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ORIGINAL

EXPLORING THE POTENTIAL BENEFITS OF SHAOYAO GANCAO DECOCTION IN ATHLETES WITH GASTRIC ULCER: A NETWORK PHARMACOLOGY STUDY

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ABSTRACT

This study delves into the mechanism of action of Shaoyao Gancao Decoction, a traditional Chinese herbal remedy, in addressing gastric ulcers. Utilizing a network pharmacology approach, we investigate the potential benefits of this decoction, particularly in the context of athletes and their unique psychological and physiological demands. Gastric ulcers can significantly impact an athlete's performance and overall well-being due to the physical and psychological stressors associated with sports activities. Understanding the mechanism by which Shaoyao Gancao Decoction may mitigate gastric ulcers in this specific population is essential for enhancing their healthcare and performance outcomes. Through a comprehensive analysis of the herbal components of Shaoyao Gancao Decoction and their potential targets, we aim to uncover the intricate network of interactions that underlie its therapeutic effects. This research not only sheds light on the potential benefits of traditional herbal remedies in sports medicine but also offers valuable insights into the psychological aspects of athletes' well-being, as psychological stress is known to influence gastric health. By bridging the gap between traditional herbal medicine, sports, and psychology, this study contributes to a more holistic understanding of how Shaoyao Gancao Decoction may play a role in supporting athletes' gastrointestinal health and psychological resilience in the face of sporting challenges.

KEYWORDS: Shaoyao Gancao Decoction; gastric ulcer; network pharmacology; signaling pathway; mechanism of action; Athlete healthcare; Sports medicine

1. INTRODUCTION

Gastric ulcers represent a common health concern with a wide-ranging impact on individuals, including athletes who often face unique physiological and psychological stressors in the pursuit of peak performance. Traditional Chinese herbal medicine has long offered a holistic approach to healthcare, and Shaoyao Gancao Decoction is one such remedy known for its potential therapeutic properties. This study employs a network pharmacology approach to investigate the mechanisms underlying the efficacy of Shaoyao Gancao Decoction in addressing gastric ulcers, with a particular focus on its relevance to athletes and the psychological aspects of their well-being.(Agrawal, 2021), (Hayati, Rahim, & Rahim, 2021), Athletes, by virtue of their rigorous training regimens and competitive pressures, are susceptible to various physical and psychological stressors. These factors can contribute to the development or exacerbation of gastric ulcers, which in turn may hinder their athletic performance and overall health. Therefore, understanding how traditional herbal remedies like Shaoyao Gancao Decoction may alleviate gastric ulcers in this specific population is of paramount importance. (Yadav, Deo, Gautam, Awale, & Pandit, 2020).

Network pharmacology provides a comprehensive framework to explore the complex interactions between the herbal components of Shaoyao Gancao Decoction and their potential molecular targets. By unraveling this intricate network, we aim to elucidate the underlying mechanisms that drive its therapeutic effects on gastric ulcers (Balreira et al., 2021). This research not only advances our understanding of the potential benefits of traditional herbal medicine in sports medicine but also sheds light on the psychological dimensions of athlete well-being, as psychological stress is intricately linked to gastrointestinal health(Yoo, Park, Kim, & Lee, 2020). (Tarnawski, Ahluwalia, & K Jones, 2013), (Le et al., 2022). The fusion of traditional herbal medicine, sports medicine, and psychology in this study offers a multidisciplinary perspective on how Shaoyao Gancao Decoction may contribute to the support of athletes' gastrointestinal health and psychological resilience in the face of the demanding challenges posed by competitive sports. This investigation represents a step toward a more integrated approach to athlete healthcare, (Jayaraman, Nathan, & Ng, 2021) emphasizing the importance of holistic well-being for those dedicated to excelling in their respective fields.(Jin et al., 2022).

2. Database and software

CNKI, Pubchem database, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TSMSP), Swiss Target Prediction database, Genecards database, GeneMANIA website, STRING website, Omicshare website, GraphPad Prism 7.0 software.

3. METHOD

3.1 Acquisition of SGD components and targets

The chemical constituents of Shaoyao Gancao Decoction were collected from CNKI and Pubchem databases, and the active ingredients of “white peony root” and “(Zhi) licorice” in SGD formulations were searched using TCMSP database, and the oral bioavailability (Oral Bioavailability, OB) > 30% and drug-likeness (Drag-likeness, DL) > 0.18 were used to screen drug components, and the above excavated components were constructed into the SGD chemical composition database and the chemical components were classified. The target of each chemical component was searched through the Swiss Target Prediction database, and all component targets were integrated and deduplicated to obtain the SGD component targets.

3.2 Acquisition of GU targets

The gene targets of GU were searched in the Gene Card database with "gastric ulcer" as the key word, the disease targets with score > 10 were selected, and the action targets of GU were obtained after combining and removing duplicate values.

3.3 Acquisition of SGD anti-GU direct targets

The obtained component targets and disease targets are intersected to obtain drug-disease common targets, that is, direct targets, and a Venn diagram is drawn.

3.4 Acquisition of SGD anti-GU indirect targets

Import the direct targets of drug targets and disease targets into the Gene MANIA website to obtain indirect drug-disease targets.

3.5 Construction of PPI Network

The obtained chemical composition of SGD and the direct and indirect targets of GU were imported into the STRING database, and the species "Homo sapiens" was selected to construct a PPI network diagram. Sort the genes according to the "Degree" value to obtain the core targets in the PPI network.

3.6 GO analysis and KEGG pathway enrichment analysis

Import the direct and indirect targets into the STRING database, and obtain and download the "functional enrichment", "component enrichment", "process enrichment" files and "KEGG pathway" files. The GO bioanalysis map was obtained through Graph Pad Prism 7.0 software, and the KEGG pathway enrichment analysis was performed through the Omicshare website. Generate

data and draw bar and bubble charts.

4. RESULTS

4.1 Components and targets of SGD

By searching the components of SGD, a total of 107 active ingredients were obtained. Among them, 35 components from Paeonia lactiflora were retrieved from CNKI and Pubchem databases, 12 components from Zhigancao, and Paeonia lactiflora was retrieved from TCMSP database. There are 14 components, and 46 components of licorice root; the above components such as paeoniflorin, kaempferol, glycyrrhizic acid, glycyrrhizic acid, rutin, glycyrrhizin, etc. have obtained 1054 component targets in the Swiss Target Prediction database.

4.2 Targets of GU

From the comprehensive database results, a total of 311 GU disease targets were obtained.

4.3 Direct targets of SGD anti-GU

After the intersection of SGD and GU targets, 32 direct targets were obtained, Figure 1.

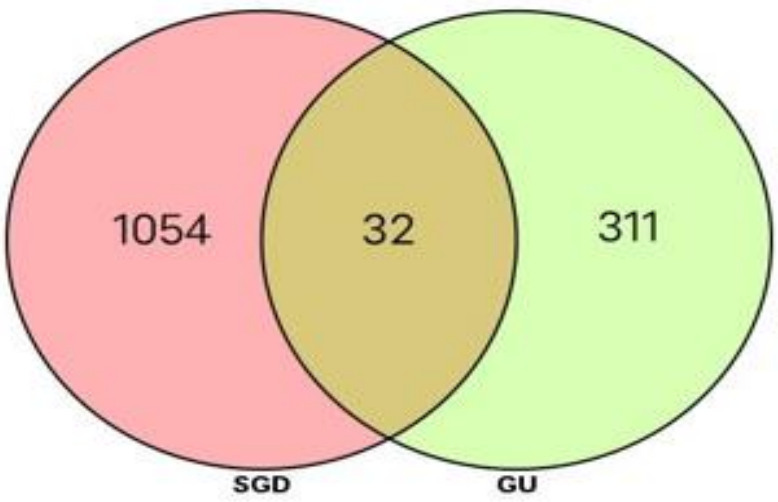

Figure 1. Venn diagram of SGD and GU intersection targets

4.4 Indirect targets of SGD anti-GU

The 32 direct targets were imported into the Gene MANIA website to obtain a total of 20 indirect targets for SGD anti-GU. The information on direct and indirect targets for SGD anti-GU is shown in Figure 2, i.e. potential targets for SGD anti-GU.

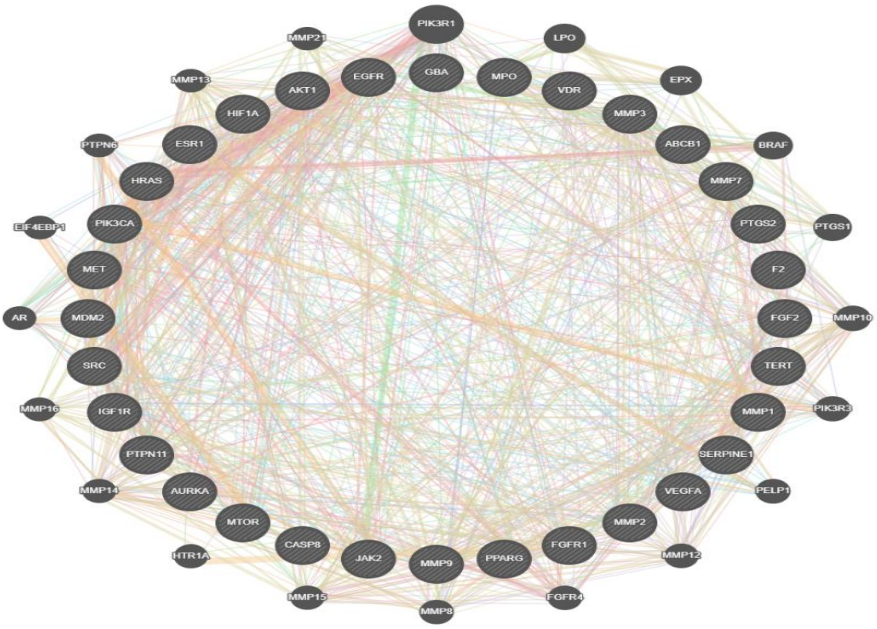

Figure 2. Potential targets of SGD anti-GU

4.5 SGD anti-GU PPI network

52 potential target proteins were imported into the String database, and a confidence level of 0.700 was selected to obtain a PPI network diagram, as shown in Figure 3. It contains a total of 52 points, 208 edges, the average node degree value is 8, and P<1.0-16 after PPI enrichment. The protein interaction data were imported into Cytoscape software to obtain the core targets in the PPI network. A total of 46 key targets were screened, of which 5 were core targets, namely AKT1, SRC, EGFR, HRAS, VEGFA, Figure 4.

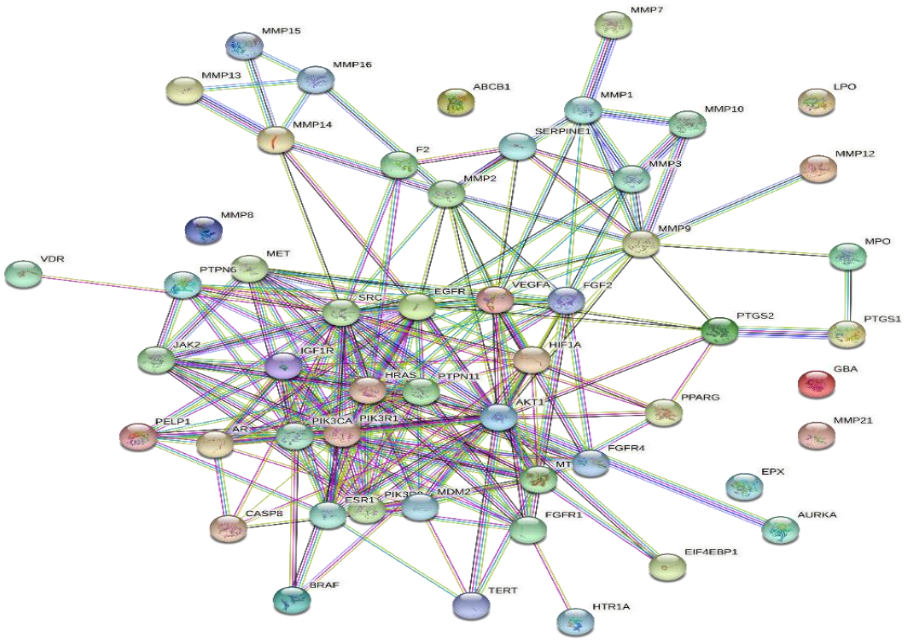

Figure 3. STRING database analysis of protein interactions

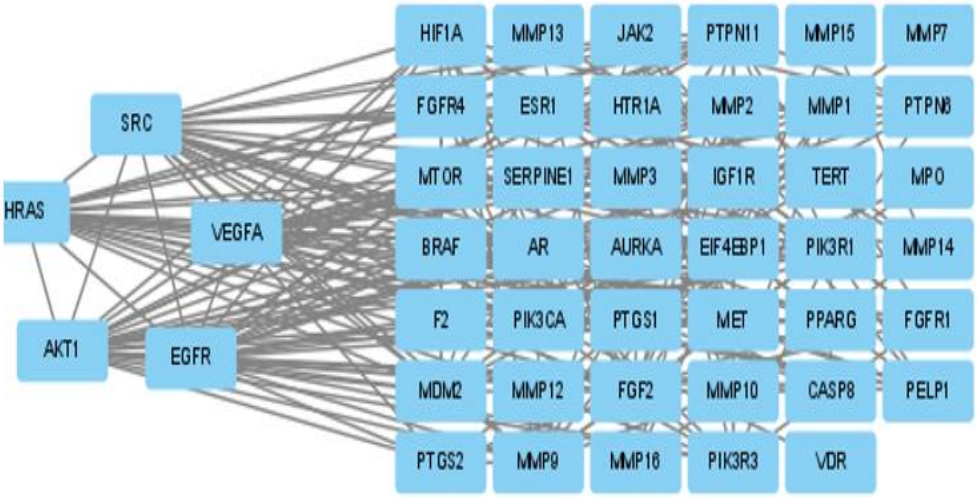

Figure 4. Protein-protein interaction network diagram

4.6 GO analysis and KEGG pathway enrichment analysis

The results of GO enrichment analysis showed that 12 items were enriched in Cellular Component (CC), indicating that the drug effect was mainly located in the extracellular matrix, Extracellular region, Extracellular space and other cell membrane sites; Molecular Function (MF) was co-enriched A total of 74 items were collected, mainly involving Metalloendopeptidase activity, Catalytic activity, acting on a protein, Endopeptidase activity, etc. The biological processes were mainly enriched to 29 items, including Collagen catabolic process, Collagen metabolic process, and Response to chemical. Tables 1 to 3.

Table 1. GO analysis table of SGD anti-GU related targets (cellular components)

Term ID	Term description	False discovery rate
GO:0031012	Extracellular matrix	9.17
GO:0005576	Extracellular region	4.27
GO:0005615	Extracellular space	4.21
GO:0031983	Vesicle lumen	1.92
GO:0005886	Plasma membrane	1.85
GO:0005943	Phosphatidylinositol 3-kinase complex, class ia	1.85
GO:0005942	Phosphatidylinositol 3-kinase complex	1.79
GO:0043235	Receptor complex	1.79
GO:0034774	Secretory granule lumen	1.45
GO:0070013	Intracellular organelle lumen	1.44
GO:0061695	Transferase complex, transferring phosphorus-containing groups	1.31
GO:1904724	Tertiary granule lumen	1.31

Table 2(a). Table of GO analysis of SGD anti-GU related targets (molecular function)

Term ID	Term description	False discovery rate
GO:0004222	Metalloendopeptidase activity	14.19
GO:0140096	Catalytic activity, acting on a protein	12.32
GO:0004175	Endopeptidase activity	9.70
GO:0003824	Catalytic activity	9.59
GO:0043167	Ion binding	9.59
GO:0008270	Zinc ion binding	9.11
GO:0005488	Binding	7.52
GO:0005102	Signaling receptor binding	7.22
GO:0043560	Insulin receptor substrate binding	7.07
GO:0016773	Phosphotransferase activity, alcohol group as acceptor	5.35
GO:0004672	Protein kinase activity	5.19
GO:0016301	Kinase activity	4.97
GO:0016772	Transferase activity, transferring phosphorus-containing groups	4.97
GO:0020037	Heme binding	4.78
GO:0004713	Protein tyrosine kinase activity	4.74
GO:0004601	Peroxidase activity	4.64
GO:0051219	Phosphoprotein binding	4.60
GO:0004252	Serine-type endopeptidase activity	4.51
GO:0005515	Protein binding	4.45
GO:0043169	Cation binding	4.27
GO:0008201	Heparin binding	4.26
GO:0019899	Enzyme binding	4.23
GO:0090722	Receptor-receptor interaction	4.18
GO:0051427	Hormone receptor binding	4.08
GO:0005158	Insulin receptor binding	4.06
GO:0004714	Transmembrane receptor protein tyrosine kinase activity	4.01
GO:0019901	Protein kinase binding	4.00
GO:0046872	Metal ion binding	3.96
GO:0016787	Hydrolase activity	3.82
GO:0097367	Carbohydrate derivative binding	3.72
GO:0019904	Protein domain specific binding	3.68
GO:0044877	Protein-containing complex binding	3.68
GO:0019903	Protein phosphatase binding	3.59
GO:0043168	Anion binding	3.52
GO:0042802	Identical protein binding	3.47
GO:0042169	SH2 domain binding	3.38
GO:0001784	Phosphotyrosine residue binding	3.36
GO:0008134	Transcription factor binding	3.18

Table 2(b). Table of GO analysis of SGD anti-GU related targets (molecular function)

Term ID	Term description	False discovery rate
GO:0004879	Nuclear receptor activity	3.16
GO:0031625	Ubiquitin protein ligase binding	3.06
GO:0097110	Scaffold protein binding	2.92
GO:0070006	Metalloaminopeptidase activity	2.66
GO:0004666	Prostaglandin-endoperoxide synthase activity	2.64
GO:0035257	Nuclear hormone receptor binding	2.46
GO:1901363	Heterocyclic compound binding	2.34
GO:0043548	Phosphatidylinositol 3-kinase binding	2.33
GO:0005524	ATP binding	2.32
GO:0042562	Hormone binding	2.32
GO:0016740	Transferase activity	2.27
GO:0051117	ATPase binding	2.27
GO:0097159	Organic cyclic compound binding	2.25
GO:0005007	Fibroblast growth factor-activated receptor activity	2.17
GO:0030235	Nitric-oxide synthase regulator activity	2.06
GO:0035639	Purine ribonucleoside triphosphate binding	2.06
GO:0043559	Insulin binding	2.06
GO:0008022	Protein c-terminus binding	2.06
GO:0140296	General transcription initiation factor binding	2.03
GO:0030331	Estrogen receptor binding	1.95
GO:0016922	Nuclear receptor binding	1.95
GO:0032555	Purine ribonucleotide binding	1.94
GO:0016303	1-phosphatidylinositol-3-kinase activity	1.75
GO:0003707	Steroid hormone receptor activity	1.72
GO:0019838	Growth factor binding	1.70
GO:0070851	Growth factor receptor binding	1.68
GO:0036094	Small molecule binding	1.65
GO:0005178	Integrin binding	1.60
GO:0005518	Collagen binding	1.50
GO:0046935	1-phosphatidylinositol-3-kinase regulator activity	1.49
GO:0035173	Histone kinase activity	1.46
GO:0004674	Protein serine/threonine kinase activity	1.44
GO:0046965	Retinoid x receptor binding	1.38
GO:0038023	Signaling receptor activity	1.36
GO:0001091	RNA polymerase II general transcription initiation factor binding	1.35

Table 3. GO analysis table of SGD anti-GU related targets (biological process)

Term ID	Term description	False discovery rate
GO:0030574	Collagen catabolic process	17.92445304
GO:0032963	Collagen metabolic process	17.92445304
GO:0042221	Response to chemical	17.92445304
GO:0070887	Cellular response to chemical stimulus	16.51570016
GO:0010033	Response to organic substance	14.99567863
GO:0010941	Regulation of cell death	14.84163751
GO:0022617	Extracellular matrix disassembly	14.66756154
GO:0030335	Positive regulation of cell migration	14.37365963
GO:0009653	Anatomical structure morphogenesis	14.24336389
GO:0060548	Negative regulation of cell death	13.8827287
GO:0051240	Positive regulation of multicellular organismal process	13.58335949
GO:0007169	Transmembrane receptor protein tyrosine kinase signaling pathway	13.3757179
GO:0071310	Cellular response to organic substance	13.34872199
GO:0050790	Regulation of catalytic activity	13.28483264
GO:0043067	Regulation of programmed cell death	12.86012091
GO:1901700	Response to oxygen-containing compound	12.86012091
GO:0080134	Regulation of response to stress	12.72584215
GO:0043069	Negative regulation of programmed cell death	12.60730305
GO:0008284	Positive regulation of cell population proliferation	12.51999306
GO:0050896	Response to stimulus	12.48811664
GO:0051173	Positive regulation of nitrogen compound metabolic process	12.48811664
GO:1902531	Regulation of intracellular signal transduction	12.48811664
GO:0010647	Positive regulation of cell communication	12.44490555
GO:0023056	Positive regulation of signaling	12.41228903
GO:0044093	Positive regulation of molecular function	12.36251027
GO:0010604	Positive regulation of macromolecule metabolic process	12.12090412
GO:0042981	Regulation of apoptotic process	12.12090412
GO:0071704	Organic substance metabolic process	12.05998184
GO:0030334	Regulation of cell migration	12.04095861

The KEGG enrichment analysis selected the first 50 pathways and made a column chart and a bubble chart, Figure 5. It is known that cancer signaling pathway (Pathways in cancer), proteoglycans in cancer signaling pathway (Proteoglycans in cancer), endocrine resistance signaling pathway (Endocrine resistance), prostate cancer signaling pathway (Prostate cancer), etc. and the mechanism of SGD in the treatment of GU closely related.

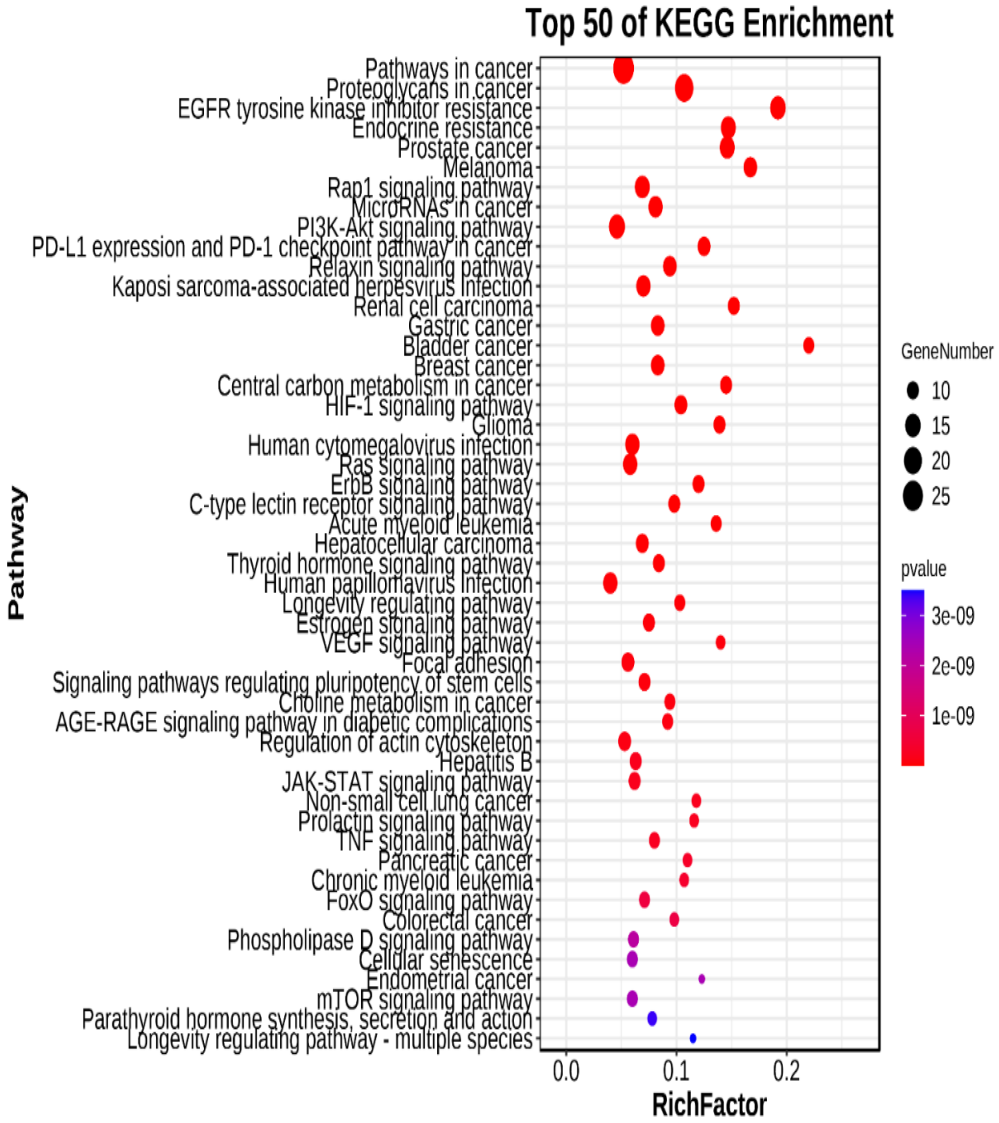

Figure 5. SGD anti-GU related target signalling pathway enrichment map

5. DISCUSSION

Gastric ulcer is a common digestive system disease. Patients often develop symptoms after meals. The symptoms are periodic epigastric pain. In severe cases, it is accompanied by pyloric obstruction, hematemesis, gastric perforation and even cancer. The disease course is long, repeated attacks and other complications, seriously affect the patient's mental and health. According to literature reports, the incidence of peptic ulcer is positively correlated with age, and middle-aged men are the high incidence group. There are about 120 million peptic ulcer patients in China alone. The pathological mechanism of gastric ulcer is that Helicobacter pylori accelerates the secretion of gastrin, which causes damage to the gastric mucosa epithelial tissue, and increases the secretion of gastric acid, which in turn leads to the occurrence of gastric ulcer. Stomach ulcer belongs to the category of "epigastric pain" in traditional Chinese medicine, which is mostly caused by spleen and stomach disorders,

liver stagnation and qi stagnation, and meridian blockage. At present, a large number of experimental studies have been carried out on the treatment of gastric ulcer by traditional Chinese medicine, which has a wide range of effects and remarkable curative effects (Wilson & Di Zhang, 2018).

Shaoyao Gancao Decoction is a classic prescription in "Treatise on Febrile Diseases". Modern pharmacological studies have shown (Yin et al., 2013) that white peony root and licorice have the functions of relaxing smooth muscle, anti-inflammatory and sedative, analgesic and antipyretic. The mechanism of Shaoyao Gancao Decoction exerting the protective effect of gastric mucosa is related to inhibiting gastric acid secretion, reducing the activity of pepsin, and promoting the synthesis of gastric protective factors and oxygen free radical scavengers. This study shows that paeoniflorin, kaempferol, glycyrrhizic acid, glycyrrhizic acid, rutin, glycyrrhizin and other components may be the effective components of anti-GU. It has been reported in the literature that paeoniflorin, an ingredient in Shaoyao Gancao Decoction, can not only change the physical and chemical structure of cell membranes to prevent ulcers, but also has a certain sedative effect and relieve pain by inhibiting smooth muscle spasm. Licorice has a certain anti-inflammatory effect. It can relax smooth muscle and skeletal muscle by inhibiting the signal transduction of peripheral nerves, and promote the regeneration of epithelial cells in the upper digestive tract (Zhang et al., 2016). Glycyrrhetinic acid has a therapeutic effect on the gastric ulcer rat model prepared by Helicobacter pylori infection after acetic acid treatment, can reduce the ulcer index and gastric acid and pepsin activities in gastric juice, inhibit the apoptosis of gastric mucosal epithelial cells, and promote the Helicobacter pylori-infected gastric ulcer healing (YANO et al., 1989). Kaempferol has obvious anti-ulcer effect in rat gastric ulcer model induced by ethanol, hydrochloric acid, indomethacin, pyloric ligation and other factors. It is effective by reducing the level of oxidation products and increasing the activity of superoxide dismutase (SOD). Reducing oxidative stress can reduce gastric acid secretion (Beber et al., 2018). Rutin, a potent antioxidant flavonoid, inhibits neutrophil infiltration and modulates nitric oxide production in the gastric mucosa, possibly by inhibiting neutrophil infiltration, inhibiting oxidative stress production and supplementing nitrite/ Nitrate levels have a protective effect on indomethacin-induced gastric ulcers. Glycyrrhizic acid maintains a high blood concentration in the body through enterohepatic circulation or distribution and reabsorption in the body, so that it can better exert its anti-gastric ulcer effect. Glycyrrhizin has obvious inhibitory effect on gastric juice secretion, gastric acid and pepsin in rats, and has obvious inhibitory effect on Shay gastric ulcer model Ⅰ and Ⅲ, and has a certain inhibitory effect on stress gastric ulcer caused by water immersion. tend to (Abdel-Raheem, 2010).

The core targets involved in this study include AKT1, SRC, EGFR, HRAS, and VEGFA. As a representative of gastric mucosal defense factor, EGF can not only inhibit gastric acid secretion and gastric mucosal cell apoptosis, but

also promote mucosal angiogenesis and induce epithelial cell synthesis, thereby protecting gastric mucosa from damage by attacking factors (Ng & Joung, 2020). EGFR is epidermal growth factor Receptor, the effect of EGF depends on the binding to EGFR. Only after EGF reaches the surface of target cells and binds to EGFR on the cell membrane, can it induce dimerization and promote the synthesis of intracellular deoxyribonucleic acid, ribonucleic acid and protein. Accelerates the proliferation, development and repair of mucosal cells (Yang et al., 2018). VEGF can protect capillary endothelial cells, stimulate cell division and proliferation, and promote the formation of new blood vessels (Gunawardhana et al., 2018). When combined with nitric oxide, it can dilate blood vessels, accelerate blood flow recovery, increase collateral circulation blood volume, and stimulate granulation tissue. and epithelialization (Datta, Chander, Gupta, Mohi, & Attri, 2019). AKT1 can regulate cell survival, proliferation and angiogenesis (Dandawate et al., 2012), and activated AKT increases the activity of the VEGF promoter and mediates the migratory response of endothelial cells to VEGF (Ferreira Mendes et al., 2020). Down-regulates the phosphorylation levels of SRC, PI3K, IKK α/β, IκB α and p50, p65 proteins in NF-κB signaling pathway, and reduces TAK1, MEK1/2, MKK4/7, MKK3/6 in AP-1 signaling pathway and ERK, JNK, p38 protein phosphorylation levels. By overexpressing HA-Src and HA-TAK1, respectively, Lm-ME inhibited the autophosphorylation of the overexpressed proteins, thereby activating fewer downstream signaling molecules. Lm-ME also alleviated gastric ulcers in HCl/EtOH-induced acute gastritis model mice, with decreased COX-2 mRNA expression and phosphorylated TAK1 levels in gastric tissue (Shin et al., 2019).

The pathways involved in the KEGG enrichment analysis of Shaoyao Gancao Decoction against gastric ulcer include AGE-RAGE signaling pathway, PI3K/Akt signaling pathway, and TNF signaling pathway. Studies have shown that the AGE-RAGE signaling pathway is involved in the regulation of angiogenesis, tissue regeneration and wound repair (Castejon, Yamashiro, Oliveira, & Veras, 2017; Zhou, Guo, Yang, Liu, & Wang, 2022). Oxidative stress and inflammation often occur together. The accumulation of oxides can induce cell damage and promote the occurrence of inflammatory responses. The PI3K/AKT signaling pathway can respond to cell damage caused by oxidative stress, thereby exerting an anti-inflammatory effect (Liu et al., 2022). This pathway can also accelerate the migration of vascular endothelial cells by activating eNOS and VEGF, increase the vascular density of the wound, and regulate angiogenesis; at the same time, it can improve the hypoxic state of the wound, thereby promoting wound healing. The TNF signaling pathway mainly induces inflammatory responses by mediating the activation of NF-κB.

6. CONCLUSION

In the pursuit of optimal performance and well-being, athletes often grapple with unique physical and psychological stressors that can contribute to

the development of gastric ulcers. This study employed a network pharmacology approach to unravel the mechanisms underlying the therapeutic potential of Shaoyao Gancao Decoction, a traditional Chinese herbal remedy, in addressing these ulcers, with a particular emphasis on its relevance to athletes and their psychological well-being. Our exploration of the complex interactions between the herbal components of Shaoyao Gancao Decoction and their molecular targets has provided valuable insights into its potential efficacy in mitigating gastric ulcers. Traditional herbal remedies, such as this decoction, hold promise as complementary approaches in sports medicine, addressing not only the physical but also the psychological dimensions of athlete health. The holistic perspective offered by this study underscores the importance of integrating traditional herbal medicine, sports medicine, and psychology to support athletes' gastrointestinal health and psychological resilience. Athlete healthcare should encompass a multidisciplinary approach that acknowledges the interconnectedness of physical and psychological well-being, particularly in the context of competitive sports.

In conclusion, this research contributes to a growing body of knowledge that underscores the potential benefits of traditional herbal remedies in athlete healthcare. By understanding the mechanisms by which Shaoyao Gancao Decoction may alleviate gastric ulcers and support athlete well-being, we take a significant step towards a more comprehensive approach to healthcare that optimizes the performance and overall health of athletes. Further research and clinical studies are warranted to validate these findings and explore the practical applications of traditional herbal medicine in the athletic community.

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