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Research Progress of Chinese Medicine in Regulating Relevant Signalling Pathways for the Treatment of GU

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Abstract: ***Gastric ulcer (GU) is a common digestive system disease in clinic. In recent years, the incidence of GU has increased year by year. Modern medical treatment mainly adopts symptomatic support therapies such as helicobacter pylori eradication therapy, acid suppression, and protection of gastrointestinal mucosa. However, these treatments have shortcomings such as high recurrence rate and many adverse reactions. Studies have shown that traditional Chinese medicine (TCM) plays an anti oxidative stress, anti-inflammatory and anti apoptotic role by regulating relevant signaling pathways through multiple pathways, multiple component and multiple targets, and promotes the repair of gastrointestinal mucosa, with PI3K/Akt, MAPK, NF-κβ and other signaling pathways as the core mechanism. This paper systematically expounds the research progress of TCM in the treatment of GU by regulating key signaling pathways, and summarizes the research progress of single TCM, TCM compound and Chinese patent medicine in the treatment of GU by regulating PI3K/Akt, MAPK and NF-κβ pathways through consulting the relevant literature.***

Keywords: Gastric ulcer, Traditional Chinese medicine, Signaling pathways, Inflammatory reaction.

1. Introduction

With the acceleration of the pace of life, the incidence of gastric ulcer (GU) is increasing year by year due to irregular diet and multiple stresses, etc. GU refers to the occurrence of localized tissue defects, inflammatory reactions and necrosis in the gastric mucosa under the action of one or more pathogenic factors, and finally forms an ulcer. The necrotic mucosa can reach deep into the muscularis mucosa or even deeper [1]. Its typical clinical manifestations include rhythmic and periodic pain in the upper abdomen. The nature of pain can be flatulence, burning pain, dull pain, nocturnal pain or hunger pain, accompanied by heartburn, acid reflux, anorexia and other symptoms, etc. The GU is closely related to the imbalance between gastric and duodenal mucosal damage factors and mucosal defense and repair factors. The pathogenic range of GU is wide, and people of any age may suffer from GU, among which the middle-aged and elderly are prone to GU [2]. The characteristics of its high prevalence, prolonged course and easy recurrence have brought great trouble to patients. At present, western medicine treatment mainly focuses on symptomatic supportive treatment such as anti Helicobacter pylori treatment, acid suppression, and protection of gastrointestinal mucosa, etc. According to the mechanism of action, the therapeutic drugs are roughly divided into anti acid agents, H2 receptor antagonists, proton pump inhibitors, gastric mucosa protectors, and anti Helicobacter pylori drugs, etc. For patients with GU complicated with hemorrhage, surgical treatment is needed when necessary [3]. It's worth noting that GU tends to recur after drug withdrawal, and there are many long-term adverse reactions. Relevant studies have shown that TCM can effectively relieve patients' clinical symptoms, reduce inflammatory reaction, improve gastrointestinal mucosal barrier function through regulating signaling pathways, with high safety.

2. Theoretical Basis of GU Treatment in Chinese Medicine

As a disease name of modern medicine, GU has not been directly discussed in ancient literature. According to its typical clinical manifestations, it can be classified into the categories of "epigastric pain", "epigastric upset", "acid regurgitation" and "epigastric fullness" in TCM, etc. [4]. The main causes of the disease include external evil controlling the stomach, improper diet, emotional disorders, physical weakness and so on. The disease is located in the stomach, which is closely related to the liver and spleen. The pathogenesis of GU is mainly caused by liver qi invading the stomach with qi-blood stagnation and obstruction; cold pathogen lodged in the stomach with cold-induced congelation and blood stagnation; food stagnation in gastrointestinal tract with internal generation of stagnant heat, clinical manifestations are predominantly of excess pattern. With prolonged disease course, the pathology progresses from qi-phase to blood-phase, wherein excess induces deficiency; alternatively, constitutional spleen-stomach weakness impairs transformation and transportation of qi-blood. This results in blood stasis due to deficient propulsion, creating deficiency-induced excess that manifests as complex patterns of intermingled deficiency and excess. [5]. The disease is always a mixture of deficiency and excess. Through oral Chinese medicine decoction, acupuncture, acupoint application and other TCM treatment methods, etc, it can effectively reduce the recurrence rate and reduce the occurrence of adverse reactions. Studies have shown that Huangqi jianzhong decoction inhibits the activation of RAF, MEK, ERK, JAK/STAT and other signaling pathways, reduces the content of TNF-α in GU rats, increases PGE2 and IL-10, p-MEK, p-ERKJAK2, STAT3mRNA, and then inhibits the inflammatory response, improves the immune

defense function of gastric mucosa, and then plays the role of protecting gastric mucosa [6].

3. GU Relevant Signaling Pathways and Regulatory Mechanisms

3.1 PI3K/Akt Signalling Pathway

PI3K/Akt (phosphatidylinositol 3-kinase / protein kinase B) signaling pathway is a key survival promoting signaling pathway in cells, which plays a vital role in maintaining tissue homeostasis by regulating cell proliferation, apoptosis, metabolism, inflammatory response and other processes. Phosphatidylinositol 3-kinase (PI3K) is an intracellular enzyme with phosphatidylinositol kinase activity and serine / threonine (Ser/Thr) kinase activity [7]. PI3K can be classified into class I, class II and class III. class I PI3K is a heterodimer structure, which is composed of a regulatory subunit p85 and a catalytic subunit P110; Class II contains three monomeric catalytic subtypes, C2α, C2β, and C2γ; While class III PIK3-c3 regulates autophagy and macrophage phagocytosis by binding to the tetrameric complex formed by the regulatory subunit and the catalytic subunit. Akt is a ser/thr kinase of AGC protein kinase group, and there are three subtypes (AKT1, AKT2 and Akt3). AKT1 is widely expressed in a variety of tissues; AKT2 is mainly dominated by insulin signaling; Akt3 is specifically expressed only in brain and testis [8].

The activation mechanism of PI3K/Akt signaling pathway is based on the activation of transmembrane receptor tyrosine kinases (RTKs), mainly including ligand receptor binding, PIK3 recruitment and activation, allosteric and activation of Akt, and downstream signaling cascades [9]. PTKs include epidermal growth factor receptor, fibroblast growth factor receptor and insulin-like growth factor 1, etc. Ligands (e.g., growth factors, cytokines or hormones) can activate the PI3K/Akt signaling pathway by activating RTKs [10]. Activated RTKs recruit the heterodimer p85α-p110αto the cell membrane and undergo autophosphorylation, exposing the SH2 domain binding site. The PI3K regulatory subunit p85 binds to phosphorylated tyrosine residues (pYXXM motif) through the SH2 domain. After p85 relieves the inhibition of the catalytic subunit P110, P110 membrane localizes and catalyzes PIP2 to generate the second messenger PIP3. PIP3 binds the PH domain of Akt and anchors Akt to the cell membrane [11]. PIP3 recruits phosphoinositide dependent kinase 1 to the cell membrane, phosphorylates the Thr308 site of Akt (activation loop), and the mTORC2 complex further phosphorylates the Ser473 site of Akt (hydrophobic motif), achieving full activation of Akt [12]. Activated Akt enters the nucleus or cytoplasm and regulates physiological processes through phosphorylation of downstream target proteins, e.g., phosphorylation of Pro apoptotic proteins Bad and Caspase-9, and activation of anti apoptotic protein Bcl-2 for cell survival; Inhibit GSK-3 β to promote glycogen synthesis, etc [13].

PI3K/Akt signaling pathway plays a key role in the regulation of cellular oxidative stress, apoptosis, inflammation and other physiological processes, and is closely related to the occurrence and development of GU. When the gastric mucosa is attacked (e.g., Helicobacter pylori infection, non steroidal anti-inflammatory drugs, alcohol, stress, etc.), it will stimulate gastric mucosal epithelial cells and infiltrating inflammatory cells (e.g., neutrophils, macrophages) to produce a large number of reactive oxygen species (ROS), which will lead to gastric mucosal damage and exacerbate the inflammatory response [14]. PI3K/Akt signaling pathway can activate nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, up regulate the expression of heme oxygenase 1, and activate catalase (CAT), glutathione (GSH) and superoxide dismutase (SOD) [15], to remove reactive oxygen species free radicals in the body, reduce the damage of oxidative stress to the gastric mucosa, enhance the antioxidant capacity of gastric mucosal cells, and maintain the gastric mucosa normal physiological function of cells, promoting the healing of GU; When the gastric mucosa is stimulated, it will trigger an inflammatory response, causing neutrophils to accumulate in the damaged area, activating macrophages and mast cells, releasing a large number of inflammatory mediators, thereby exacerbating the inflammatory response and aggravating gastric mucosal damage [16]. The activation of PI3K/Akt signaling pathway can inhibit the expression of inflammatory factors such as NF-κβ, reduce the production of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and promote the production of interleukin-10 (IL-10), so as to reduce the inflammation of gastric mucosa and protect gastric mucosa from further damage [17]. Under normal physiological conditions, cells will undergo normal proliferation and apoptosis processes to maintain the integrity of the mucosal barrier. However, the accumulation of ROS, the stimulation of inflammatory factors and the direct injury of gastric mucosal cells may all cause abnormal apoptosis of gastric mucosal cells. PI3K/Akt signaling pathway inhibits the occurrence of apoptosis and ensures the integrity of gastric mucosa by regulating the expression of anti apoptotic protein Bcl-2 and pro apoptotic proteins Bax, Caspase-9, Caspase-3, etc. [18-19]. PI3K/Akt signaling pathway plays a crucial role in the process of GU mucosal repair. Through its main regulatory mechanisms (including inhibition of mucosal cell apoptosis, reduction of oxidative stress injury, down-regulation of inflammatory factor release, etc.), it can effectively alleviate the further aggravation of gastric mucosal damage and alleviate the deterioration of the condition of patients with GU to a certain extent.

3.2 MAPK Signalling Pathway

MAPK (mitogen activated protein kinase) signalling pathway is a key cell signaling pathway, which is involved in the regulation of cell growth, proliferation, differentiation and apoptosis. MAPK family includes four subtypes, among which extracellular regulated protein kinase (ERK), p38 mitogen activated protein kinase (p38MAPK) and c-jun amino terminal kinase (JNK) have been widely studied [20].

The core of the occurrence and development of GU lies in the imbalance between the factors of gastrointestinal mucosal injury (attack factors) and the self defense and repair ability of gastrointestinal mucosa (protective factors). However, the core mechanism of MAPK signaling pathway intervention in GU is to promote inflammatory response and induce epithelial cell apoptosis. When the gastrointestinal mucosa is stimulated (e.g., Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs, alcohol, stress, etc.), extracellular growth factors activate tyrosine kinase receptors. Activated RTK

binds to the adaptor protein GRB2, providing a binding site for recruiting SOS. SOS activates Ras, which then binds to c-Raf and activates downstream MEK1/2. Activated MEK1/2 phosphorylation activates multiple transcription factors (e.g., NF-κβ, AP-1), which enter the nucleus and promote gene expression and release of a large number of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, IL-8) [21]. At the same time, the MAPK pathway also promotes the production of chemokines, recruits more inflammatory cells (e.g., neutrophils and macrophages) to the site of gastric mucosal injury, forms a positive feedback loop of inflammatory factors, further activates the MAPK pathway, amplifies local inflammatory reactions, and strong inflammatory reactions lead to tissue edema, increased vascular permeability, and increased production of reactive oxygen species, directly damaging gastric mucosal epithelial cells and microvessels, and disrupting the mucosal barrier; Meanwhile, the main trigger of GU can significantly activate the JNK and p38 MAPK pathways. Activated JNK and p38MAPK can phosphorylate and activate pro apoptotic transcription factors, upregulate the expression of pro apoptotic proteins (e.g., Bax, Bak), inhibit the function of anti apoptotic proteins (e.g., Bcl-2, Bcl xL), increase mitochondrial outer membrane permeability, release cytochrome C, activate caspase cascade reactions, and induce programmed cell death of gastric mucosal epithelial cells [22]. Ultimately, excessive apoptosis of gastrointestinal mucosal epithelial cells damages the integrity of the gastric mucosa, weakens its function as a physical and secretion barrier, and makes the mucosa more susceptible to erosion by gastric acid and pepsin.

3.3 NF-κβ Signalling Pathway

The NF-κβ signaling pathway is a critical intracellular signaling pathway, with core members including NF-κβ1 (P50/P105), NF-κβ2 (P52/P100), RELA (P65), RELB, and CREL. Nuclear factor kappa β (NF-κβ) is a transcription factor activated by most members of the tumor necrosis factor receptor (TNFR) and toll like receptor (TLR) superfamily, as well as metabolic or genotoxic stress inducers [23]. NF-κβ is mainly involved in regulating inflammatory response, immune response, and cell apoptosis process. Under normal physiological conditions, NF-κβ binds to Iκβ to form the NF-κβ/Iκβ complex, which is in an inactive state in the cytoplasm. The activation of NF-κβ can occur through typical and atypical pathways, depending on the type of stimulus. The typical pathways are mainly activated by interleukin (IL) -1β, tumor necrosis factor -α(TNF-α), lipopolysaccharide (LPS), and antigens; The atypical pathway may be activated by CD40 ligand (CD40L), B lymphocyte activating factor (BAFF), and lymphotoxin beta (LTβ) [24]. When the gastrointestinal tract is stimulated by inflammation transmitted from cell membrane receptors or intracellular signaling pathways, the NF-κβ signaling pathway is activated, and Iκβ proteins (e.g., Iκβ-α) are phosphorylated and degraded by specific kinases, thereby releasing NF-κβ. NF-κβ translocates to the nucleus and binds to specific sequences of DNA, promoting the transcription of inflammation related genes such as TNF-α, IL-1β, IL-6 and other inflammatory factors, leading to the occurrence of gastrointestinal mucosal inflammation and further exacerbating gastrointestinal mucosal damage [25].

The NF-κβ signaling pathway plays a crucial role in regulating the formation and progression of GU, mainly by modulating inflammatory responses and inhibiting oxidative stress processes [26]. Research has revealed that during the formation and progression of acute gastric ulcer, the mitogen activated protein kinase (MAPK) family member P38, after phosphorylation activation, can trigger the activation of NF-κβ. Once P38MAPK is activated by external stimuli, NF-κβ is activated through the phosphorylation of its specific substrate and migrates to the nucleus to bind to the κ B site on DNA, initiating transcriptional enzymes and activating gene expression programs, thereby regulating the production of inflammatory factors such as tumor necrosis factor-α(TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). At the same time, this process can also induce excessive or sustained expression of vascular cell adhesion molecule-1(VCAM-1) and other molecules, ultimately leading to sustained infiltration of neutrophils in ulcer tissue and exacerbating inflammatory reactions [27]. These inflammatory factors can also reverse activate NF-κβ, producing a large number of inflammatory factors through pro-inflammatory pathways, triggering an inflammatory cascade reaction [28-29]; The signaling mechanism related to oxidative stress involves biochemical reactions involving reactive oxygen species (ROS). Research has shown that the majority of intracellular ROS sources can be influenced or affected by NF-κβ activity. On the one hand, the main mechanism by which NF-κβ regulates ROS levels includes upregulating the expression of antioxidant proteins and stimulating the production of enzymes that promote ROS production. On the other hand, ROS can oxidize cysteine CYS-62 to glutathinate NF-κβ, leading to a decrease in NF-κβ transcriptional activity and affecting its DNA binding ability; The stimulation of ROS can also promote the phosphorylation and degradation of Iκβ, thereby increasing the release of NF-κβ [30].

4. Experimental Study on the Treatment of GU by Regulating Related Signaling Pathways with Traditional Chinese Medicine

Using keywords such as “gastric ulcer, NF-κβ, PI3K/Akt, MAPK,” search for relevant literature included in databases such as Web of Science, PubMed, and the Chinese Knowledge Resource Database. The literature satisfying two topics at the same time was selected and summarized in three aspects: single Chinese medicine, Chinese patent medicines and Chinese medicine compound.

4.1 Single Chinese Medicine

Based on the core mechanisms of signal transduction pathways such as NF-κβ, PI3K/Akt, MAPK, etc. in ulcer formation, TCM for treating ulcers can be divided into two categories: anti-inflammatory, antioxidant, and anti apoptotic. Research has shown that Bletilla striata (Baiji) possesses bitter flavor and cold nature, with demonstrated effects in hemostasis, detumescence, tissue regeneration, and wound healing. It is often combined with medicinal herbs such as Huanglian, Beimu, and qingfen to treat diseases such as ulcers, ulcers, and long-term non healing. Its main component, Bai Ji polysaccharide, can inhibit the PI3K/Akt signaling pathway,

downregulate the mRNA and protein expression of PI3K and Akt, and thereby inhibit the abnormal secretion of inflammatory factors IL-2R and IL-4, thereby inhibiting cell apoptosis, reducing inflammatory reactions, and exerting a protective effect on gastric mucosal tissue [31]. Wang Pengcheng [32] et al. found through network pharmacology and animal experiments that agarwood may act on key targets such as AKT1, TP53, IL6, and Caspase3 through its main active ingredients quercetin, β- sitosterol, and 6,7-dimethoxy-2- (2-phenylethyl) ketone, etc., regulating key signaling pathways such as TNF signaling pathway and cancer pathway, and exerting therapeutic effects on GU through anti-inflammatory and anti apoptotic mechanisms. Chenpi glycoside can significantly reduce the levels of myelo per oxidase (MPO) and MDA in the gastric tissue of mice with GU, increase SOD levels, and reduce the production of inflammatory factors such as IL-1β, IL-6, TNF-α, etc. This indicates that Chenpi glycoside may exert anti-inflammatory and antioxidant effects on acute GU mice by inhibiting the MAPK/NF-κβ pathway, and this inhibitory effect shows a clear dose-response relationship [33]. The advantage of using a single TCM to treat peptic ulcers lies in the synergistic effect of multiple targets, and the side effects are significantly lower than those of Western medicine. The cost-effectiveness is more prominent, but there are limitations such as the lack of large sample RCT research support and low bio avail ability of active Medicines

4.2 Chinese Medicine Compound.

In recent years, numerous experimental studies have revealed the unique advantages of TCM formulas in treating GU, and their "Multicomponent, Multitarget, Multimechanism Action" therapeutic mechanism has shown significant effects in regulating related signaling pathways. Huangqi jianzhong decoction has been proven to improve the pathological changes of gastric mucosa by activating the signaling pathway mediated by TLR2 and NF-κβ, promoting the repair of gastric mucosal damage, and downregulating the expression of TLR2 protein and p-NF-κβ protein [34]. Tongxie Yaofang exerts therapeutic effects by: harmonizing the Liver and Spleen, fortifying the Spleen and Softening the Liver, arresting Diarrhea by Dispelling Dampness. Zhang Jiaqi et al. [35] revealed its potential mechanism of action in regulating the serum levels of NE, GAS, 5-HT, and D-xylose in rats with GU liver qi stagnation and spleen deficiency syndrome through non targeted metabolomics technology, which may involve intervening in metabolites e.g., glycero phosphatidylethano lamine, deoxycholic acid, 2-arachidonoylglycerol, phenyl pyruvic acid, melatonin, linoleic acid, as well as citrate cycle (TCA cycle), amino acid metabolism, energy metabolism, lipid metabolism, etc., thereby reducing the area of GU, protecting mucosal tissue, and promoting ulcer healing. Sanhuang Xiexin decoction has the effect of purging fire and drying dampness. Zhong Yilin et al. [36] found through network pharmacology, molecular docking, and animal experiments that it activates PTEN, regulates the PI3K/Akt/NF-κβ signaling pathway, downregulates inflammatory factors such as IL-1β and TNF-α, inhibits inflammatory reactions, and thus improves stress-induced gastric mucosal injury. Research has shown that qibei Xiaoyun decoction can improve the clinical symptoms of helicobacter pylori positive GU patients, reduce gastric inflammatory reactions, promote ulcer healing, and reduce the risk of recurrence by reducing oxidative stress response, inhibiting NF-κβ signaling pathway expression [37]. TCM formulas exhibit multidimensional effects such as anti-inflammatory, acid suppressing, and mucosal repair in the treatment of GU by regulating signaling pathways such as MAPK, JAK/STAT, and H2R through multiple targets.

4.3 Chinese Patent Medicine

Research has shown that weikang capsule can treat ethanol induced GU model rats by inhibiting the expression of inflammatory mediators mediated by the Akt/NF-κβ signaling pathway and reducing oxidative stress levels. They can effectively reduce ulcer area, increase ulcer inhibition rate, and protect ulcer tissue [38]. Kangfu Xin Liquid is a liquid preparation made from dried extracts of American cockroaches, which has the effects of promoting blood circulation, nourishing yin and developing muscle. Research has shown that Kangfuxin liquid negatively regulates the PI3K/Akt/NF-κβ signaling pathway, inhibits the expression of TNF-α and IL-1β, significantly reduces the phosphorylation level of IκB, inhibits the nuclear translocation of NF-κβ p65, and exerts antioxidant, anti apoptotic, and anti-inflammatory effects, thereby promoting gastric mucosal injury repair [39]. Sanqi and Baiji powder can alleviate inflammation and oxidative stress in blood stasis type GU rats by inhibiting the activation of the PI3K/AKT signaling pathway, improving their hemorheological indicators and gastric mucosal blood circulation, thereby reducing gastric mucosal damage in rats [40].

5. Conclusion and Outlook

As a typical "attack defense" imbalance disease, the pathogenesis of GU is essentially the dynamic balance between the repair mechanism of gastric mucosal barrier and the cascade reaction of inflammatory damage being disrupted. TCM has demonstrated unique advantages in the prevention and treatment of ulcers through multi-target, multi-level, and holistic regulation of signal networks Numerous studies have shown that TCM can precisely intervene in the three core mechanisms of MAPK/NF-κβ inflammation axis, EGFR/PI3K/Akt repair axis, and H2R/cAMP acid suppression pathway, exerting anti-inflammatory and immune regulation, mucosal regeneration and repair, and dynamic balance reconstruction. This treatment strategy of "dispelling evil and supporting the body" not only conforms to the core pathogenesis theory of "strengthening the spleen, clearing heat, and removing blood stasis" in TCM, but also deeply integrates with the concept of "mucosal defense reconstruction" in modern medicine. However, the material basis of its research is not clear, and it is necessary to combine metabolomics to analyze the active ingredients. At the same time, the multi-target synergistic mechanism is unclear, and network pharmacology and molecular docking techniques need to be used for further clarification of the mechanism. The research on TCM treating GU through signal pathway regulation not only provides unique solutions for gastrointestinal diseases, but also provides new ideas for multi-target intervention models for complex diseases.

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