

Multi-Signaling Pathway Cross-Regulatory Network of Fortified Qifang Stomachache-Relieving Granules against Precancerous Lesions of Gastric Cancer: A Comprehensive Review

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Abstract

Precancerous Lesions of Gastric Cancer (PLGC) represent a crucial reversible node in the malignant progression from gastritis to gastric cancer. Effectively blocking and reversing PLGC is the core strategy for reducing the incidence of gastric cancer. Fortified Qifang Stomachache-relieving Granules (FQSG) have shown significant clinical efficacy in the clinical prevention and treatment of PLGC. As an effective traditional Chinese medicine compound for the clinical treatment of chronic atrophic gastritis, FQSG could strengthen the spleen, replenish qi, clear heat and resolve dampness, as well as promote blood circulation and remove blood stasis. Clinical observations suggest that it could improve the pathological damage of the gastric mucosa and reverse intestinal metaplasia and dysplasia in PLGC. Compared with single-target drugs, this compound with its characteristics of multiple components, multiple targets, and multiple pathways, could interfere with the inflammation-cancer transformation process of PLGC through a cross-regulatory network of multiple signaling pathways. This paper systematically reviews the relevant research progress in recent years, focusing on core pathways such as Wnt/ β -catenin, PI3K/Akt, NF- κ B, MAPK, and TGF- β . It emphasizes the regulatory mechanisms of cell proliferation, apoptosis, inflammation, and epithelial mesenchymal transition mediated by each pathway, analyzes the network rules of cross-talk and synergistic anti-cancer effects among pathways to clarify the scientific

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connotation of FQSG in anti-PLGC and provide theoretical support for its precise clinical application and subsequent new drug research and development.

Keywords

Fortified Qifang Stomachache-Relieving Granules, Precancerous Lesions of Gastric Cancer, Multi-Signaling Pathways, Cross-Regulatory Network

1. Introduction

Gastric cancer is the third leading cause of cancer mortality worldwide. Its development follows the classic pathological evolution of the Correa cascade reaction. Normal gastric mucosa successively undergoes chronic non-atrophic gastritis, chronic atrophic gastritis (CAG), intestinal metaplasia (IM), dysplasia (Dys), and finally progresses to invasive gastric cancer [1]. In this review, “CAG” refers to the chronic atrophic gastritis stage (glandular atrophy of the gastric mucosa); “IM” denotes intestinal metaplasia and “Dys” denotes dysplasia; “PLGC” (precancerous lesions of gastric cancer) is used specifically for the IM and Dys stages, which are regarded as the key reversible nodes in the transformation from gastritis to gastric cancer. Established invasive gastric cancer is a terminal-stage disease and is explicitly excluded from the disease scope to which the “reversal of PLGC” conclusions in this review apply. Evidence derived from gastric cancer cell lines or tumor-bearing mouse models is used only as mechanistic background and is clearly distinguished from direct evidence obtained in PLGC/PLGC-model systems throughout the text. Studies have shown that the prevalence of CAG can reach 20% - 30% in specific high-risk populations globally, and the risk of developing gastric cancer in patients with incomplete IM is about 13.4 times higher than that in patients with complete IM [2] [3]. Therefore, clarifying the pathogenesis of PLGC and finding effective treatment strategies to block or even reverse its malignant transformation are of great significance for the secondary prevention of gastric cancer.

In recent years, traditional Chinese medicine (TCM) has demonstrated unique advantages in the prevention and treatment of PLGC. The comprehensive intervention characteristics of TCM, with multiple components, multiple targets, and multiple pathways, are highly consistent with the complex pathological mechanisms of PLGC. Multiple studies have confirmed that Chinese herbal compounds can significantly improve the clinical symptoms of CAG patients and reverse glandular atrophy and intestinal metaplasia at the histopathological level [4] [5]. This provides a solid practical foundation for TCM intervention in PLGC and implies that its mechanism of action may be closely related to the regulation of multiple signaling pathways.

FQSG has been widely used clinically in the treatment of CAG. Preliminary clinical observations have confirmed that this formula can reduce the infiltration

of inflammatory cells, increase the thickness of the gastric mucosa, and reverse glandular atrophy and intestinal metaplasia. However, the exact molecular mechanism by which it exerts its anti-PLGC effect remains to be systematically elucidated. Modern pharmacological studies have shown that PLGC involves the abnormal activation and cross-talk of multiple signaling pathways such as Wnt/ β -catenin, PI3K/Akt, NF- κ B, JAK/STAT and Hippo [6]-[8]. Therefore, analyzing the molecular mechanism of FQSG against PLGC based on the cross-regulatory network of multiple signaling pathways has important academic and application values. This paper aims to systematically review the relevant research progress in recent years and explore the molecular mechanism by which it exerts its therapeutic effect through the regulation of multiple key signaling pathways and their cross-networks, in order to provide a theoretical basis for in-depth research and clinical application.

To avoid overclaiming, this review applies an explicit three-tier evidence classification. i) Direct evidence: studies in which FQSG itself was tested in PLGC, CAG, or PLGC-related models; only these data are used to support definitive conclusions about FQSG mechanisms. ii) Indirect/analogous evidence: findings from other herbal formulas or single compounds in PLGC or CAG models; these are explicitly labeled as “analogous interventions suggest... but have not been directly validated in FQSG” and are treated as hypotheses rather than established FQSG mechanisms. iii) Background evidence: studies in gastric cancer cell lines, tumor-bearing mice, or human gastric cancer tissues; these serve only to establish the relevance of a given pathway to gastric carcinogenesis and are never used as evidence that FQSG reverses PLGC.

2. Composition and Pharmacological Basis of FQSG

FQSG are an adaptation of the traditional Qifang Stomachache-relieving Granules, designed to “invigorate the spleen and replenish qi, clear heat and resolve dampness, and promote blood circulation to remove stasis.” The constituents and dosages of FQSG are as follows: Red Ginseng 10 g, Poria Cocos 10 g, Largehead Atractylodes Rhizome 10 g, Honey-fried Licorice Root 9 g, Coptis Rhizome 6 g, Aucklandia Root 6 g, Evodia Fruit 3 g, Immature Bitter Orange 6 g, Pinellia Tuber 10 g, Astragalus Root 30 g, Solomonseal Rhizome 6 g, Snakegourd Peel 20 g, Snakegourd Root 10 g, White Peony Root 30 g, Salvia Miltiorrhiza Root 10 g, Stir-fried Chicken's Gizzard-membrane 9 g, Burreed Tuber 15 g, Zedoary Rhizome 15 g, Spreading Hedyotis Herb 20 g. The formula primarily uses Codonopsis Radix and Atractylodis Macrocephalae Rhizoma as the main components. Supporting ingredients like Salviae Miltiorrhizae Radix and Rhizoma and Curcumae Zedoariae Rhizoma enhance blood circulation, aiming to alleviate blood stasis caused by qi stagnation and damp obstruction, thereby improving gastric mucosal microcirculation. Adjuvant ingredients such as Citri Reticulatae Pericarpium and Pinelliae Rhizoma help regulate qi, harmonize the stomach, relieve nausea and vomiting, and balance the formula's properties. This comprehensive approach ad-

dresses the complex pathology of chronic atrophic gastritis (CAG), characterized by “deficiency in origin and excess in superficiality.”

Modern pharmacological research highlights astragaloside IV, a key active component from *Astragali Radix*, for its anti-inflammatory, antioxidant, and immunomodulatory properties. It mitigates oxidative damage to the gastric mucosa by modulating the ferroptosis-related signaling pathway [9]. Berberine from *Coptidis Rhizoma* and dehydroevodiamine (DHE) from *Evodiae Fructus* form a pair that clears heat and dries dampness. DHE has been shown to improve gastric mucosal damage in CAG rats induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and inhibit GES-1 cell migration and invasion by targeting the HIF-1 α /VEGF angiogenesis pathway [10]. Tanshinone IIA from *Salviae Miltiorrhizae Radix et Rhizoma* also regulates ferroptosis-related pathways [9]. Network pharmacological analysis identifies naringenin, luteolin, and quercetin as crucial components that work synergistically through multiple targets [11]. It should be noted that most of the monomer-level mechanistic data in this paragraph derive from active compounds tested individually or from network pharmacology predictions, rather than from FQSG as a whole administered in PLGC models; they are therefore treated as pharmacological hypotheses regarding FQSG's potential mechanism rather than established findings.

These active components interact within a multi-target, multi-pathway synergistic network. Astragaloside IV and tanshinone IIA inhibit cell proliferation and induce apoptosis via the PI3K/Akt signaling pathway. The combination of berberine and dehydroevodiamine reduces inflammation and gastric mucosal damage in *H. pylori*-induced CAG rat models by inhibiting the JMJD2B/COX-2/VEGF axis and the HMGB1/NF- κ B signaling pathway [12]. The “monarch, minister, assistant, and conductant” principle is evident at the molecular level, where different active components synergistically regulate various nodes of the same signaling pathway or intervene in multiple parallel pathways. This multi-component, multi-target synergistic mechanism is considered a plausible advantage of this formula, although direct confirmation in intact FQSG-treated PLGC models remains to be established.

3. Molecular Pathological Mechanisms of PLGC

The pathological progression of PLGC is characterized by distinct stage-specific features. In the context of CAG, pathological changes include atrophy of the gastric mucosal epithelium and glands, marked by a reduction in gland numbers, thinning of the mucosal layer, and often thickening of the muscularis mucosa. This is sometimes accompanied by pyloric or intestinal gland metaplasia, and dysplasia may be observed in certain cases. The PLGC rat model, induced by N-methyl-N'-nitro-N-nitrosoguanidine, similarly exhibits significant pathological changes such as atrophy, intestinal epithelial metaplasia, and dysplasia [13]. As the lesion advances, the gastric mucosal epithelium is replaced by intestinal-type cells, forming intestinal metaplasia (IM), a common precancerous lesion of intes-

tinal-type gastric cancer. Pathological features of IM include the presence of intestinal-type epithelial cells like goblet, Paneth, and absorptive cells in the gastric mucosa, indicating abnormal cell differentiation [14]-[16]. IM and dysplasia (Dys) have also been successfully induced in *Atp4a*^{-/-} mice and the gastrectomy mouse model. Dysplasia is a stage with higher malignant potential in PLGC, characterized by abnormal cell morphology and tissue structure. Histologically, gastric dysplasia is often accompanied by an inflammatory background (60.42%) and intestinal epithelial metaplasia (64.58%), with a blurred lesion boundary and retention of the maturation gradient (97.72%). The nuclei are typically round (97.92%), with a high nuclear-cytoplasmic ratio, though cell polarity is usually maintained (89.58%). Identifying dysplasia, compared to low-grade intraepithelial neoplasia (LGD) and high-grade intraepithelial neoplasia (HGD), requires immunohistochemical analysis. In Dys, MUC5AC/MUC6 expression retains the maturation gradient but is significantly reduced or absent in LGD/HGD. P53 is mainly expressed in its mutant form in HGD (66.67%), while in Dys and LGD, it is in the wild-type form (100%/93.33%). The expression pattern of Ki67 shifts from a “gastric pit pattern” in Dys to a “polar pattern” in LGD and a “diffuse pattern” in HGD. This combined analysis of cell morphology and molecular markers is crucial for the objective diagnosis and differentiation of various stages of gastric precancerous lesions [17] [18].

3.1. Key Molecular Markers and Roles

The progression of PLGC involves three core markers: p53, Ki-67, and E-cadherin, which regulate DNA damage repair, cell proliferation, and epithelial phenotype stability, respectively. p53, a critical tumor suppressor gene, plays a central role in PLGC progression when functionally inactivated. Studies indicate that p53 protein expression is significantly higher in gastric cancer tissues compared to adjacent normal tissues, with high expression negatively correlated with the cell apoptosis index and positively correlated with the proliferation index. Traditional Chinese medicine compounds can intervene in PLGC by modulating p53-related signaling pathways. Animal studies have shown that these compounds can induce apoptosis in gastric mucosal cells by inhibiting the PI3K/AKT/mTOR pathway, upregulating pro-apoptotic protein Bax, and downregulating anti-apoptotic protein Bcl-2. They can block PLGC's malignant transformation by inhibiting the EGFR-PI3K-AKT pathway, reducing β -catenin and N-cadherin protein levels. Network pharmacology analysis also suggests the involvement of the P53 pathway in their mechanism of action [19].

Ki-67 serves as a marker of cell proliferation activity, directly reflecting the state of cell proliferation. Research shows that the cell proliferation index in gastric cancer tissues is significantly higher than in adjacent tissues, with a notably reduced apoptosis/proliferation ratio, indicating uncontrolled cell proliferation as a key characteristic of PLGC's malignant transformation. Traditional Chinese medicine compounds or active ingredients can delay PLGC progression by inhibiting

cell proliferation. For instance, 6-gingerol effectively inhibits MC cell proliferation, invasion, and metastasis, inducing cell cycle arrest and apoptosis by regulating the PI3K/Akt pathway [20]. Erianin, the main active ingredient of *Dendrobium*, significantly inhibits MC cell viability, arrests the cell cycle at the G2/M phase, and induces apoptosis by inhibiting the HRAS-PI3K-AKT signaling pathway and downregulating cell cycle-related proteins like Cyclin D1 [21].

E-cadherin is crucial in epithelial-mesenchymal transition (EMT). Its downregulation or functional loss is a key indicator of PLGC cells acquiring invasive and migratory capabilities. Multiple studies confirm that traditional Chinese medicine compounds can reverse EMT by restoring E-cadherin expression. Huayu Xiaopi Decoction significantly increases E-cadherin protein expression in PLGC rat gastric mucosal tissue and reduces mesenchymal markers like N-cadherin and Vimentin by regulating the JNK/c-Jun/Slug signaling pathway, thereby inhibiting EMT and improving PLGC [22].

3.2. Abnormal Activation of Key Signaling Pathways

The pathogenesis of PLGC is a multifaceted process involving numerous genes and steps, primarily driven by the abnormal activation of several signaling pathways. These pathways create a complex regulatory network that facilitates the malignant transformation of gastric mucosal epithelial cells. Notably, the Wnt/ β -catenin, NF- κ B, PI3K/Akt, and MAPK pathways are pivotal in PLGC's pathology. The Wnt/ β -catenin pathway is essential for maintaining gastric mucosal stem cell homeostasis and epithelial cell renewal. *Helicobacter pylori* infection can activate this pathway, leading to β -catenin accumulation in the cytoplasm and its nuclear translocation [23]. In the nucleus, β -catenin binds to TCF/LEF transcription factors, initiating the transcription of target genes like c-myc and cyclin D1, which promote abnormal cell proliferation and inhibit apoptosis.

The NF- κ B pathway links inflammation and cancer. Huopuxialing Decoction treatment can downregulate IL-6, TNF- α , and NF- κ B expression, significantly improving gastric mucosal damage in PLGC rats [24]. The PI3K/Akt pathway, crucial for regulating cell survival, proliferation, metabolism, and apoptosis, is often abnormally activated in PLGC. Carcinogenic factors like EGFR can induce PI3K phosphorylation and activation. Epigallocatechin gallate (EGCG) can mitigate gastric mucosal damage in MNNG-induced PLGC rats by inhibiting the PI3K/Akt/mTOR pathway and upregulating cleaved caspase-3, a pro-apoptotic protein [13]. Traditional Chinese medicine, such as Qigesiaopi Decoction, reduces PLGC damage by inducing autophagy and apoptosis through PI3K/Akt/mTOR inhibition [24]. Similarly, Zuojin Pills reverse MNNG-induced PLGC by regulating cell proliferation and apoptosis via the MEK/ERK/c-myc pathway [25]. This intricate signaling network collectively influences PLGC's pathological process, making the comprehensive regulation of these pathways a key strategy for PLGC prevention and treatment.

3.3. Relationship between Inflammatory Microenvironment and PLGC

Chronic inflammation is a central driver in the development and progression of precancerous gastric lesions. Persistent stimuli, such as *Helicobacter pylori* infection and chemical carcinogens, create a chronic inflammatory microenvironment in the gastric mucosa, characterized by inflammatory cell infiltration and pro-inflammatory factor release. This environment promotes the malignant transformation of gastric mucosa from chronic non-atrophic gastritis to atrophy, intestinal metaplasia, dysplasia, and eventually gastric cancer by inducing gene mutations, promoting abnormal cell proliferation, inhibiting apoptosis, and remodeling the extracellular matrix.

Cyclooxygenase-2 (COX-2), an enzyme induced by various inflammatory factors, is significantly upregulated in the gastric mucosa of *Helicobacter pylori*-positive patients and correlates with infection severity and inflammatory activity. The COX-2-mediated inflammatory response is crucial in gastric cancer transformation. Multiple immune cells and their secreted inflammatory factors form the core components of the PLGC inflammatory microenvironment. Macrophages can polarize into M1 (pro-inflammatory) and M2 (anti-inflammatory/pro-repair) types. Sustained inflammation disrupts M1/M2 balance, with increased M1 macrophage infiltration releasing pro-inflammatory factors like TNF- α and IL-1 β , exacerbating mucosal damage. In the CAG rat model, increased CD68+ cell aggregation in the gastric mucosa correlates with CDX2 expression, indicating macrophage-mediated inflammation's direct role in intestinal metaplasia formation [26].

The neutrophil/lymphocyte ratio (NLR) and monocyte/lymphocyte ratio (MLR) are significantly higher in dysplasia than non-dysplasia groups, serving as potential dysplasia risk biomarkers. Activated immune cells promote epithelial cell malignant transformation by activating JAK2/STAT3 and NF- κ B pathways through inflammatory factors like IL-6 and TNF- α . Paeonol can inhibit MNNG-induced malignant cell proliferation, migration, and invasion, reducing gastric mucosal damage by blocking the JAK2/STAT3 pathway [27]. Weifuchun Tablets can halt intestinal metaplasia progression by inhibiting the NF- κ B pathway, reducing p65 binding to the CDX2 promoter, and downregulating CDX2 expression [5]. These findings elucidate the complex mechanisms by which the inflammatory microenvironment drives PLGC development through multiple signaling pathways.

4. Key Signaling Pathways Regulated by FQSG

4.1. Regulation of the Wnt/ β -Catenin Signaling Pathway

The Wnt/ β -catenin signaling pathway is pivotal in regulating cell proliferation, differentiation, and maintaining stemness, playing a significant role in the transition from precancerous gastric lesions to gastric cancer (GC). FQSG may target this pathway through a multi-target mechanism, showing promise against PLGC. Studies indicate that the nuclear translocation of β -catenin, a key effector in this

pathway, is crucial for maintaining gastric cancer stem cells (GCSCs) and tumor progression. Sijunzi Decoction, known for its ability to reduce GCSCs' stemness by inhibiting β -catenin's nuclear aggregation and DNA binding, aligns with the spleen-invigorating and qi-replenishing effects of FQSG [28]. This suggests that these granules could similarly block the malignant progression of PLGC.

However, a methodological clarification is warranted here. The relevance of the Wnt/ β -catenin pathway in PLGC/gastric cancer is supported by background studies; however, within the scope of the literature retrieved in this review, no data from PLGC models directly demonstrate that FQSG regulates the Wnt/ β -catenin pathway. The formula's composition base (e.g., related Sijunzi decoction evidence) suggests that FQSG may exert anti-PLGC effects through analogous mechanisms; this inference remains a hypothesis awaiting direct validation in FQSG-treated PLGC models.

Related but tertiary evidence: studies demonstrating Lgr5/Wnt/ β -catenin pathway reversal in PLGC models by other Chinese herbal compound formulas may be cited as background relevance only—they are not direct FQSG mechanisms and should be labeled accordingly.

4.2. Mediating Role of the PI3K/Akt Signaling Pathway

The PI3K/Akt signaling pathway is essential for cell survival and plays a central role in PLG development and progression. FQSG have demonstrated biological activity against PLGC by modulating this pathway [29]–[32]. Animal experiments and transcriptomic studies reveal that these granules improve the overall condition and gastric mucosal pathology in PLGC model rats. They reduce inflammatory factors IL-6 and TNF- α in serum and lower the expression of proteins related to “inflammation-cancer transformation,” such as p53 and Ki-67, thereby interrupting this transformation process. Western blot analysis shows that the granules decrease the elevated levels of p-PI3K and p-Akt in gastric tissues of model rats. Additionally, they inhibit glycolysis in gastric cancer cells via the PI3K/AKT/HIF-1 α pathway, as evidenced by reduced tumor growth in HGC-27 tumor-bearing mice, with inhibition rates of 11.90%, 33.61%, and 52.70% for low, medium, and high doses, respectively. This mechanism involves inhibiting the PI3K/AKT/HIF-1 α pathway, reducing GLUT1, PFK1, HK2, and LDHA expression, and decreasing ATP and lactic acid production.

Active monomer components in traditional Chinese medicine also target the PI3K/Akt pathway. For instance, 6-Gingerol inhibits PLGC cell proliferation, invasion, and metastasis while promoting apoptosis and cell cycle arrest [20]. Erianin, from *Dendrobium chrysotoxum*, reduces HRAS, AKT, p-AKT, MDM2, and Cyclin D1 expression and upregulates p21, inhibiting PLGC cell viability and migration [21]. Ursolic and oleanolic acids prevent MNNG-induced malignant transformation of gastric mucosal cells by inhibiting the PI3K/AKT/NF- κ B p65/NLRP3 pathway. The PI3K/AKT agonist 740YP can reverse this effect, underscoring the pathway's mediating role [33]. These findings suggest that FQSG'

active components synergistically inhibit PI3K/Akt pathway activation, regulating downstream molecules related to cell survival, proliferation, apoptosis, and epithelial-mesenchymal transition, ultimately aiding PLGC intervention and treatment.

4.3. Regulation of the NF- κ B Signaling Pathway and Inflammatory Response

The NF- κ B signaling pathway is crucial in chronic atrophic gastritis development and progression. FQSG effectively inhibit this pathway, providing anti-inflammatory and gastric mucosal protective effects. Studies show that these granules reduce NF- κ B p65 expression in CAG model rats and decrease inflammatory factor release [31]. Ultrastructural studies reveal improvements in gastric mucosal chief and parietal cell morphology, normalizing cell growth cycles and reducing CyclinD1 and NF- κ B expression. The treatment mechanism for chronic atrophic gastritis likely involves ameliorating gastric mucosal damage and regulating the NF- κ B pathway.

Further studies clarify how traditional Chinese medicine components exert anti-inflammatory effects by modulating the NF- κ B pathway and its key molecules. Berberine (BBR) inhibits NF- κ B and MAPK pathways, reducing serum inflammatory factors and reshaping intestinal flora, thus mitigating gastric mucosal damage [34] [35]. Astragaloside IV (AS-IV) protects against MNNG-induced CAG by upregulating protease-activated receptor-1 (PAR-1) and inhibiting NF- κ B p65 phosphorylation [36]. Other natural products, such as icariin II and jatrorrhizine, also show strong anti-inflammatory potential. Icariin II delays CAG progression to gastric cancer by inhibiting NF- κ B/STAT3 signaling and reducing pro-inflammatory cytokines [37]. Jatrorrhizine reduces *Helicobacter pylori*-induced gastritis inflammation by inhibiting NLRP3 inflammasome and NF- κ B pathway activation [38]. These findings indicate that FQSG's active components synergistically inhibit excessive NF- κ B pathway activation, effectively controlling chronic gastric mucosal inflammation and providing a molecular foundation for reversing PLGC.

4.4. Regulatory Mechanism of the MAPK Signaling Pathway

The MAPK signaling pathway is a crucial intracellular signal transduction system, consisting of three main branches: ERK, JNK, and p38 MAPK. It plays a pivotal role in regulating cell proliferation, differentiation, stress response, and apoptosis. In the pathological progression of PLG, gastric mucosal epithelial cells are persistently exposed to environmental stimuli like *Helicobacter pylori* infection, inflammatory factors, and oxidative stress. This exposure leads to abnormal activation of the MAPK pathway, a key event in malignant cell transformation. Integrated omics analysis indicates that FQSG can reduce the expression levels of HSPA4L, ERK, JNK, and RAS in rat gastric tissues, implicating the regulation of the MAPK signaling pathway [32]. Research confirms that these granules decrease the ex-

pression of the MEK gene and protein, down-regulate p-ERK and NF- κ B protein levels, and inhibit the ERK/NF- κ B signaling pathway in human gastric cancer cells [31]. This action promotes epithelial repair, inhibits gastric cancer cell proliferation, and induces apoptosis.

Furthermore, the MAPK pathway extensively interacts with other signaling pathways such as NF- κ B and PI3K/Akt. FQSG may enhance their anti-inflammatory and pro-apoptotic effects by influencing these interaction nodes [31]. Activation of p38 MAPK can promote NF- κ B's transcriptional activity. By regulating p38, FQSG may indirectly weaken the NF- κ B-mediated inflammatory cascade, creating a synergistic therapeutic effect. In summary, these granules restore cell homeostasis by inhibiting abnormal cell proliferation and inducing stress-induced apoptosis through precise regulation of the MAPK pathway's branches. This mechanism may be crucial for reversing PLG and blocking the "inflammation-cancer" transformation process. Future research should confirm the specific regulatory targets of FQSG on each MAPK pathway branch *in vivo* and *in vitro* and clarify their cross-regulation with other signaling pathways. This will provide a solid molecular pharmacological basis for treating PLGC with traditional Chinese medicine compounds.

4.5. TGF- β Signaling Pathway and Tissue Remodeling

The TGF- β signaling pathway is central to gastric mucosa damage repair and tissue remodeling. It serves a dual function as both a key driver of mucosal healing and a potential risk factor for fibrosis and disease progression, making it crucial for understanding the complex pathology of precancerous gastric lesions. The intervention effect of FQSG on PLGC is closely linked to its regulation of the TGF- β /Smad signaling pathway. Research indicates that these granules inhibit the mRNA and protein expression of ZEB2, N-cadherin, and Vimentin in AGS-EMT cells, up-regulate E-cadherin expression, enhance cell adhesion, and reduce cell migration and invasion. Post-intervention, the expression of downstream proteins 14-3-3 ζ , Smad2, and p-Smad2/3 in the TGF- β /Smad pathway is down-regulated, inhibiting the EMT process and weakening the invasion and migration abilities of gastric cancer cells [39].

4.6. Impact on the Notch Signaling Pathway

The Notch signaling pathway plays a critical role in cell-fate decisions, proliferation, and differentiation, and its dysregulation has been implicated in gastric carcinogenesis. To date, no published data directly demonstrate that FQSG modulates the Notch pathway in PLGC models. Available evidence indicates that Notch1 expression and its correlations have been observed in gastric cancer tissues [40] [41], and that its expression varies across different disease stages [42]-[45].

Whether FQSG participates in anti-PLGC activity by regulating the Notch pathway therefore remains speculative and requires direct validation in PLGC models

treated with FQSG. Further studies combining FQSG treatment with Notch pathway analysis in PLGC models are warranted to clarify the potential involvement of this pathway.

5. Integrated Analysis of the Cross-Regulatory Network of Multiple Signaling Pathways

The therapeutic mechanism of FQSG in treating PLGC involves a complex cross-regulatory network rather than a single linear signaling pathway. Transcriptomic analysis reveals numerous differentially expressed genes (DEGs) in the gastric tissues of PLGC rats following treatment with these granules, with significant enrichment in the PI3K-Akt signaling pathway [29]-[31]. This pathway is crucial for regulating cell survival and proliferation, as its activation leads to the phosphorylation and inhibition of downstream transcription factors like FoxO3a, promoting proliferation and inhibiting apoptosis. Additionally, the PI3K-Akt pathway interacts extensively with the Raf-1/MEK/ERK pathway. Raf-1, a pivotal node in the RAS-RAF-MEK-ERK signaling cascade, is significantly down-regulated by FQSG in a chronic atrophic gastritis rat model [46]. Activation of Raf-1 not only advances the ERK signal to promote the cell cycle but also co-regulates apoptosis and autophagy by phosphorylating Bcl-2 family members or interacting with Akt. Thus, the granules may inhibit both the PI3K-Akt and Raf-1/ERK pathways, synergistically blocking the malignant transformation of PLGC.

Moreover, cell-cycle regulation is central to PLGC progression. FQSG significantly down-regulate CDK2 and CDK4 protein expression in the gastric mucosa of PLGC rats [47]. These proteins are key drivers of the G1/S checkpoint in the cell cycle, co-regulated by the PI3K-Akt and Raf-1/ERK pathways. The ERK signal enhances Cyclin D1 expression and CDK4/6 activation, while Akt alleviates CDK2 inhibition by suppressing CDK inhibitors like p21 and p27. The down-regulation of CDK2/4 by the granules likely results from the downstream cascade effect following the inhibition of the PI3K-Akt and Raf-1/ERK pathways. Concurrently, the granules reduce the expression of p53 and Ki-67. It should be emphasized that the expression level of p53 must be distinguished from its functional status. Wild-type p53 has a short half-life and is barely detectable under normal conditions; the p53 protein accumulation detected in dysplasia and gastric cancer typically reflects the abnormal accumulation of mutant p53 (which loses its tumor-suppressive function and may even acquire oncogenic properties). Reported positive rates rise along the progression from intestinal metaplasia (approximately 12.1%) to dysplasia (approximately 34.6%) and gastric cancer (approximately 61.5%), with p53 gene mutation rates increasing from approximately 31.3% in dysplasia to approximately 60.1% in gastric cancer. Therefore, the decreased p53 protein positivity observed after FQSG intervention should be interpreted as inhibition of pathological p53 abnormal accumulation rather than restoration of normal wild-type p53 tumor-suppressive function. Since no mutation-sequencing or functional data are provided in this review, the downregulation of p53 should be reported as

an observational finding rather than a mechanistic marker of curative reversal. Ki-67, in contrast, serves as a reliable marker of cell proliferation.

The comprehensive therapeutic effect of FQSG arises from precise intervention in multiple key nodes. The PI3K-Akt and Raf-1/ERK pathways are core hubs, influencing each other through shared downstream effectors (mTOR, GSK-3 β) and negative-feedback mechanisms (Akt phosphorylates Raf-1 to inhibit its activity). By inhibiting both pathways, the granules prevent compensatory activation, effectively blocking pro-cancer signals. Additionally, regulation of CDK2/4 and p53 directly impacts cell cycle and DNA damage repair modules. This multi-level network regulation may explain why the granules outperform single-target drugs in improving gastric mucosa pathology and reducing inflammatory factors (IL-6, TNF- α) in PLGC rats [31]. Identifying key nodes like PI3K, Akt, Raf-1, and CDK2/4 holds significant clinical importance.

6. Conclusions

Leveraging its formula's strengths in enhancing spleen function, replenishing qi, clearing heat, removing dampness, and promoting blood circulation, FQSG regulates core signaling pathways such as Wnt/ β -catenin, PI3K/Akt, NF- κ B, MAPK, and TGF- β . This creates a multidimensional cross-regulatory network that effectively inhibits chronic gastric mucosa inflammation, blocks abnormal cell proliferation, prevents epithelial-mesenchymal transition, and stabilizes gastric mucosal cell homeostasis, reversing pathological changes like glandular atrophy, intestinal metaplasia, and dysplasia in PLGC. Compared to single-target drugs, the granules' multi-pathway, network-based regulation aligns better with PLGC's complex pathology. Future research should deepen understanding of this multi-pathway cross-network mechanism and enhance clinical translation to clarify its scientific basis.

Several limitations regarding the mechanistic evidence should be noted. For several pathways, including Wnt/ β -catenin and Notch, the evidence is either derived from indirect/background studies (e.g., gastric cancer tissue observations, or other Chinese herbal formulas in PLGC models) rather than from FQSG-treated PLGC models, or no FQSG-specific data are yet available. Regarding p53, the observed downregulation is reported as an observational finding rather than direct mechanistic evidence, owing to the absence of mutation-status and functional assays. Future studies should therefore directly validate these pathway modulations in FQSG-treated PLGC models, ideally incorporating p53 functional/mutation analyses, to distinguish hypothesis-driven mechanisms from confirmed FQSG actions. Methodological caveat: owing to the absence of p53 mutation-status and functional assays in the cited studies, the observed p53 downregulation is treated in this review as an observational finding rather than direct mechanistic evidence of restored wild-type p53 tumor-suppressive function. This work offers new theoretical and practical support for preventing and treating precancerous gastric lesions and inhibiting inflammation-cancer transformation with tradi-

tional Chinese medicine.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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