identified in S. barbata, comprising 28 flavones, 6 dihydroflavones, and 16 flavonoid glycosides, with scutellarin, scutellarein, luteolin, apigenin, hispidulin, and chrysin being representative compounds. Meanwhile, Wang et al. successfully isolated and identified 12 monomeric compounds, including hispidulin, scutellarein, scutellarin, luteolin, apigenin, chrysin, 4'-hydroxychrysin, naringenin, 7-hydroxy-5,8,2'-trimethoxyflavanone, and cosmosiin, among others. These findings not only provide a material basis for the pharmacological activities of S. barbata but also shed light on the complex chemical foundation underlying its diverse therapeutic effects.

2.3. Applications of Flavonoid Compounds

Further analyses have demonstrated that among the representative flavonoids of Scutellaria barbata, scutellarin, scutellarein, luteolin, apigenin, hispidulin, and chrysin are the most extensively studied and exhibit the most prominent pharmacological activities. Scutellarin and scutellarein have shown beneficial effects in the prevention and treatment of Alzheimer's disease by inhibiting neuronal apoptosis and reducing excessive tau protein phosphorylation, thereby improving cognitive function. Luteolin and apigenin possess significant anti-inflammatory and antioxidant properties, and they can suppress cancer cell proliferation while inducing apoptosis. Chrysin has demonstrated notable inhibitory effects in various tumor models and is closely associated with immunomodulation. Hispidulin, as a representative dihydroflavone, exhibits both antioxidant and anticancer potential, contributing positively to the maintenance of cellular homeostasis. The importance of these compounds is reflected not only in experimental studies but also in their gradual translation into clinical applications. For instance, S. barbata is often combined with Hedyotis diffusa for the adjuvant treatment of various malignancies. Compound Shenyuan tablets containing S. barbata have been used to alleviate diabetes and its complications [8]. Tonglong Buzhong decoction, applied in colorectal cancer patients, has been reported to inhibit tumor growth, mitigate chemotherapy-induced adverse effects, and improve clinical symptoms. Moreover, Ankangxin capsules, a patented formulation with S. barbata as a core ingredient, have been applied in the treatment of lung, cervical, liver, and gastric cancers. Collectively, these findings indicate that the flavonoids of S. barbata not only exhibit diverse pharmacological activities at the molecular and cellular levels but also play a significant role in modern clinical practice and novel drug development. Their representative compounds provide a solid theoretical and practical foundation for the development of natural anticancer and neuroprotective agents.

3. Flavonoid Constituents of Scutellaria Barbata

3.1. Luteolin

Luteolin exerts its anti-gastric cancer effects by targeting hypoxia-inducible factor HIF-1α, with mechanisms primarily involving dual regulation of gastric cancer cell proliferation and migration. Studies have demonstrated that luteolin significantly inhibits the proliferative activity of BGC-823 and MGC-803 gastric cancer cells in a concentration- and time-dependent manner, an effect closely associated with the suppression of phosphorylation levels of key proteins in the Akt/mTOR signaling pathway, thereby blocking pro-proliferative signal transduction. Regarding its anti-migratory role, luteolin acts by reversing the epithelial–mesenchymal transition (EMT) process, downregulating mesenchymal markers N-cadherin and vimentin while upregulating the epithelial marker E-cadherin, thereby attenuating the invasive and metastatic capacity of gastric cancer cells. Mechanistically, luteolin directly regulates HIF-1α expression. Experimental validation has confirmed that luteolin suppresses HIF-1α expression at both the mRNA and protein levels in a dose-dependent manner. As a central transcription factor within the hypoxic tumor microenvironment, HIF-1α promotes proliferation via activation of the downstream Akt/mTOR pathway and facilitates metastasis by inducing EMT and angiogenesis. Crucial verification experiments further revealed that siRNA-mediated knockdown of HIF-1α markedly diminished the inhibitory effects of luteolin on proliferation-associated proteins and cell migration, demonstrating that HIF-1α serves as the core target of luteolin's anti-gastric cancer activity. This mechanism is consistent with findings from studies in melanoma and other cancers, highlighting a cross-cancer regulatory commonality of luteolin. Collectively, luteolin inhibits gastric cancer progression by suppressing HIF-1α expression and synergistically blocking both Akt/mTOR-mediated proliferative signaling and EMT-driven migration [9].

3.2. Apigenin

Apigenin exerts anti-gastric cancer effects by dually targeting the mTOR (mammalian target of rapamycin) and STAT3 (signal transducer and activator of transcription 3) signaling pathways, thereby inhibiting cell proliferation and inducing lethal autophagy. Studies have shown that apigenin significantly suppresses the proliferative activity of HGC-27 (poorly differentiated gastric carcinoma) and MKN-28 (well-differentiated adenocarcinoma) gastric cancer cells in a concentration-dependent manner. Mechanistically, this effect involves simultaneous inhibition of phosphorylation and activation of the mTOR and STAT3 pathways. Western blot analysis revealed that apigenin markedly reduced the protein expression levels of p-mTOR and p-STAT3, thereby blocking pro-proliferative signaling. With respect to autophagy regulation, apigenin increased the number of intracellular acidic vesicular organelles, upregulated the autophagy marker LC3B-II, and downregulated p62 (an autophagy adaptor protein), confirming the activation of autophagic flux. Key validation experiments demonstrated that co-treatment with the autophagy activator rapamycin (RAPA) synergistically enhanced the apigenin-mediated degradation of p62 and further suppressed cell viability, indicating that apigenin induces "lethal autophagy," a form of excessive autophagy leading to gastric cancer cell death. Notably, in HGC-27 cells, apigenin also promoted AMPK (AMP-activated protein kinase) phosphorylation, suggesting a cell type-specific regulatory mechanism, whereas this effect was not observed in MKN-28 cells. Collectively, apigenin suppresses gastric cancer progression by synergistically inhibiting the mTOR/STAT3-driven proliferative signaling and activating lethal autophagy [10].

3.3. Naringenin

Naringenin is a naturally occurring flavonoid widely found in citrus fruits, exhibiting diverse biological activities including antioxidant, anti-inflammatory, and antitumor effects. To investigate its role in gastric cancer, researchers selected human gastric cancer SGC-7901 cells as an in vitro model and systematically analyzed the underlying mechanisms through a series of experimental approaches. In cytological assays, cell viability tests demonstrated that naringenin significantly inhibited gastric cancer cell proliferation in a concentration- and time-dependent manner. Morphological observations under an inverted microscope revealed that, under different concentrations of naringenin, SGC-7901 cells exhibited shrinkage, rupture, and even condensation into a rounded form, indicating evident cytotoxic effects on tumor cells. Furthermore, flow cytometry confirmed that naringenin effectively induced apoptosis, with apoptosis rates increasing markedly along with higher concentrations. At the molecular level, RT-PCR and Western blot analyses showed that naringenin upregulated the expression of pro-apoptotic factors Bax, Caspase-3, and Caspase-9, while downregulating the anti-apoptotic protein Bcl-2, thereby promoting programmed cell death. More importantly, at the signaling pathway level, naringenin exerted significant regulatory effects by inhibiting the PI3K/Akt signaling pathway, reducing the expression of p-PI3K and p-Akt proteins, and thereby blocking cell survival signaling and enhancing apoptosis. In conclusion, naringenin exerts anticancer effects in gastric cancer cells through multilayered and multi-pathway interventions, suggesting its potential as a promising candidate for future targeted therapy in gastric cancer [11].

3.4. Wogonoside

Wogonoside is a flavonoid compound isolated from plants of the Scutellaria genus and has attracted attention in recent years due to its remarkable pharmacological activities. In studies on gastric cancer, researchers used human gastric cancer HGC-27 cells as the experimental model and systematically investigated its mechanisms through various cellular and molecular biology techniques. First, cell viability assays showed that wogonoside significantly inhibited the proliferation of HGC-27 cells, with IC50 values of 87.08 μM at 24 h and 61.69 μM at 48 h, exhibiting both concentration- and time-dependent effects. Further Hoechst staining revealed that wogonoside markedly induced nuclear condensation and enhanced fluorescence in HGC-27 cells, suggesting its pro-apoptotic effect. In cell migration and invasion assays, scratch wound healing and Transwell experiments

demonstrated that wogonoside effectively suppressed cellular migration and invasion, indicating strong anti-metastatic potential. Mechanistically, ROS detection and JC-1 staining indicated that wogonoside treatment led to a significant increase in intracellular reactive oxygen species and induced mitochondrial membrane potential depolarization, suggesting that it may promote cell death via oxidative stress pathways. Additionally, FerroOrange staining showed that wogonoside increased intracellular Fe^{2+} levels, further supporting its role in inducing ferroptosis. Combined with protein interaction network analysis and Western blot experiments, it was found that wogonoside downregulated EGFR (Epidermal Growth Factor Receptor) expression and upregulated COX2 (Cyclooxygenase-2) levels, thereby regulating ferroptosis through the EGFR/COX2 signaling pathway. Overall, wogonoside not only exerts anticancer effects by promoting apoptosis but also inhibits gastric cancer progression through the induction of ferroptosis, providing new insights and potential therapeutic targets for gastric cancer treatment [12].

4. Advances in the Antitumor Applications of Scutellaria Barbata

As a traditional Chinese medicinal herb, Scutellaria barbata has demonstrated remarkable potential in anticancer research and has recently become a research hotspot in gastric cancer therapy. Extensive studies have shown that S. barbata and its major active constituents exhibit significant anticancer effects in cellular, animal, and clinical settings.

4.1. Progress in Pharmacological Research in Cell and Animal Models

At the cellular level, studies have found that aqueous extracts of S. barbata and its flavonoid components can effectively inhibit gastric cancer cell proliferation and promote apoptosis. For instance, naringenin in SGC-7901 cells induces apoptosis and suppresses malignant proliferation by inhibiting the PI3K/Akt signaling pathway, downregulating p-Akt and p-PI3K expression, and upregulating Bax, Caspase-3, and Caspase-9. Wogonoside in HGC-27 cells exhibits pronounced anticancer activity not only by promoting apoptosis through increased ROS levels and decreased mitochondrial membrane potential but also by inducing ferroptosis via elevated Fe^{2+} levels and regulating cell growth through the EGFR/COX2 signaling pathway, significantly inhibiting migration and invasion. Moreover, studies have indicated that total flavonoids from S. barbata can modulate signaling pathways such as STAT3 and NF-κB, thereby blocking the survival advantage of gastric cancer cells, suggesting a multi-targeted and multi-pathway anticancer mechanism [13].

In animal studies, extracts of S. barbata have been shown to significantly suppress tumor growth and metastasis in vivo. For example, Sheng et al. employed a 22RV1 mouse xenograft model and found that oral administration of medium to high doses of S. barbata extract effectively reduced tumor volume and weight without notable toxicity. Additionally, treated tumor tissues showed decreased expression of proliferation markers such as Ki-67, upregulation of E-cadherin, and downregulation of N-cadherin, indicating that S. barbata may exert anti-metastatic effects by modulating EMT and the PI3K/Akt pathway. Similar findings have been confirmed in other animal experiments, demonstrating the stable in vivo anticancer efficacy of S. barbata [14].

4.2. Clinical Use and Therapeutic Potential

In clinical applications, Scutellaria barbata and its compound formulations have been widely used as adjuvant therapies for digestive system tumors. A review by Chen Lei and colleagues highlighted that TCM formulas containing S. barbata demonstrated advantages in multiple clinical studies, including improving patients' quality of life, enhancing sensitivity to radiotherapy and chemotherapy, and reducing adverse reactions [15]. For example, the combination of S. barbata and Hedyotis diffusa in patients with advanced gastrointestinal tumors showed a relatively high objective response rate, and some studies also suggested improvements in immune function and prolonged patient survival. Compared with chemotherapy alone, patients receiving combined S. barbata formulations exhibited better tolerance, indicating its significant value in modern clinical practice [16].

5. Conclusion

Flavonoid components, such as apigenin and luteolin, exert anti-gastric cancer effects by regulating multiple keys signaling pathways through a multi-targeted approach. Current studies indicate that their mechanisms primarily include: (1) Inhibition of proliferation and migration: by downregulating the mTOR/STAT3 pathway (reducing p-mTOR and p-STAT3 protein expression) and HIF-1α-mediated AKT/mTOR signaling, flavonoids can arrest the cell cycle and inhibit EMT, decreasing N-cadherin and Vimentin expression; (2) Induction of autophagy and apoptosis: activating the AMPK pathway, upregulating autophagy markers such as LC3-II and Beclin-1, promoting p62 degradation, and triggering mitochondrial apoptosis via the AMPK/p53 pathway; (3) Reversal of drug resistance: when combined with chemotherapeutic agents such as 5-FU, flavonoids enhance drug sensitivity and downregulate the expression of multidrug resistance genes. These findings highlight the synergistic multi-pathway anticancer potential of flavonoid compounds, providing theoretical support for the development of low-toxicity, high-efficacy herbal anti-gastric cancer drugs.

Current research has mainly focused on the anticancer mechanisms of compound Scutellaria barbata formulations, while the mechanisms of its core flavonoid constituents remain insufficiently explored. The specific molecular targets and signaling pathways of individual flavonoid components require further elucidation. Additionally, the mechanisms of TCM intervention in gastric cancer are complex; besides known pathways such as AMPK/mTOR and STAT3, other key pathways like Wnt and NF-κB are involved, and the crosstalk network among these pathways has yet to be systematically analyzed. Multi-omics approaches are needed to explore these synergistic effects. Moreover, most current studies are limited to cell and animal models, and clinical translational evidence is lacking. Research on compound formulations far exceeds that on single constituents, resulting in limited knowledge on the extraction processes, in vivo metabolism, and druggability of active components. Future studies should focus on elucidating the mechanisms of individual S. barbata flavonoids, integrating cross-pathway regulation research, and advancing clinical validation to promote translational applications.

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