

Discussion on Professor Li Yi ' s Fuyang Thought in Treating Chronic Atrophic Gastritis Based on Network Pharmacology

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Abstract

As one of the good diseases of the digestive system, chronic atrophic gastritis has the characteristics of long course and easy recurrence. According to its main clinical symptoms, traditional Chinese medicine can be classified as ' stomachache ', ' fullness ', ' noisy ' and so on. Professor Li Yi believes that in the development of chronic atrophic gastritis, spleen and kidney yang deficiency runs through the beginning and end of the disease, so the treatment also takes warming and tonifying spleen and kidney as the main method, and has achieved good clinical results. The author has been with Professor Li Yi for more than one year. This paper summarizes Professor Li Yi ' s Fuyang thought in the treatment of chronic atrophic gastritis, and analyzes the core drug pairs with modern network pharmacology to provide reference for clinical practice.

Keywords

Professor Li Yi ; Fu-Jiang-Gui ; Fuyang thought ; cAG ; Network pharmacology.

1. Introduction

Chronic atrophic gastritis (CAG) is a chronic non-specific gastritis characterized by atrophy of gastric mucosa and glands, reduced number, thinning of gastric mucosa, or accompanied by pyloric gland metaplasia or intestinal metaplasia. Common clinical symptoms are abdominal fullness, pain, loss of appetite, belching, anemia, acid reflux heartburn, weight loss, anemia, etc. The treatment of CAG by Western medicine is limited to slowing down the existing symptoms of patients, reducing inflammation, relieving pain, etc., and cannot completely reverse the atrophy of gastric mucosa and glands. However, traditional Chinese medicine has a unique advantage in the treatment of CAG [2]. According to the main symptoms of CAG patients, traditional Chinese medicine can divide CAG into ' stomach pain ', ' noisy ', ' fullness ' and other categories. According to its main symptoms, tongue and pulse, CAG can be roughly divided into five syndromes : spleen and stomach yang deficiency (also known as spleen and stomach deficiency and cold, spleen and stomach weakness), spleen and stomach damp heat, blood stasis (also known as blood stasis), liver and stomach disharmony (also known as liver qi invading stomach), stomach yin deficiency. Many clinical statistics found that [3-5], the spleen and stomach yang deficiency type accounted for the largest proportion, and in the investigation of Xu GeLin [3] In 124 patients with CAG, the proportion of spleen and stomach yang deficiency type is as high as 33.87 %, followed by spleen and stomach damp-heat type, liver and stomach disharmony type, stomach yin deficiency type, blood stasis type, and these syndromes are not alone, mostly accompanied by syndromes, such as spleen and stomach yang deficiency combined with blood stasis, spleen and stomach yang deficiency combined with stomach yin deficiency type. Professor Li Yi was born in Yunyang, Chongqing, and is located in the Sichuan Basin. The local people are prone to dampness, which is easy to interfere with the spleen and stomach and injure their yang qi. Sichuan and other places are the gathering places of ' Huoshen School ' doctors. Therefore, Professor Li has a unique view on the idea of supporting yang, and

is better at using the medicine of warming and tonifying the spleen and kidney, especially for the treatment of spleen and stomach diseases. The author has been a teacher for more than one year. Now, the author introduces Li 's thought of syndrome differentiation and treatment as follows, and analyzes the core drug pairs in Fuyang method with modern network pharmacology.

2. Examination of the cause, pathogenesis preliminary study

Professor Li gathered the advantages of various schools and summarized years of clinical experience to find that the pathogenesis of this disease is complex, but it is always a syndrome of deficiency in origin and excess in superficiality, and mostly based on deficiency in origin, including blood stasis, dampness and other diseases, and Professor Li believes that deficiency in origin is mainly spleen, stomach and kidney yang deficiency, especially spleen and kidney yang deficiency has always existed in the beginning and end of the disease.

2.1. Congenital deficiency, spread to the day after tomorrow

Professor Li studied 'Huangdi Neijing', 'Treatise on Febrile Diseases', 'Classic On Medical Problems' and other medical books, very respected the late Qing Dynasty typhoid doctor Zheng Qin'an 's thought of supporting Yang, and very recognized Zheng Lao 's 'life is all in the middle of Kan'. It is not difficult to find through clinical practice that CAG patients are more common in older people [6]. Therefore, Li believes that old age and body failure, kidney qi deficiency are the main causes. The deficiency of kidney qi for a long time leads to the deficiency of kidney yang. The kidney, the life gate, the yang of the five zang organs and the six fu organs are all affected by the kidney. If the spleen is not warm, the transportation and transformation are lost. It can be seen that the appetite is weak and the appetite is poor. It can also be seen that the stool is loose and the shortness of breath is weak. If the stomach is not warm, it can be seen that the stomach is cold and painful.

2.2. Yang deficiency for a long time, damage its Yin

The 'Internal Classic' points out the view that yin and yang follow each other. Yang loss must be related to yin, especially the yang of the spleen and stomach, which leads to the deficiency of stomach yin. Li Shiyan said, 'after the birth of a person, there is no plain and unprovoked Yang, and there is no plain and unprovoked Yin'. After the birth of a person, the material of Yin and Yang comes from the acquired water and grain essence. For CAG patients, they are old and weak, and the kidney Yang is deficient. Therefore, the spleen and stomach Yang deficiency above appears, and the spleen and stomach are the acquired foundation. The spleen loses transportation and the stomach loses accommodation, so the water and grain essence cannot be transported and transformed, and the acquired material source of Yin is scarce, which in turn aggravates the deficiency of stomach Yin. At the beginning of the deficiency of spleen and kidney Yang, there is a deficiency of Yin, but Yin deficiency lags behind Yang deficiency. This also explains why patients with stomach yin deficiency are far less than those with spleen and stomach yang deficiency. Therefore, patients with stomach yin deficiency often have hunger, dull burning pain in the stomach, dry stool, and short urine.

2.3. Yang does not move, Yin blood stops in

Professor Li 's "long illness into stasis, long illness into collaterals," which also explains why the proportion of CAG patients with blood stasis type is the least, because only in the end stage of the disease can blood stasis appear. 'Qi, Yang also, Yang line an inch, Yin line an inch, Yang stop a moment, Yin stop a moment', Li believes that the spleen and stomach Yang deficiency for a long time, or the stomach directly cold, Yang gas is choked, blood can not be line, long-

term accumulation of blood stasis, blood does not line the stomach dystrophy, ' no glory is pain, no pass is pain ', so there can be stomach fixed position pain, pain such as acupuncture.

2.4. Lack of warmth, water does not melt

Professor Li said that ' elderly CAG patients with spleen and stomach damp-heat are born with deficiency rather than damp-heat '. The spleen governing dampness is the physiological function of the spleen, which refers to the spleen has the function of transporting and transforming water and dampness. This function is also inseparable from the participation of kidney yang. If the spleen and kidney yang are sufficient, the dampness can be transported and transformed. If the spleen and kidney yang are deficient, the water and dampness stay. The spleen has the characteristics of preference for dryness and aversion to dampness. Yang deficiency of spleen and kidney leads to dampness stagnation, which in turn injures the spleen. Spleen injury seriously affects the metabolism of water and dampness, so a vicious circle and infinite reciprocating. Spleen and kidney yang deficiency, dampness in the body does not change, and heat over time, here should pay attention to the difference with exogenous cold and dampness, so it can be seen that the mouth is dry and bitter, the stomach is burning, and the stool is sticky and uncomfortable.

2.5. Liver stomach disharmony, catharsis lost division

Li Shiyan ' ate into the stomach, transported by the spleen, and transported by the liver '. In terms of the relationship between the liver and the spleen, the liver belongs to the wood, the main catharsis, the spleen belongs to the soil, the main transport. The transportation and transformation of the spleen depends on the warmth of the kidney yang qi, and the transportation of the subtle substances after transportation and transformation is inseparable from the dredging of the liver. When the liver disease is seen, the catharsis is not done, the subtle substances are accumulated in the stomach but not scattered, the stomach is reduced, and the physiological function of the spleen is also affected. Therefore, there is a saying that ' seeing the disease of the liver, knowing that the liver transmits the spleen, it is necessary to strengthen the spleen first '. The liver and spleen are ill at the same time. Although the root of the disease is in the liver, it is located in the spleen and stomach. Therefore, the stomach pain of such CAG patients is often related to emotions. In the treatment, the spleen should be strengthened first, and the spleen and stomach yang should be strengthened.

3. Clinical prescription, with the evidence of the cutting

Professor Li often says that medication is like military deployment, so it is also very elegant in terms of medication, and special prescription, not rigidly adhere to the use of a classical prescription, mostly clinical prescription, and with the card, but it is not difficult to find that Professor Li takes warming and tonifying the spleen and kidney as the first treatment, which is interspersed with pain relief, nourishing yin and other treatment methods.

In the prescriptions of Professor Li, Fuzi Lizhong Decoction plus cinnamon is the most common, and it is especially good at using warm and hot drugs such as aconite, dried ginger and cinnamon. The dosage of aconite is often more than the conventional dosage. It is common between 15g and 30g, and it is good to use without abuse. Even 1 gram is extremely elegant, more than 1 gram of heat, less than 1 gram of insufficient. In Li Shifang, the amount of processed aconite is slightly more than that of other drugs. The processed aconite (20g) is the monarch, and the processed aconite is used to specifically walk the spleen and kidney, which is both congenital and acquired. The dried ginger (10g) in the prescription is the minister, ' Fuzi has no ginger and is not hot '. Although Fuzi is good at tonifying, it is scattered and too much, walking without leaving, half of the dried ginger, which is kept but not scattered, each takes its advantages, and is compatible with each other to warm the spleen and kidney ; if the aconite is

good at tonic, and the dried ginger is good at harvest, then the cinnamon (10g) must be good at communication, and the dried ginger is the same as the ministerial medicine. The description of cinnamon in ' Shennong 's Herbal Classic ' is ' the main disease, the spirit, and the color, the first to hire for the medicine ', and the cinnamon is especially good at inducing the fire to go down, so that the kidney yang is more sufficient, so the three drugs of aconite, dried ginger and cinnamon in Li Shifang are indispensable. Kidney Yang foot, and then the spleen and kidney to warm, and ' Taiyin wet soil, Yang began to transport ', spleen Yang filling, metaplasia, and nourishing kidney Yang, complement each other. Li Shiyun 's ' only tonifying yang is dead yang ', so ginseng (8g) and *Atractylodes macrocephala* (15g) are used together as adjuvants to play the role of invigorating spleen and replenishing qi, so that the yang cycle is repeated throughout the body ; a small amount of licorice (3g) to make, one to take its sweet and gentle meaning, ease the fierce monarch, the second to restrict the poison of aconite.

4. Based on network pharmacology, the mechanism of core drug pair Fuzi-Ganjiang-Rougui in the treatment of CAG was analyzed.

4.1. The acquisition and screening of active ingredients in couplet medicines

In this study, TCMSP (<http://lsp.nwu.edu.cn/tcmsp.php>), a traditional Chinese medicine system pharmacology database and analysis platform, was used to search for the active ingredients of these three medicines with the key words of prepared aconite (unified name as aconite), dried ginger and cinnamon. The active ingredients were screened with oral availability (OB) $\geq 30\%$, drug-likeness (DL) $\geq 0.18\%$ (cinnamon DL $\geq 0.08\%$), and other important active ingredients were supplemented through China Knowledge Network, Wanfang Network, and Weipu Network. A total of 21 active ingredients of prepared aconite (aconite), 5 active ingredients of dried ginger, and 15 active ingredients of cinnamon were screened. The corresponding targets of the above effective components were obtained in the TCMSP database, and the target protein names were unified on the Uniprot (<https://www.uniprot.org/>) database). After the effective components of the drug pair were corresponded to the genome, a total of 24 final effective active components were obtained (6 aconite, 5 dried ginger, 14 cinnamon, 1 aconite and dried ginger repeated component), as shown in Table 1.

Table 1: Attached-Jiang-Gui basic information

English name	Chinese name	source
Karanjin	水黄皮素	附子
Delphin	花翠素3,5-二糖苷	附子
Deoxyandrographolide	去氧穿心莲内酯	附子
Deltoin	德尔妥因	附子
11,14-eicosadienoic acid	花生二烯	附子
sitosterol	谷甾醇	附子、干姜
1-Monolinolein		干姜
3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate	瓜叶菊素 I	干姜
Sexangularetin	草质素-8-甲醚	干姜
beta-sitosterol	β -谷甾醇	干姜
EIC	亚油酸	肉桂
α -cubebol	α -毕橙茄醇	肉桂

zoomaric acid	棕榈油酸	肉桂
β -caryophyllene	β -石竹烯	肉桂
(-)-ALLOAROMADENDRENE	香树烯	肉桂
beta-cubebene	β -葶澄茄烯	肉桂
junipene	长叶烯	肉桂
(+)-Sativene	(+)-环苜蓿烯	肉桂
T-Muurolol	T-依兰醇	肉桂
(+)-Ledene	(+)-喇叭烯	肉桂
Caryophyllene oxide	石竹素	肉桂
DIBP	邻苯二甲酸二异丁酯	肉桂
(-)-alpha-cedrene	(-)- α -柏木烯	肉桂
oleic acid	油酸	肉桂
Karanjin	水黄皮素	附子
Delphin	花翠素3,5二糖苷	附子
Deoxyandrographolide	去氧穿心莲内酯	附子
Deltoin	德尔妥因	附子
11,14-eicosadienoic acid	花生二烯	附子、干姜
sitosterol	谷甾醇	干姜
1-Monolinolein		干姜
3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate	瓜叶菊素 I	干姜
Sexangularetin	草质素-8-甲醚	干姜

4.2. Acquisition of CAG-related genes

With 'chronic atrophic gastriti' as the key word, the targets of chronic atrophic gastritis in DisGenNet database (<https://www.disgenet.org>), Genecards database (<https://www.genecards.org>), OMIM database (<https://omim.org/search/advanced/geneMap>) and Drugbank database (<https://go.drugbank.com>) were searched, and 203 disease targets in DisGenNet database, 818 disease targets in Genecards database, 86 disease targets in OMIM database and 0 disease targets in Drugbank database were obtained, and 970 disease-related genes were obtained by deleting duplicate target genes.

4.3. Screening of common target genes of drug pair and CAG and establishment of Venn diagram

The drug and disease target genes were introduced into Venny 2.1 (<https://bioinfogp.cnb.csic.es/tools/venny>) to screen out the common targets of drugs and diseases. A total of 23 common targets and disease-related genes were obtained. As shown in Figure 1, the common target genes were AR, BAX, BCL2, CASP3, CASP8, CASP9, CAT, CCK, CHRM3, ERBB2, MPO, NOS2, PAM, PDX1, PGR, PLAU, PPARG, PRKCA, PTGS1, PTGS2, PYY, SERPINE1, SOD1.

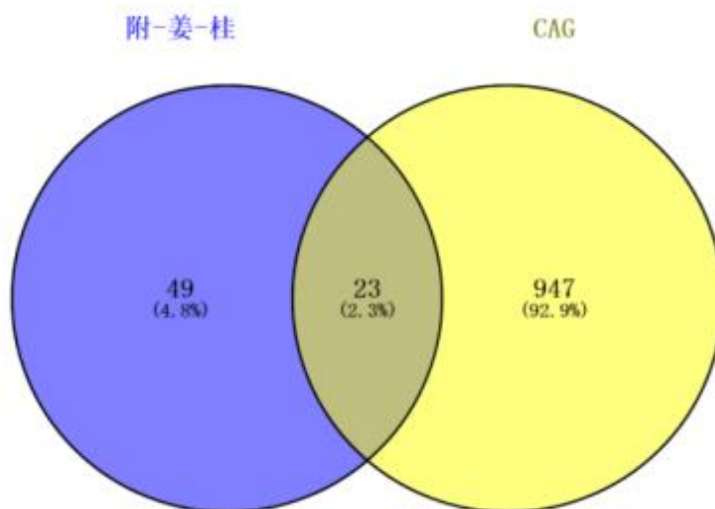


Figure 1: Venn diagram of drug pair and CAG target gene intersection

4.4. PPI network and core targets

The PPI network of 23 drug-disease intersection targets was constructed by using String database, as shown in Fig.2. A total of 17 core targets were obtained by topological structure analysis, including PLAU, SERPINE1, BAX, BCL2, CAT, SOD1, CASP3, CASP9, CASP8, AR, NOS2, ERBB2, PGR, MPO, PTGS1, CCK and PYY.

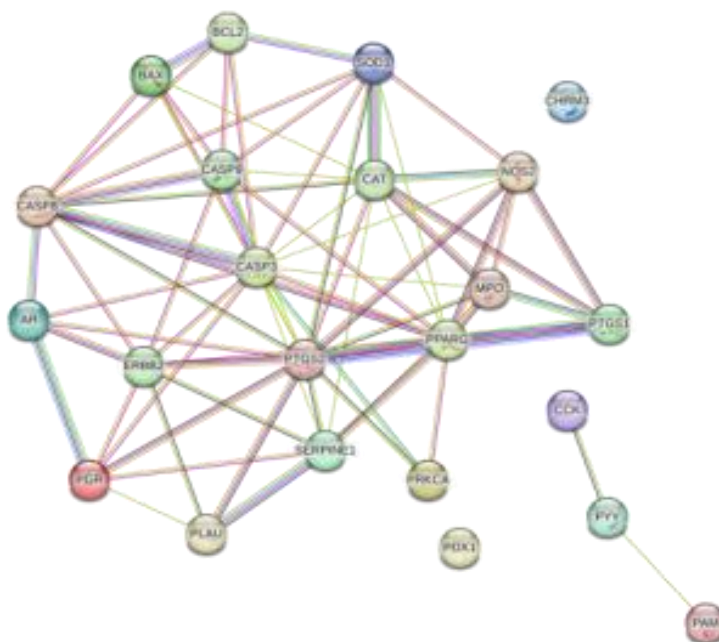


Figure 2: Attached-Ginger-Gui pair and CAG intersection target PPI network

4.5. GO functional enrichment analysis

GO enrichment analysis was performed on 23 drug-disease intersection targets after metascap (https://metascap.org/gp/index.html # / main / step1) treatment. The top 10 biological processes (BP), cell composition (CC), and molecular function (MF) were selected to form a

GO enrichment bar chart, as shown in Figure 3. And can be seen by the picture. The enrichment of BP involves cell response to inorganic substance, cell response to toxic substance, positive regulation of cell death, epithelial cell apoptotic process, and cell morphogenesis involved in differentiation. CC enrichment involved organelle outer membrane, outer membrane, mitochondrial envelope, mitochondrial outer membrane, nuclear envelope, etc. MF enrichment involved antioxidant activity, heme binding activity, and perox activity.

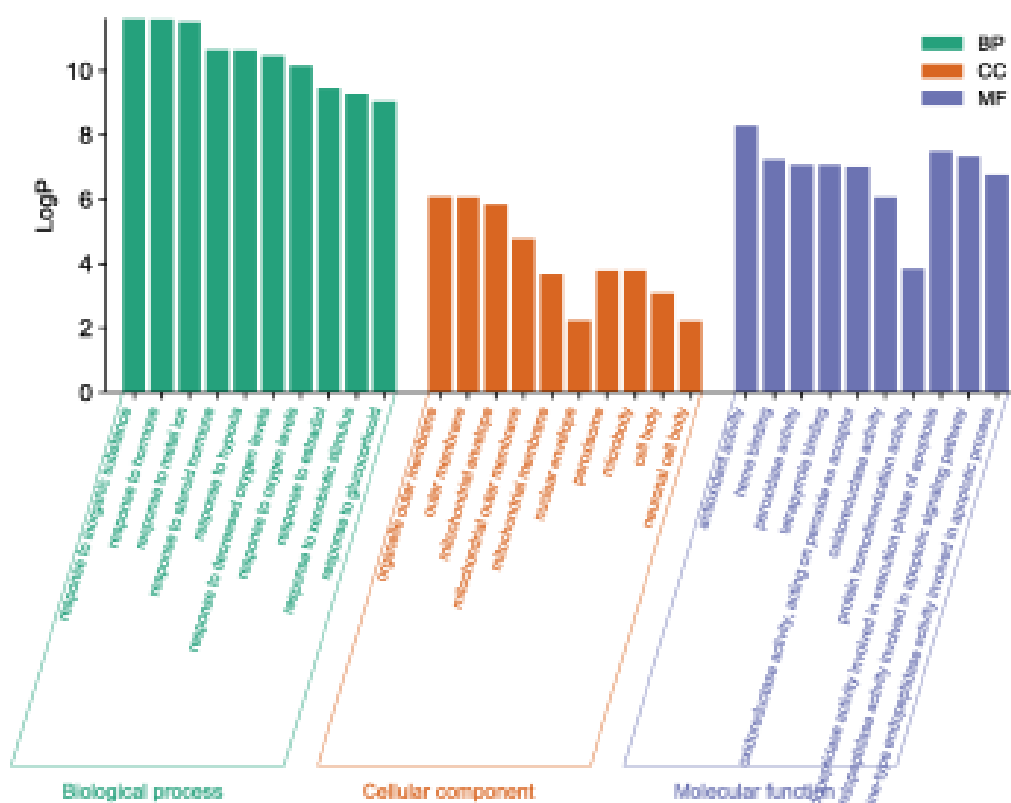


Figure 3: GO enrichment analysis of Fu-Jiang-Gui herb pair in the treatment of CAG

4.6. KEGG pathway enrichment analysis

The drug-disease intersection target was subjected to KEGG pathway enrichment analysis, and a total of 65 signal pathways were obtained. The top 10 significant ones were selected to form a KEGG enrichment map, as shown in Fig.4. The related pathways include pathways of neurodegeneration-multiple diseases, pathways in cancer, platinum drug resistance, p53 signaling pathway, Apoptosis-multiple species, Small cell lung cancer, Lipid and atherosclerosis, Hepatitis B, Tuberculosis, Amyotrophic lateral sclerosis and so on.

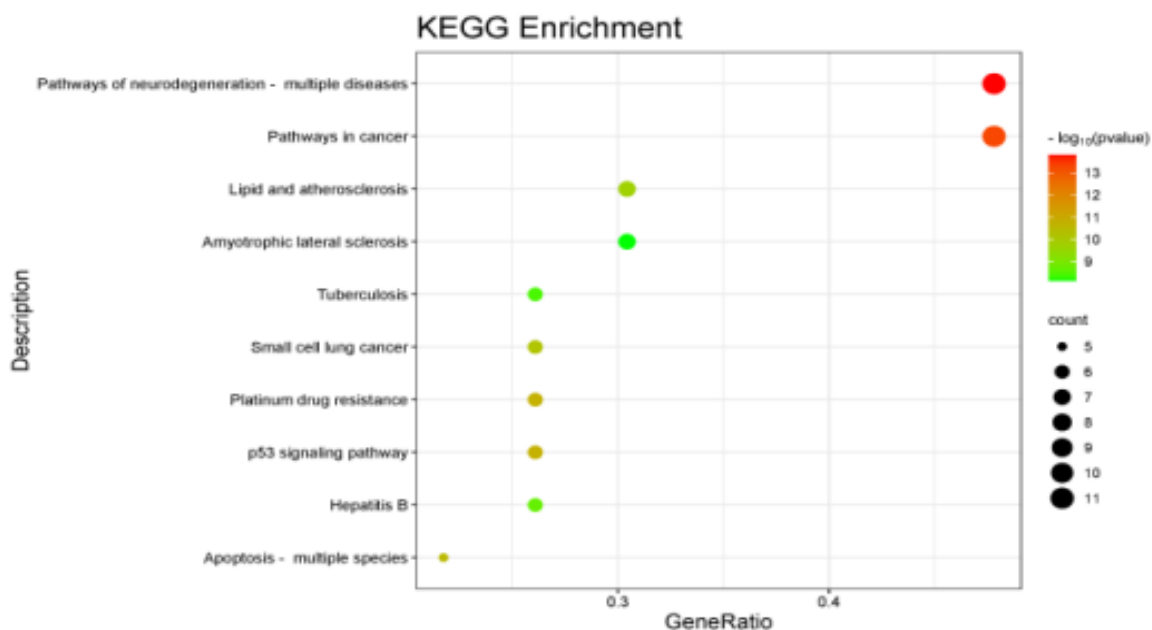


Figure 4:Enrichment analysis of KEGG pathway in the treatment of CAG with Fu-Jiang-Gui herb pair

5. Discussions

From normal gastric mucosa to CAG, to dysplasia and intestinal metaplasia, and finally to gastric carcinoma (GC), this is almost a recognized evolution process and law. CAG is a crucial part of the evolution process and the most critical link in the prevention and treatment of GC. In modern Chinese medicine, GC belongs to the category of 'stomach accumulation' [7]. The pathogenesis of GC in the later stage is nothing more than deficiency of yin and yang and internal obstruction of blood stasis, which is the same as the basic pathogenesis of CAG. Therefore, the advantages of treating CAG with Fuyang thought are also obvious. Through a lot of clinical practice, the rational use of Fuyang thought in the treatment of CAG has the characteristics of significant clinical effect, safety and reliability, and also shows the advantages of integrated traditional Chinese and Western medicine.

In this study, the basic drug pair (Fu-Jiang-Gui) of Professor Li Yi 's Fuyang thought in the treatment of CAG was analyzed by using the method of network pharmacology. It was found that the Fu-Jiang-Gui drug pair acted on 23 targets such as BAX, CASP3, CASP9, PTGS1 of CAG through 24 main active components such as β -sitosterol, β -caryophyllene, diisobutyl phthalate and so on. It has been found that [8] β -sitosterol can not only inhibit the activity of IL6, thereby alleviating the symptoms of CAG, but also enhance the antibacterial activity of antibiotics [9], which plays a synergistic role in the treatment of CAG caused by Helicobacter pylori combined with western medicine. As another important active ingredient, β -caryophyllene also has strong anti-inflammatory, antibacterial and anti-tumor effects. Recent human studies [10] have found that β -caryophyllene can significantly reduce the expression of inflammatory factors, especially the expression of IL-1 β , IL-6, LI-12, NTF- α , and can significantly increase the expression of anti-inflammatory factor IL-10. The most noteworthy is that the preventive use of β -caryophyllene is more obvious than the use of β -caryophyllene after the onset of NTF- α . This conclusion further validates the important idea of traditional Chinese medicine in the treatment of CAG. At present, some studies have found that diisobutyl phthalate inhibits the proliferation of colon cancer cells by targeting TMEM16A, which also has a certain inhibitory effect on intestinal metaplasia of gastric mucosa. From the perspective of biomolecules, Bax

protein is a pro-apoptotic protein and belongs to the Bcl-2 family. It is involved in the induction of apoptosis at the mitochondrial level, and the regulation of Bax protein level is the key to promoting apoptosis [12]. CASP3 and CASP9 pathways have been shown to inhibit the occurrence and invasion of GC, and miRNA secreted by GC tumor cells can inhibit CASP9, resulting in drug resistance [13,14]. PTGS1 [15] is involved in the regulation of prostaglandin G/H synthase, which is a key enzyme in the synthesis of prostaglandins. The final product of prostaglandins is involved in the pathological processes of inflammation, cancer and other diseases. GO enrichment analysis showed that Fu-Jiang-Gui couplet medicines interfered with the occurrence and development of diseases through positive regulation of cell death, epithelial cell apoptosis process, cell morphogenesis involved in differentiation and other biological processes, reflecting the multi-channel characteristics of core couplet medicines. Through KEGG pathway enrichment analysis, it was found that the pathways mainly involved in the regulation of Fu-Jiang-Gui drug pairs were neurodegenerative pathways-pathways in various diseases, pathways in cancer, platinum resistance, P53 signaling pathway, apoptosis-multispecies, small cell lung cancer, etc., thereby regulating cell proliferation, differentiation, apoptosis, inflammatory response, etc. to play an anti-CAG role.

In summary, based on the concept of holistic view of traditional Chinese medicine and modern system biology technology, this study constructed a network of ' Professor Li Yi 's commonly used drug pair-active ingredient-intersection target-CAG' through data visualization analysis, and explained the mechanism of action of Fu-Jiang-Gui drug pair in treating CAG through multi-component, multi-target and multi-pathway. Although it is only predicted and discussed at present, it provides a certain theoretical basis and provides a new perspective for exploring the mode of action of Fuyang thought in treating diseases.

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