


Research on Buyang Yiwei Decoction in the Treatment of Gastric Cancer Based on PI3K/AKT Signaling Pathway: A Review

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Abstract: Gastric cancer is a digestive tract malignant tumor with high incidence and high mortality rate in the world, and patients with advanced gastric cancer often face clinical difficulties such as drug resistance and significant toxic and side effects. Traditional Chinese medicine shows unique advantages of multi-target and multi-pathway regulation in the comprehensive treatment of gastric cancer. Buyang Yiwei Decoction is a classic prescription for replenishing qi and nourishing blood, and combining tonification with dispersion. Clinical studies have confirmed that Buyang Yiwei Decoction combined with chemotherapy can significantly improve the performance status of patients with advanced gastric cancer, decrease the levels of tumor markers, and alleviate chemotherapy-induced organ damage/toxicities. In this paper, we systematically combed the key biological processes of the PI3K/AKT signaling pathway in the occurrence and development of gastric cancer. Our study found that the core active ingredients of Buyang Yiwei Decoction have been shown to inhibit the abnormal activation of the PI3K/AKT pathway, down-regulate the key phosphorylated proteins in this pathway, regulate downstream effector molecules, and thereby exert the molecular mechanism of inhibiting gastric cancer cell proliferation, inducing apoptosis, suppressing invasion and metastasis, and reversing chemotherapy resistance. However, current studies on the holistic mechanism of Buyang Yiwei Decoction remain insufficient; the evidence for clinical translation is weak; and the precision of its therapeutic targets needs to be improved. The next step is to further elucidate the multi-component synergistic mechanisms by which Buyang Yiwei Decoction regulates the PI3K/AKT pathway through an integrated approach combining network pharmacology, animal model validation, and multi-center clinical research. It is also essential to clarify its precise therapeutic value in targeting specific pathological processes. This will provide a more targeted, mechanism-elucidated, and higher-level evidence-based scientific foundation for its clinical application as an adjunctive strategy in the precision treatment of gastric cancer.

Keywords: Buyang Yiwei decoction, gastric cancer, PI3K/AKT signaling pathway, anti-tumor mechanism

Background

Gastric cancer (GC) is a malignant tumor of the digestive tract originating from the gastric mucosal epithelium, which occupies an important position in the global public health burden. According to the data of the World Health Organization Global Cancer Statistics Database in 2022, there are about 1 million new cases and 660,000 deaths in GC, ranking fifth in the world in terms of mortality rate of malignant tumors, and there are significant gender differences in morbidity and mortality, with male morbidity and mortality significantly higher than female.¹ According to the latest data from the National Cancer Surveillance Center of China, GC ranked third in the incidence of malignant tumors in the male population, second only to lung cancer and liver cancer; the incidence of GC in the female population did not enter the top five, but the mortality rate of GC ranks third among malignant tumors in both men and women. It is worth noting that in the past 20 years, with the decrease of *Helicobacter pylori* (Hp) infection rate, the improvement of cold chain and food preservation (which reduces nitrite intake) and the optimization of dietary structure, the age-standardized incidence of GC has shown an overall downward trend, but the absolute number of GC cases in China remains high, and the prevention and control of the disease still needs a lot of resources.²

According to the Asian Cancer Research Group classification criteria, GC can be divided into four molecular subtypes: microsatellite unstable type (MSI); microsatellite stable type (MSS) with p53 characteristics (abnormal expression of CDKN1A and MDM2); MSS type without p53 characteristics; epithelial-mesenchymal transition (EMT) phenotype. Among them, patients with MSS/EMT subtype GC have a higher risk of recurrence and a worse overall survival rate, which is significantly different from other subtypes.³ The key risk factors of GC include Hp infection, poor dietary habits (such as high salt diet), obesity, smoking and genetic susceptibility. Early intervention of GC has a good prognosis, and early detection through a comprehensive diagnostic procedure is essential to optimize the treatment outcome. However, due to the insidious symptoms of early GC, the clinical diagnosis rate is low, about 70–80% of patients have progressed to the middle and late stages when diagnosed, and the 5-year survival rate is significantly reduced. At present, the first-line treatment of locally advanced GC is mainly surgery, while for advanced GC, systemic therapies such as chemotherapy, targeted therapy or immunotherapy are the main options.⁴ In recent years, with the application of immunotherapy and targeted therapy in the field of advanced gastric cancer, systematic treatment strategies have been continuously improved, and emerging therapies have also shown promising results in GC treatment, such as novel targeted agents and next-generation immune checkpoint inhibitors, which have shown hope in improving survival and quality of life.⁵ It is worth noting that during radiotherapy, chemotherapy or targeted therapy, patients often have problems such as treatment-related side effects and decreased tolerance. Treatment based on syndrome differentiation of traditional Chinese medicine combined with intervention of traditional Chinese medicine can effectively reduce the adverse reactions of radiotherapy and chemotherapy such as nausea and vomiting, bone marrow suppression, etc. For the core symptoms such as cancer pain and anorexia, traditional Chinese medicine compound can significantly improve the quality of life of patients. When combined with modern therapies, TCM can enhance anti-tumor efficacy by regulating the tumor immune microenvironment, leading to a 15–22% increase in the objective response rate (ORR). Especially in the clinical dilemma of stagnant efficacy of traditional chemotherapy drugs, limited selection of targeted drugs and poor response rate of immune monotherapy, traditional Chinese medicine treatment provides an important complementary therapeutic strategy for advanced gastric cancer.^{6,7}

Given the bottleneck issues in the treatment of GC, particularly advanced and specific molecular subtypes such as MSS/EMT-type gastric cancer which are closely associated with the abnormal activation of intracellular survival, proliferation, and anti-apoptotic signaling pathways, it is of paramount importance to explore intervention strategies capable of multitarget regulation of such core signaling networks. Among these pathways, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway serves as a critical molecular bridge connecting the aforementioned clinical challenges with potential therapeutic strategies, owing to its central role in regulating the cell cycle, apoptosis, metabolism, and epithelial-mesenchymal transition, as well as its frequent abnormal activation in gastric cancer. Therefore, in-depth investigation into the regulatory mechanisms targeting this pathway holds clear scientific value and clinical relevance.⁸ PI3K can produce specific inositol lipids, which play an important role in regulating key processes such as cell growth, proliferation, survival, differentiation and cytoskeletal changes.⁹ Serine/threonine protein kinase (AKT) plays a central role in a variety of pathological conditions, including developmental and overgrowth syndromes, cancer, cardiovascular disease, insulin resistance and type 2 diabetes, inflammation, autoimmune diseases and neurological diseases.¹⁰ The PI3K/AKT signaling pathway is abnormally activated in many cancers, and the abnormally activated PI3K/AKT signaling pathway is involved in cellular processes such as cancer cell survival, proliferation, growth, metabolism, angiogenesis and metastasis, and the activation of downstream substrates is associated with AKT isoforms. Activation of AKT by PI3K can activate or inhibit downstream target proteins through phosphorylation, causing cell proliferation and avoiding apoptosis. Excessive activation of PI3K/AKT/mTOR signaling has been observed in almost all solid tumors.^{11,12} Although targeting the PI3K/AKT pathway has become a key strategy in anticancer drug development, with multiple PI3K/AKT inhibitors now in clinical trials or approved for certain cancer types, their clinical use may lead to side effects such as increased drug resistance and reduced tolerance.⁸

In China, traditional Chinese medicine (TCM) has unique advantages in the prevention and treatment of GC. In recent years, the application of TCM in clinical treatment has shown a growing trend and TCM has shown good prospects in the treatment of GC.¹³ Clinical studies have shown that TCM has a comprehensive regulatory effect on multiple targets and pathways of the body, and plays an important role in the perioperative period, synchronous period of chemotherapy and

rehabilitation/maintenance period of GC, which can improve the clinical signs and symptoms of GC patients, significantly enhance the sensitivity to chemotherapy drugs, enhance the anti-cancer effect, and significantly improve the adverse reactions such as cancer-related fatigue and bone marrow suppression.¹⁴ Related mechanism studies have shown that the anti-tumor, chemo-sensitizing and toxicity-attenuating effects of TCM are related to the remodeling of the body's immune microenvironment, including the positive regulation of cytotoxic T cell and natural killer cell activity, dendritic cell function and cytokine axis such as interleukin-12; By modulating classical signaling pathways including NF- κ B, PI3K/AKT, and TLR4, it regulates inflammatory responses, cell proliferation, and apoptosis, thereby indirectly improving the immunosuppressive microenvironment.¹⁵ Buyang Yiwang Decoction is a common prescription for the treatment of GC, and its therapeutic effect is acceptable, but its mechanism is not clear. In this context, this review will focus on Buyang Yiwang Decoction, systematically elucidating its potential molecular mechanisms and current research status in influencing gastric cancer progression through regulation of the PI3K/AKT signaling pathway, aiming to provide new directions and insights for the subsequent diagnosis and treatment of gastric cancer.

The Mechanism of PI3K/Akt Signaling Pathway Regulating GC

Activation Mechanism of PI3K/AKT Signaling Pathway

As a highly conserved signal transduction network in eukaryotic cells, PI3K/AKT signaling pathway precisely regulates the core physiological processes such as cell survival, growth regulation and cell cycle progression through cascade reactions. Recent studies have confirmed that the abnormal activation of this pathway is closely related to the occurrence and development of gastric cancer, lung cancer, breast cancer and other malignant tumors, and its mechanism involves cell malignant proliferation, apoptosis resistance and enhanced metastasis ability caused by signal transduction imbalance. From a clinical point of view, the analysis of the molecular mechanism of this pathway provides an important theoretical basis for targeted cancer therapy.

PI3K belongs to the lipid kinase family, which is classified into class I, class II, and class III based on structural characteristics and functional differences. Among these, class I PI3K has become a research focus due to its key role in tumorigenesis. Class I PI3K exists as a heterodimer and is further divided into two subtypes: IA and IB. Subtype IA is a functional complex composed of a regulatory subunit p85 and a catalytic subunit p110. The p85 regulatory subunit contains domains such as SH2 and SH3, which specifically recognize phosphorylated tyrosine sites generated by activation of upstream receptor tyrosine kinases or G protein-coupled receptors (GPCRs). This recognition induces a conformational change that recruits the p110 catalytic subunit and activates its kinase activity. Subtype IB is mainly regulated by G α proteins, plays an important role in immune cell signal transduction, and has a relatively weak association with tumors.¹⁶ Notably, the PIK3CA gene, which encodes the p110 α catalytic subunit of class IA PI3K, is one of the most frequently mutated proto-oncogenes in human cancers. Hotspot mutations in this gene lead to constitutive activation of PI3K, enabling it to initiate downstream pathways independently of upstream signals and drive malignant proliferation and disease progression of tumor cells.¹⁷

Type I PI3K has a unique lipid kinase activity that specifically phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) on the inner side of the cell membrane.¹⁸ As a key second messenger, PIP3 constructs cell membrane signaling microdomains by binding to proteins containing PH domains (such as AKT and PDK1), and initiates downstream signaling cascades. The precise regulation of PI3K signaling pathway depends on the balance of positive and negative feedback mechanisms: positive regulation: upstream receptor activation relieves the inhibition of p85 on p110 through conformational changes, or Ras protein directly binds to p110 to enhance its catalytic activity. Negative regulation: Lipid phosphatases encoded by the tumor suppressor gene phosphatase and tensin homolog (PTEN) specifically remove the 3'-phosphate group of PIP3 and convert it to PIP2, thereby terminating signaling. In human tumors, the loss of PTEN function often coexists with the abnormal increase of PIP3 level, which becomes an important molecular marker of tumorigenesis.^{19–21}

AKT belongs to the serine/threonine kinase family and mainly includes three isoforms: Akt1, Akt2, and Akt3. These isoforms differ slightly in tissue distribution and function but are all key downstream effectors of the PI3K signaling pathway, playing critical roles in cell signal transduction.²² When PI3K is activated, its p110 catalytic subunit

phosphorylates membrane-localized PIP2 to form PIP3. As a key second messenger, PIP3 specifically binds to the PH domain of AKT—a precise “navigational signal” that promotes the translocation of AKT (primarily cytoplasmic under resting conditions) to the plasma membrane. Meanwhile, the upstream activating kinase of AKT, 3-phosphoinositide-dependent protein kinase 1 (PDK1), also localizes to the plasma membrane via binding PIP3 through its PH domain, where it waits for AKT to translocate. Subsequently, constitutively active PDK1 phosphorylates AKT at Thr308 (in the kinase domain), while the carboxyl-terminal Ser⁴⁷³ is mainly phosphorylated by mTOR complex 2 (mTORC2); these two phosphorylations together drive full activation of AKT.²³ Fully activated AKT phosphorylates multiple substrates involved in cell metabolism, proliferation, survival, and motility, making it a major regulator of tumor cell invasion, migration, and metastasis.²⁴ For example, AKT inhibits apoptosis by phosphorylating Bcl-2 associated X protein (Bax) at Ser184, which prevents Bax from translocating to the outer mitochondrial membrane.²⁵ The activation state of AKT is reversible: protein phosphatase 2A (PP2A) and PH domain leucine-rich repeat protein phosphatase (PHLPP) can dephosphorylate activated AKT, restoring it to an inactive state and enabling dynamic regulation of AKT activity.²⁶ Activated PI3K and its downstream phosphorylated AKT together constitute the PI3K/AKT signaling cascade, which acts as a classical cancer metabolism regulatory pathway to widely participate in the occurrence and development of GC by regulating upstream and downstream effectors and related pathways.

The Role of PI3K/AKT Signaling Pathway in GC

Due to the complex pathology of GC and unclear pathogenesis, the intracellular signal regulatory network in cancer cells is highly intricate. A key feature of the PI3K/AKT pathway is its constitutive activation in various cancers, including GC, where it plays a critical role in regulating cell migration, proliferation, differentiation, and apoptosis—closely linking it to cancer development and other diseases.²⁷ Recent studies have shown that the activated PI3K/AKT pathway promotes GC cell proliferation and inhibits apoptosis; it further accelerates GC initiation and metastasis by regulating EMT, angiogenesis, and chemoresistance. Additionally, studies have found that in GC, the PI3K/AKT pathway inhibits apoptosis, induces a chemoresistant phenotype, promotes metastasis, angiogenesis, and EMT, thereby driving malignant tumor progression.^{28,29} However, the PI3K/AKT pathway is regulated by numerous upstream signaling proteins and modulates multiple downstream effectors through crosstalk with compensatory signaling pathways. By regulating the expression of downstream effectors, inhibition of the PI3K/AKT signaling pathway helps reduce GC cell proliferation, colony formation, cell cycle progression, migration, and invasion, thereby inhibiting the occurrence and development of GC.³⁰ On one hand, the PI3K/AKT signaling pathway contributes to GC pathogenesis; on the other hand, targeting this pathway can exert therapeutic effects against GC. Meanwhile, tumor cell invasion and metastasis are key events in the malignant progression of solid tumors and the primary cause of low survival rates in GC patients.³¹ Researcher³² found that endogenous stimulatory factors activate the PI3K/AKT pathway to regulate processes such as cell growth and cell cycle progression, and this pathway is significantly associated with carcinogenesis by modulating cell proliferation, survival, migration, angiogenesis, and metabolism.

The activation mechanism of PI3K/AKT signaling pathway in GC is complex, which involves the abnormal activation of upstream receptors and signaling molecules and the inactivation of tumor suppressor genes, and promotes the occurrence and development of GC by regulating downstream cell proliferation, apoptosis, migration, invasion and angiogenesis. The virulence factor CagA of *Helicobacter pylori* enters gastric epithelial cells and dysregulates key cellular signaling pathways such as MAPK, PI3K/Akt, and NF- κ B through both phosphorylation-dependent and phosphorylation-independent mechanisms, thereby promoting the development of gastric cancer. Under the regulation of the PI3K/Akt pathway, CagA inhibits apoptosis and the DNA damage response. It also mediates autophagy and promotes the expression of downstream inflammatory cytokines via the C-met/Akt signaling pathway, contributing to gastric carcinogenesis.³³ As a member of the EGFR/ERBB subfamily of receptor tyrosine kinases (RTKs), the epidermal growth factor receptor (EGFR) plays a critical role in the progression of a variety of cancers. The activation of EGFR can trigger classical downstream signaling pathways including PI3K/AKT/mTOR and ERK/MAPK, which are involved in cell proliferation, cell cycle progression, primary tumorigenesis and metastasis. Studies have confirmed that reducing the expression of EGFR can inhibit the activity of PI3K/AKT signaling pathway, thereby weakening the proliferation and metastasis of cells and triggering a series of downstream signaling events.³⁴ G protein-coupled estrogen receptor

(GPER1) is a membrane estrogen receptor that regulates cell growth, migration, apoptosis, cell death, and other biological functions associated with cancer. The role of GPER1 in different cancers is contradictory, either as a tumor promoter or as a tumor suppressor. Specifically, in GC, activated GPER1 signaling can trigger PI3K activation, and then initiate downstream AKT signaling, which can promote the progression and metastasis of gastric cancer by mediating EMT of gastric cancer cells. Meanwhile, the current study found that knockdown of GPER1 can down-regulate the activation of PI3K/AKT, inhibit the EMT process by up-regulating E-cadherin and down-regulating N-cadherin and vimentin, and ultimately reduce the migration and invasion ability of gastric cancer cell lines.³⁵ Secondly, PTEN is an important negative regulator of PI3K/AKT signaling pathway, which can dephosphorylate PIP3 into PIP2, thus terminating the signal transmission of the pathway. In gastric cancer, PTEN is often inactivated by gene mutations, deletions, or epigenetic modifications. Loss of PTEN function can not effectively degrade PIP3, resulting in increased levels of PIP3 in cells, and then continue to activate AKT, leading to one of the key mechanisms of abnormal activation of PI3K/AKT pathway, which is related to the degree of malignancy and poor prognosis of gastric cancer.³⁶ Cytotoxin-associated gene virulence island (CAGPAI) and outer membrane inflammatory protein A (OIPA) are key virulence factors of Hp. These two factors play a significant role in the development of GC by synergistically regulating the PI3K/AKT signaling pathway. Firstly, CAGPAI mainly regulates the phosphorylation of Akt at Thr308, while OIPA regulates the phosphorylation of Akt at Ser473. Second, Ser473 and Thr308 phosphorylation of Akt are the key markers of its activation, which participate in the complete activation of Akt. The activated AKT signaling pathway plays a key role in the regulation of cell survival, proliferation, motility and other biological functions, and the upregulation of Akt activation level can be observed in tissues adjacent to GC, and its activation status can also affect the chemoresistance of gastric cancer cells.³⁷

PIP3 produced by PI3K activation activates AKT, which participates in various biological processes of GC cells by phosphorylating downstream target proteins, thereby promoting tumorigenesis and development. Mammalian target of rapamycin (mTOR) is a key downstream effector of AKT, and the PI3K/AKT/mTOR axis is the core signaling pathway controlling cell growth and apoptosis. AKT indirectly activates mTOR by phosphorylating its negative regulator tuberous sclerosis complex 2 (TSC2) at Ser939, or by phosphorylating the mTORC2 subunit Rictor, leading to mTOR activation (marked by phosphorylation at Ser2448). Activated mTOR further phosphorylates its downstream targets: ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Phosphorylation of S6K1 and 4E-BP1 significantly enhances protein anabolism, providing a material basis for cell proliferation. Inhibition of the PI3K/AKT/mTOR pathway significantly reduces cell proliferation, further highlighting its core role in regulating GC cell proliferation.³⁸ Additionally, AKT promotes GC cell migration and invasion by regulating the expression of matrix metalloproteinases (MMPs): AKT activates transcription factors such as nuclear factor κ B (NF- κ B), which upregulates the expression of MMPs and facilitates GC cell invasion and metastasis.³⁹ The PI3K/AKT pathway also plays a critical role in tumor angiogenesis: activated AKT upregulates the expression and activity of hypoxia-inducible factor-1 α (HIF-1 α), which binds to the promoter region of the vascular endothelial growth factor (VEGF) gene, promoting VEGF transcription and expression. This stimulates endothelial cell proliferation, migration, and lumen formation, thereby promoting tumor angiogenesis.⁴⁰

Concurrently, several key molecules have been identified to regulate the PI3K/AKT pathway during GC progression. For example, Shayi Wu et al²⁸ showed that calcium release-activated calmodulin 2 (ORAI2) is significantly upregulated in GC lymph node metastatic tissues, and its positive expression frequency is strongly correlated with poor differentiation, invasion, lymph node metastasis, and poor prognosis of GC. ORAI2 has been shown to promote cell motility, tumor formation, and metastasis in a murine GC model. ORAI2 regulates its own protein activity and oncogenic properties by activating the PI3K/AKT pathway, thereby promoting GC cell proliferation, inhibiting apoptosis, and accelerating GC development and metastasis. Qi Liu et al⁴¹ demonstrated abnormal expression of receptor tyrosine kinase-like orphan receptor 2 (ROR2) in GC patients via bioinformatics analysis, and further confirmed through in vitro cell experiments and in vivo animal models that ROR2 is associated with G2/M phase progression of the GC cell cycle. Studies on Twist1 transcriptional expression confirmed that ROR2 accelerates G2/M phase progression by activating the PI3K/AKT/mTOR/S6K signaling pathway, ultimately promoting GC cell proliferation. Meng et al⁴² found that phosphoglycerate mitochondrial mutant enzyme family member 5 (PGAM5) participates in regulating mitochondrial homeostasis and cell death; it induces mitophagy to modulate apoptosis and necrosis by interacting with cell membrane or mitochondrial

membrane proteins. PGAM5 protein expression is positively correlated with the progression of various cancers and serves as an independent potential prognostic marker for poor outcomes in these diseases. In GC, PGAM5 over-expression activates the PI3K/AKT pathway, accelerating GC development and invasion; its positive expression is highly correlated with GC clinicopathological features and poor patient prognosis.

MicroRNAs (miRNAs or miRs) are small, single-stranded non-coding RNAs that regulate gene expression at the post-transcriptional level by cleaving target mRNAs or repressing their translation. Functional studies have shown that miRNAs regulate nearly all cellular processes studied to date, including cell proliferation, differentiation, immune response, metastasis, senescence, autophagy, and apoptosis. By regulating genes and participating in various cell signaling pathways, changes in their expression are associated with numerous human pathologies; however, miRNA function depends on the specific pathological type and physiological context. Currently, the miR-34 family has been extensively studied and is considered a tumor suppressor miRNA due to its synergistic interaction with the tumor suppressor p53.⁴³ Among other miRNAs, miR-4677-3p and miR-3650 promote GC cell proliferation, migration, and invasion by targeting and downregulating negative regulators of the PI3K/AKT pathway, thereby activating the pathway.^{44,45}

The PI3K/AKT signaling pathway is a key regulator of GC occurrence and development, with a complex activation mechanism involving multiple factors (Figure 1). On one hand, abnormal activation of upstream signaling molecules, inactivation of tumor suppressor genes, and stimulation by Hp virulence factors collectively contribute to abnormal activation of the pathway. On the other hand, abnormal expression of ORAI2, ROR2, and PGAM5, as well as regulation by miRNAs, collectively promote GC cell proliferation, inhibit apoptosis, and accelerate GC formation, progression, and metastasis by enhancing EMT, angiogenesis, chemoresistance, and cell migration/invasion. This fully confirms the inherent and close mechanistic link between the PI3K/AKT pathway and GC, highlighting the pathway and its related regulatory molecules as potential new targets for GC treatment.

Research Status of Buyang Yiwei Decoction and Gastric Cancer

Buyang Yiwei Decoction is typically composed of Radix Astragali (Huang qi), Radix Angelicae Sinensis (Dang gui), Rhizoma Chuanxiong (Chuan xiong), Radix Paeoniae Alba (Bai shao), Herba Salviae Chinensis (Shi jian chuan), Radix Actinidiae Chinensis (Radix Actinidiae Chinensis), Rhizoma Curcumae (E zhu), Herba Epimedii (Yin yang huo), and Flos Armeniacae Mume (Bai mei hua). Astragalus mongholicus, as the monarch drug, has the effects of invigorating qi and raising Yang, consolidating the exterior and stopping sweating, inducing diuresis and detumescence, removing toxin and promoting granulation, and the like, and can invigorate the qi of the spleen and stomach, provide power for the transportation and transformation of the spleen and stomach, and promote the biochemistry of qi and blood. The angelica can enrich the blood and activate the blood circulation, regulate the menstruation and relieve the pain, and is compatible with the Astragalus to tonify both the qi and the blood. Ligusticum chuanxiong Hort. Is the drug of qi in the blood, which has the efficacy of promoting blood circulation, expelling wind and relieving pain, and can enhance the power of promoting blood circulation of Angelica sinensis, so as to smooth the circulation of qi and blood. Radix Paeoniae Alba can nourish blood and regulate menstruation, astringe yin and stop sweating, soften liver and relieve pain, and is compatible with Radix Angelicae Sinensis and Rhizoma Chuanxiong to enrich blood without stagnating blood, promote blood circulation without damaging blood, and regulate qi and blood together. Herba Salviae Chinensis has effects in promoting blood circulation, removing blood stasis, clearing away heat, promoting diuresis, dissipating stagnation, and relieving swelling. Radix Actinidiae Chinensis can clear away heat and toxic materials, dispel wind and remove dampness, promote urination and stop bleeding, which is an empirical drug for cancer. Rhizoma Curcumae can break blood, promote the circulation of qi, remove food retention and relieve pain. Herba Epimedii can tonify kidney-yang, strengthen bones and muscles, and dispel rheumatism. Flos Armeniacae Mume has a sour and astringent taste and neutral nature, with effects of soothing the liver, regulating qi flow, harmonizing the stomach, and relieving pain.

The entire prescription is formulated based on the TCM theory of “qi-blood interaction”, featuring simultaneous regulation of qi and blood, combination of tonification and dispersion, and emphasis on replenishing qi and activating blood circulation. Herbs that activate blood circulation, resolve stasis, dissipate stagnation, and reduce swelling improve local tumor microcirculation to inhibit tumor growth; herbs that warm and tonify kidney-yang regulate the body’s holistic

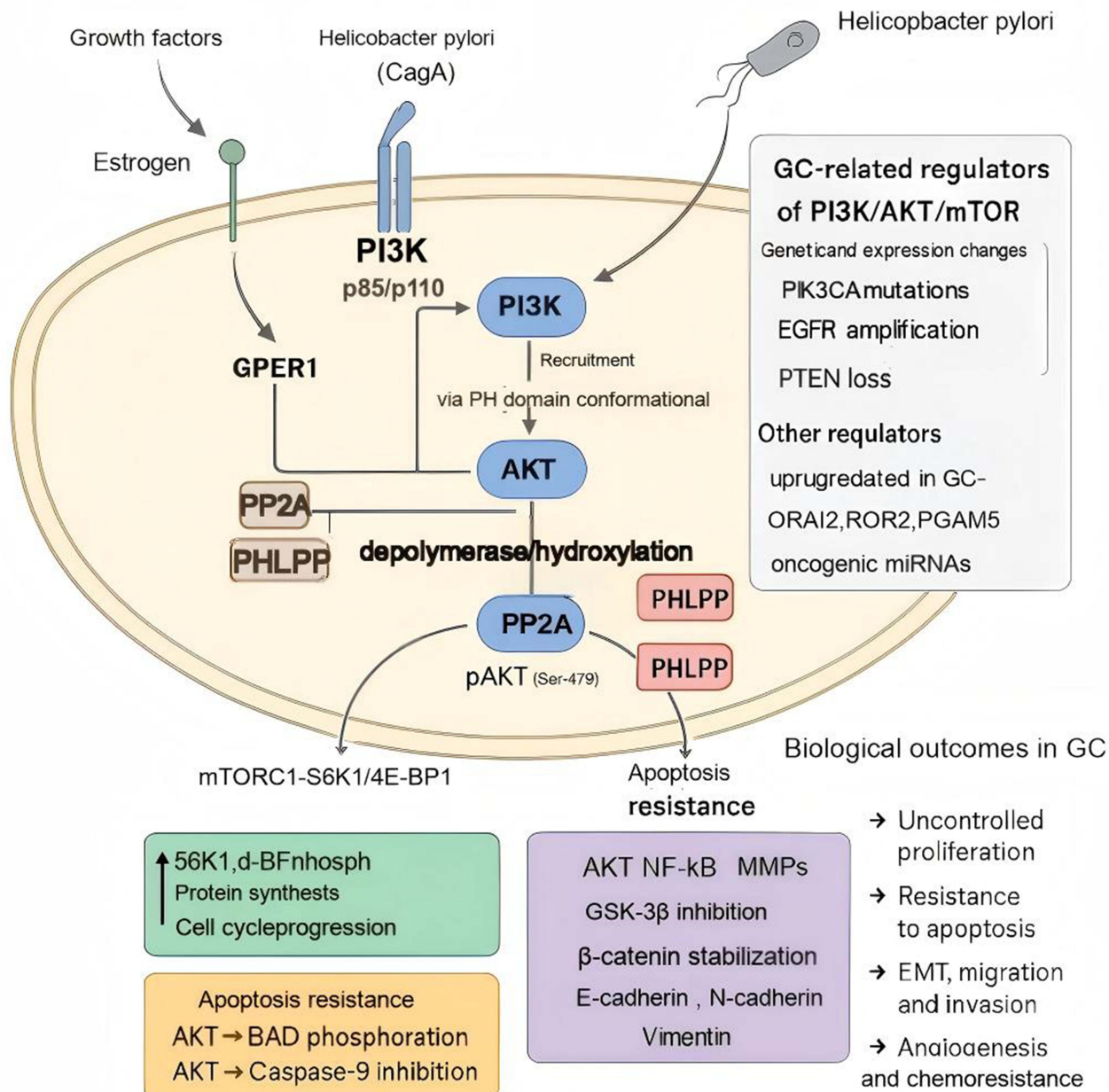


Figure 1 The mechanism of PI3K/Akt signaling pathway regulating GC. Top: External stimuli such as growth factors, *Helicobacter pylori* (CagA), and estrogen activate PI3K via GPER1, leading to PIP3 production and subsequent AKT phosphorylation (pAKT at Ser-479). Activated AKT promotes mTORC1-mediated S6K1 and 4E-BP1 activation, enhancing protein synthesis and cell cycle progression. AKT also phosphorylates BAD and inhibits Caspase-9, conferring resistance to apoptosis. Middle: Key negative regulators of this pathway include PTEN (which converts PIP3 back to PIP2), PHLPP (which dephosphorylates AKT), and PP2A (which dephosphorylates pAKT). Bottom left: Genetic and expression alterations frequently observed in GC, such as PIK3CA mutations, EGFR amplification, PTEN loss, and upregulation of ORAI2, ROR2, PGAM5, and oncogenic miRNAs, contribute to constitutive activation of the PI3K/AKT/mTOR axis. Bottom right: Downstream oncogenic effects of AKT in GC include: activation of NF- κ B and MMPs; inhibition of GSK-3 β leading to β -catenin stabilization and epithelial-mesenchymal transition (EMT) (marked by decreased E-cadherin and increased N-cadherin and vimentin); and promotion of angiogenesis and chemoresistance. Collectively, these alterations drive uncontrolled proliferation, apoptosis resistance, EMT, migration, invasion, angiogenesis, and chemoresistance in GC.

function and enhance anti-tumor immunity. Current researchers⁴⁶ have found that Buyang Yiwei Decoction can restore physical strength in patients with advanced GC, improve their clinical signs and symptoms, reduce tumor marker levels, and exert efficacy-enhancing and toxicity-reducing effects when combined with the SOX chemotherapy regimen. This prescription is of great significance for improving patients' quality of life and delaying disease progression.

Astragalus membranaceus is Leguminosae *Astragalus* plant. Modern pharmacological studies have shown that *Astragalus membranaceus* can increase the number of peripheral blood leukocytes, significantly enhance the function of monocyte-macrophage system and the phagocytic activity of leukocytes. *Astragalus polysaccharide* (APS), the main active ingredient, has a clear anti-gastric cancer effect: on the one hand, it can independently induce GC cell apoptosis by down-regulating the expression level of CD4⁺ and CD25⁺ regulatory T cells and inhibiting their immunosuppressive function; On the other hand, it can enhance the apoptosis-promoting effect of adriamycin on GC cells, which can not only improve the immune function of gastric cancer patients, but also delay tumor progression. The main chemical components of *Angelica* are volatile oil, coumarins, organic acids, flavonoids, polysaccharides, etc. The volatile oil, polysaccharides, organic acids and other components in *Angelica* have anti-tumor effects.⁴⁷ Its key active ingredient *n*-butenyl phthalide (BP) has clear anti-proliferation and pro-apoptosis effects on GC, can significantly inhibit the growth activity of GC cells in vitro, induce GC cell apoptosis, reduce tumor volume in vivo, delay tumor progression, and has low toxicity to normal cells, reflecting a certain degree of tumor targeting.⁴⁸ The core active ingredient of *Ligusticum chuanxiong* Hort is tetramethylpyrazine (TMP, also known as ligustrazine), which has broad-spectrum anti-tumor activity. Pharmacological studies have found that TMP can significantly reduce the activity of cancer cells, block cell cycle progression, reduce the ability of cancer cells to divide, activate apoptosis-related pathways, promote programmed cell death, reduce the ability of cancer cells to migrate, and block their spread to distant tissues. Improve the efficacy of traditional anti-tumor therapy, while reducing treatment-related side effects.⁴⁹ *Paeoniflorin* is the main active ingredient of *Paeonia lactiflora* Pall. Many studies have shown that *paeoniflorin* has a good anti-tumor effect in a variety of tumors, including liver cancer, gastric cancer, breast cancer, lung cancer, pancreatic cancer, colorectal cancer and bladder cancer. At the same time, *paeoniflorin* can play an anti-tumor role through a variety of molecular mechanisms, specifically, it can induce apoptosis of tumor cells and inhibit the proliferation, invasion and metastasis of tumor cells.⁵⁰ *Herba Salviae Chinensis* has been proven to exert anti-cancer effects on hepatocellular carcinoma, GC, nasopharyngeal carcinoma, breast cancer, and other cancers. Studies have found that its extract significantly inhibits the proliferation of nasopharyngeal carcinoma cells and GC cells, blocks cancer cells in the G1/S or G2/M phase of the cell cycle, thereby inhibiting tumor cell growth and mediating mitochondrial pathway-dependent apoptosis.⁵¹ *Actinidia arguta* root contains a variety of components (polysaccharides, flavonoids, saponins, etc.), and *Actinidia arguta polysaccharide* is one of the active ingredients that have been proved to have a clear inhibitory effect on gastric cancer. Pharmacological studies have found that *Actinidia arguta polysaccharide* can effectively inhibit the invasion and metastasis of GC cells, and restore the body's immunosuppressive effect on GC cells through immune regulation, indirectly inhibiting the growth of GC tissues.⁵² *Curcuma zedoary* is a plant derived from *Curcuma* of Zingiberaceae. Its main active components include curcumol, curzerenone and β -elemene, which constitute the key material basis for *Curcuma zedoary* to exert its efficacy, inhibit the viability, migration and invasion of gastric cancer cells, and induce apoptosis of gastric cancer cells. The basic pharmacological mechanisms of curcumol effectiveness include induction of apoptosis and autophagy, arrest of cell cycle, inhibition of EMT process, inhibition of cell invasion and migration, and regulation of multiple signaling pathways.⁵³ Modern pharmacological studies have found that flavonoids and polysaccharides in *Epimedium* have significant anti-tumor activity, which can effectively inhibit the abnormal proliferation of tumor cells, induce apoptosis of tumor cells by regulating related signaling pathways, and promote autophagy of tumor cells to eliminate abnormal cells. In addition, it can also reduce the drug resistance of tumor cells to chemotherapy drugs, improve the tumor immune microenvironment, and create favorable conditions for the body's anti-tumor immune response.⁵⁴ The main active ingredients of *Flos Armeniacae Mume* are phenylpropanoids and flavonoids. Studies have found that *Flos Armeniacae Mume* extract has antidepressant, antioxidant, bacteriostatic, anti-platelet aggregation and other effects, and is mainly used to treat depression and stomach diseases in clinic.⁵⁵

Modern pharmacological studies have shown that the core active ingredients of various traditional Chinese medicines in the prescription have the functions of inducing tumor cell apoptosis, inhibiting proliferation and invasion, regulating immune microenvironment and other mechanisms, showing anti-gastric cancer activity, and improving chemotherapy resistance. Clinical studies have further confirmed that *Buyang Yiwei* Decoction combined with SOX chemotherapy in the treatment of advanced gastric cancer can effectively promote the physical recovery of patients, improve clinical signs and symptoms, reduce the level of tumor markers, play a synergistic attenuation, alleviate the role of chemotherapy

damage, and have important significance in improving the quality of life of patients and delaying the progress of the disease.

Study on the Mechanism of Buyang Yiwei Decoction in Treating GC Based on PI3K/AKT Signaling Pathway

As a core regulator of cell survival, proliferation, and metabolism, the PI3K/AKT signaling pathway represents a critical therapeutic target in GC. Buyang Yiwei Decoction, through its multi-component, multi-target pharmacological profile, exerts direct anti-tumor effects by modulating this pathway at multiple molecular levels. The following section systematically summarizes how key active constituents derived from the formula's herbal components inhibit GC progression through interference with PI3K/AKT signaling and its downstream effectors, thereby inducing apoptosis, suppressing proliferation, inhibiting EMT, and attenuating metastatic potential.

Direct Anti-GC Effects of Buyang Yiwei Decoction Active Constituents via the PI3K/AKT Pathway

Current studies have found that the therapeutic effect of ASP on GC is primarily achieved by inducing apoptosis, inhibiting proliferation, and modulating immune factors such as promoting spleen lymphocyte proliferation, enhancing natural killer cell activity, and increasing serum immunoglobulin levels.⁵⁶ Scholars including Jun Wu et al have demonstrated that ASP combined with atinib significantly reduces the expression level of phosphorylated AKT in GC cells, thereby blocking the cell growth and survival signals mediated by the AKT pathway, which inhibits proliferation and promotes apoptosis. This combination also markedly reduces the expression of MMP-9, directly impairing the migration and invasion capabilities of GC cells.⁵⁷ Furthermore, Astragaloside IV, another key component of Astragalus, plays an anti-metastatic role in gastric cancer by inhibiting EMT. It intervenes in the EMT process induced by transforming growth factor- β 1 (TGF- β 1). The PI3K/Akt/NF- κ B pathway is the key signaling axis for TGF- β 1-induced EMT. Astragaloside IV inhibits the activation of PI3K, reduces AKT phosphorylation, prevents NF- κ B nuclear translocation, and blocks the entire signaling cascade from upstream to downstream, ultimately reversing TGF- β 1-induced EMT and significantly suppressing the viability, invasion, and migration of gastric cancer cells.⁵⁸

BP is the main active component of *Angelica sinensis*, has demonstrated antitumor activity across various cancer cell types. Given the crucial role of the PI3K/AKT/mTOR pathway in GC development and prognosis, research indicates that BP significantly upregulates the expression of REDD1 mRNA and protein in GC cells. This enhanced accumulation of REDD1 directly reduces the phosphorylation level and kinase activity of mTOR protein. Inhibition of the mTOR pathway subsequently leads to synchronized decreases in the phosphorylation of downstream key molecules regulating the cell cycle and protein synthesis, resulting in G0/G1 phase arrest and inhibition of cell division and proliferation. Moreover, mTOR inhibition indirectly upregulates the expression of pro-apoptotic proteins and downregulates the anti-apoptotic protein Bcl-2, ultimately inducing apoptosis in GC cells. In conclusion, BP induces GC cell death by activating the mitochondrial inner membrane pathway and upregulating REDD1 expression, leading to the inhibition of the mTOR signaling pathway.⁴⁸ In the context of an abnormally activated PI3K/AKT/mTOR pathway, Akt inhibits GC cell apoptosis by phosphorylating and inactivating cleaved caspase-9, blocking the caspase-dependent apoptotic cascade, and suppressing the expression of the pro-apoptotic protein Bax.⁵⁹ TMP is the main active component of *Rhizoma Chuanxiong*, counters this by upregulating the expression of cleaved caspase-9 and cleaved caspase-3 through the inhibition of AKT phosphorylation, thereby activating the caspase cascade and initiating apoptosis. Additionally, by inhibiting mTOR phosphorylation, TMP relieves the suppression of autophagy, upregulates the expression of the autophagic marker protein LC3-II, enhances autophagic activity in GC cells, promotes the degradation of abnormal cellular components, and inhibits tumor growth.⁶⁰

Paeoniflorin, the principal active component of *Radix Paeoniae Alba*, significantly increases the expression level of miR-124 in GC cells, a microRNA known to inhibit GC cell proliferation and invasion and play a key role in the pathogenesis of GC. Overexpression of miR-124 inhibits the expression within the PI3K/AKT and phospho-STAT3 pathways. Notably, the effects of paeoniflorin on inhibiting GC cell proliferation can be reversed by overexpression of

a PI3K agonist or STAT3, confirming that its anti-tumor effect is achieved through the “inhibition of cell proliferation and induction of apoptosis” via these pathways.⁶¹ The main mechanism by which *Salvia chinensis* Bunge polysaccharide (SCBP) exerts its anti-tumor effect on GC cells is to target and inhibit the PI3K/Akt signaling pathway, either by regulating miRNA-145 or by directly and significantly reducing the expression levels of PI3K and Akt proteins. This subsequently affects the expression of downstream regulatory factors such as c-Myc, P21, and MMP-2/MMP-9, ultimately achieving the inhibition of proliferation, promotion of apoptosis, and attenuation of invasion and migration.⁶² Ursolic acid, an active component of *Radix Actinidiae Chinensis*, effectively inhibits GC cell proliferation and migration by suppressing EMT. It down-regulates the expression of Bcl-2, p65, and MMP-9 proteins, inhibits the activation of the PI3K/AKT signaling pathway, and up-regulates the expression of Caspase-3. This modulation improves the status of inflammatory cells, factors, and chemokines in the tumor microenvironment, thereby inhibiting proliferation, inducing apoptosis, and stimulating anoikis.⁵² Curcumol significantly inhibits the phosphorylation of key proteins in the PI3K/AKT/mTOR signaling pathway in GC cells. It up-regulates the expression of the pro-apoptotic proteins Caspase-3 and Bax while down-regulating the anti-apoptotic protein Bcl-2, thereby inhibiting GC cell growth and inducing apoptosis. Concurrently, curcumol exhibits anti-angiogenic effects by inhibiting the formation of new blood vessels essential for tumor growth and metastasis and interfering with various pro-survival molecules, including MMPs and VEGF.^{63,64} The active constituents of *Epimedium* include various flavonoids, with icariin being the most significant. Icariin exhibits a dose-dependent dual effect on angiogenesis mediated through the PI3K/AKT pathway: at low doses, it activates signaling modulators (ERK, PI3K, AKT, eNOS) to promote normal vascular repair, while at high doses, it inhibits tumor angiogenesis.⁶⁵

Chemotherapy Synergism and Toxicity Reduction via PI3K/AKT Pathway Modulation

The PI3K/AKT pathway is among the most frequently activated in tumor cells and is closely linked to chemotherapeutic drug sensitivity. Traditional Chinese medicine (TCM) components can modulate this chemoresistance, producing synergistic anti-cancer effects.^{15,66} TCM can enhance tumor tissue sensitivity to chemotherapy, improve tumor inhibition, alleviate adverse reactions like cancer-related fatigue and bone marrow suppression, and regulate the tumor microenvironment to promote apoptosis or autophagy.¹⁵

Synergistic Effects with Chemotherapy Regimens

ASP combined with the FOLFOX regimen as part of Buyang Yiwei Decoction can effectively improve the clinical efficacy of GC treatment, enhance patients' daily living function and treatment tolerance, and alleviate chemotherapy-induced adverse reactions. The anti-inflammatory and immunomodulatory properties of ASP may further reduce chemotherapy-induced neurotoxicity and other side effects.⁶⁷ Similarly, *Angelica* polysaccharide has been shown in animal experiments to significantly shorten the recovery time from cyclophosphamide-induced leukopenia, allowing for increased dosing frequency and enhanced efficacy. It reduces the damage to gastric and duodenal mucosal vasculature and proliferative cells caused by cyclophosphamide, thereby improving nutrition, oxygen supply, and the defense/repair capacity of gastrointestinal tissues. Importantly, it reduces cyclophosphamide's bone marrow suppression and gastrointestinal toxicity without interfering with its fundamental anti-tumor effect via the p53 pathway.⁶⁸ TMP also demonstrates a protective effect on non-tumor tissues. When combined with chemotherapeutic agents like cisplatin and paclitaxel, it inhibits angiogenesis by suppressing the ERK1/2 and AKT pathways and promotes tumor cell apoptosis compared to single-agent treatment, thereby enhancing anti-tumor efficacy while potentially reducing toxic adverse effects and renal toxicity.⁶⁹

Reversal of Chemoresistance

A core challenge in GC chemotherapy is multidrug resistance (MDR), often associated with the upregulation of ABC transporters and abnormal activation of the PI3K/AKT pathway. Quercetin, a major active ingredient found in *Flos Armeniaca* Mume, addresses both mechanisms in a dose-dependent manner. First, it reduces the expression and activity of P-gp, decreasing oxaliplatin efflux and increasing its intracellular accumulation. Second, it directly increases the

apoptosis rate of drug-resistant cells by modulating the PI3K/AKT pathway, ultimately reversing oxaliplatin resistance and reducing the survival of resistant cells, positioning it as a promising adjuvant for GC chemotherapy.⁷⁰

Attenuation

The PI3K/Akt signaling pathway plays a dual role in cellular homeostasis regulation. In tumor cells, abnormal hyperactivation of this pathway is a key mechanism driving malignant proliferation, invasion, and treatment resistance. However, under normal physiological conditions, appropriate Akt signaling is crucial for maintaining cell survival, promoting tissue damage repair, and responding to external stress.⁷¹ The “toxicity-reducing” wisdom of Buyang Yiwei Decoction and its constituent herbs lies precisely in their context-selective regulatory capacity for this pathway, their ability to protect normal tissues while simultaneously inhibiting tumor cells. Some of their active components can preferentially maintain or activate beneficial PI3K/Akt survival signals in damaged normal cells, or indirectly preserve the function of this pathway through systemic anti-inflammatory and antioxidant effects, thereby effectively counteracting the widespread damage caused by radiotherapy and chemotherapy.

Astragalus (Huang Qi) plays a central role in this multi-organ protection process. Its key component, APS has been shown to act directly on hematopoietic stem cells. By activating downstream signals of the PI3K/Akt pathway, APS alleviates chemotherapy-induced myelosuppression and maintains hematopoietic function.⁷² Furthermore, APS can modulate the gut microbiota and immune system, mitigating chemotherapy-induced intestinal mucosal damage and systemic immunosuppression, thereby providing a favorable microenvironment for hematopoietic recovery.⁷³ Clinical evidence also indicates that Astragalus-based formulations can effectively delay peripheral neuropathy induced by agents such as oxaliplatin, significantly improving patients’ quality of life.⁷⁴ TMP demonstrates remarkable efficacy in alleviating chemotherapy-specific organ toxicity. Studies have shown that TMP significantly ameliorates cisplatin-induced nephrotoxicity. Its protective mechanisms involve activating the Nrf2 antioxidant defense pathway and inhibiting the HMGB1/TLR4/NF- κ B inflammatory signaling axis. Through these actions, TMP exerts potent antioxidant, anti-inflammatory, and anti-apoptotic effects, demonstrating great potential as a novel renal protective agent.⁷⁵

In summary, the active ingredients in Buyang Yiwei Decoction exert anti-GC effects primarily through multi-level targeting of the PI3K/AKT signaling pathway. Components such as astragaloside IV and icariin regulate immune function and tumor microenvironment, while others like ferulic acid and paeoniflorin alleviate treatment-induced bone marrow suppression and digestive tract injury. TMP and curcumin further inhibit angiogenesis and stromal fibrosis. Importantly, while suppressing oncogenic PI3K/AKT activation in tumor cells to induce apoptosis and inhibit proliferation, it simultaneously activates protective PI3K/AKT signaling in normal tissues to mitigate chemotherapy-induced damage. This dual modulation is exemplified by APS maintaining hematopoietic function via PI3K/Akt activation in bone marrow and TMP protecting against nephrotoxicity through coordinated regulation of Nrf2 and NF- κ B pathways. Through such concerted and tissue-specific modulation of the PI3K/AKT axis and related signaling networks, Buyang Yiwei Decoction demonstrates significant anti-GC efficacy and unique advantages in GC management, particularly in enhancing chemotherapy sensitivity, reversing drug resistance, and reducing treatment-associated toxicities through its sophisticated multi-target, multi-pathway pharmacological approach.

Conclusion

GC is one of the most common gastrointestinal malignancies worldwide. Given its complex molecular pathology and clinical challenges such as drug resistance and significant toxicity, there is an urgent need to develop multi-target and multidimensional therapeutic strategies. This review systematically examines the central role of the PI3K/AKT signaling pathway in the pathogenesis and progression of GC as well as the molecular mechanisms and clinical value of Buyang Yiwei Decoction in treating GC through modulation of this pathway. The PI3K/AKT pathway serves as a critical hub in GC, whose aberrant activation regulates key malignant processes including cell proliferation, apoptosis, EMT, angiogenesis, and chemoresistance, thereby promoting disease progression. Buyang Yiwei Decoction exerts its anti-GC effects primarily through multi-component synergistic inhibition of the PI3K/AKT pathway. Key active constituents such as APS and astragaloside IV suppress AKT phosphorylation, block pro-survival signals, and down-regulate MMP-9 to inhibit invasion. BP from *Angelica sinensis* activates REDD1 to inhibit mTOR, leading to cell-cycle arrest and apoptosis.

TMP down-regulates AKT and mTOR, thereby activating the caspase-dependent apoptotic cascade and enhancing autophagy. Paeoniflorin up-regulates miR-124, which indirectly suppresses the PI3K/AKT pathway. Moreover, curcuminol and Actinidia arguta polysaccharides inhibit EMT and angiogenesis by attenuating phosphorylation of key proteins within the pathway. Collectively, these components form a coherent network that inhibits pathway activation, modulates downstream effectors, and remodels the tumor microenvironment, providing a molecular foundation for the anti-GC activity of Buyang Yiwei Decoction.

Clinically, Buyang Yiwei Decoction demonstrates a unique “efficacy-enhancing and toxicity-reducing” profile in GC management. Studies confirm that Buyang Yiwei Decoction combined with chemotherapy regimens such as SOX or FOLFOX can potentiate the killing of GC cells by suppressing aberrant PI3K/AKT activation. Concurrently, Buyang Yiwei Decoction modulates the immune microenvironment, alleviates chemotherapy-induced myelosuppression, gastrointestinal injury, and neurotoxicity, and significantly improves patients’ performance status and quality of life, offering a practical basis for the comprehensive treatment of advanced GC.

Current studies mainly have one of the following deficiencies: first, most of the mechanism studies focus on single traditional Chinese medicine or single component, and lack of studies on the synergistic effect of Buyang Yiwei Decoction on the overall regulation of PI3K/AKT pathway, which makes it difficult to reflect the overall effect of the compound; second, most of the clinical evidence is small sample, single-center studies, and lack of large sample RCT and long-term survival data; Thirdly, the accuracy of the target is insufficient, the direct binding site between the core active component and the key protein of PI3K/AKT pathway is not clear, and the cross-regulation mechanism between the pathway and other signaling networks is insufficient. Future studies will focus on screening the core active components and synergistic sites of PI3K/AKT pathway regulated by prescriptions by means of network pharmacology and molecular docking technology, and verifying the regulatory effects of Buyang Yiwei Decoction on PI3K/AKT pathway. At the same time, a multi-center and large sample RCT study was carried out to clarify the best intervention scheme of Buyang Yiwei Decoction in different stages of GC, which provided a new strategy for the synergistic immunotherapy of traditional Chinese medicine and Western medicine.

In summary, Buyang Yiwei Decoction acts through multi-component, multi-target modulation of the PI3K/AKT pathway, providing a therapeutically innovative and clinically applicable approach for GC. However, deeper mechanistic insights and stronger clinical evidence are still needed. Through interdisciplinary research, Buyang Yiwei Decoction is poised to become an important component of precision-based integrated Chinese–Western medicine for gastric cancer.

Abbreviation

GC, Gastric cancer; Hp, Helicobacter pylori; MSI, Microsatellite unstable; MSS, Microsatellite stable; EMT, Epithelial-mesenchymal transition; PI3K, Phosphatidylinositol-3 kinase; AKT, Serine/threonine protein kinase; TCM, Traditional Chinese medicine; GPCR, G protein-coupled receptors; PIP2, Phosphatidylinositol-4,5-bisphosphate; PIP3, Phosphatidylinositol-3,4,5-trisphosphate; PTEN, Phosphatase and tensin homolog; PDK1, 3-phosphoinositide-dependent protein kinase 1; RTKs, Receptor tyrosine kinases; EGFR, Epidermal growth factor receptor; GPER1, G protein-coupled estrogen receptor; mTOR, Mammalian target of rapamycin; S6K1, S6 kinase 1; 4E-BP1, 4E-binding protein 1; MMPs, matrix metalloproteinases; NF- κ B, Nuclear factor κ B; VEGF, vascular endothelial growth factor; ORAI2, Calcium release-activated calmodulin 2; ROR2, receptor tyrosine kinase-like orphan receptor 2; PGAM5, Phosphoglycerate mitochondrial mutant enzyme family member 5; APS, Astragalus polysaccharide; TMP, Tetramethylpyrazine; TGF- β 1, transforming growth factor β 1; BP, N-butylidenephthalide.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. The results of this study will be published in a peer-reviewed journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

There are no conflicts of interest.

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