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Original Article

Network pharmacology unveils spleen-fortifying effect of *Codonopsis Radix* on different gastric diseases based on theory of "same treatment for different diseases" in traditional Chinese medicine

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ABSTRACT

Objective: "Same treatment for different diseases" is a unique treatment strategy under the guidance of traditional Chinese medicine (TCM) theory. *Codonopsis Radix* (*Codonopsis pilosula*, Dangshen in Chinese) with spleen-fortifying effect was employed to understand the strategy of "Same treatment for different diseases", based on its common mechanism in the treatment of gastric diseases including gastric ulcer, gastritis and gastric cancer via network pharmacology research.

Methods: Network pharmacology research methods were used to analyze the interaction network and potential mechanisms of Dangshen in treating gastric ulcer, gastritis and gastric cancer. The active components and their target proteins of Dangshen were integrated from TCMSP, BATMAN-TCM databases. The targets of gastric ulcer, gastritis and gastric cancer were collected through GeneCards, PubMed, TDD and DisGeNET Database. Through screening, the key components and the key targets of Dangshen in treating gastric ulcer, gastritis and gastric cancer were obtained. After KEGG pathway analysis and GO analysis, the important pathways and biological processes were analyzed.

Results: Through data and literature mining, the common and specific pharmaceutical effects and mechanism of Dangshen were summarized in these three gastric lesions. It was shown that Dangshen mainly acted on gastric ulcer, gastritis and gastric cancer through the overall regulation of the PI3K-AKT signaling pathway. With the development of the disease, it will gradually increase the control of inflammation through TNF, NF-κB and other inflammation-related signaling pathways to reduce inflammatory damage. For tumorigenesis, it pays more attention to inhibiting the ErbB signaling pathways to reduce the proliferation and migration of tumor cells. In addition, Dangshen's regulation of HIF-1 signaling pathway may also be beneficial for the treatment of gastric ulcer, gastritis and gastric cancer.

Conclusion: Dangshen achieves spleen-fortifying effect on gastric diseases including gastric ulcer, gastritis and gastric cancer through multiple targets in multiple pathways, especially PI3K-AKT pathway and HIF-1 pathway. It could provide a scientific basis for understanding the strategy of "Same treatment for different diseases" in traditional Chinese medicine.

1. Introduction

"Same treatment for different diseases" refers to a principle of treatment that applying the same strategy to patients with different diseases but same syndrome (Chen & Xu, 2018). It originated from the spirit of "different treatments for the same disease" in the "*Internal Classic*", but there is no clear written record (Lin, Li, Liu, & Tian, 2014). In the Han Dynasty, Zhang Zhongjing's "*Treatise on Cold Damage Diseases*" and "*Synopsis of Prescriptions of the Golden Chamber*" also did not have a clear written record of "Same treatment for different diseases", but has fully embodied its spirit in the combination of disease and syndrome, the treatment based on identification syndrome differentiation and the application of specific prescriptions (Zheng, Wang, & Gu, 2015). "Same treatment for different diseases" was put forward by later TCM practitioners based on the actual situation of clinical treatment (Lin et al., 2014), and has been proved in practice to treat a variety of diseases with significant effects. Buzhong Yiqi (Tonifying middle and replenishing *qi*) Decoction, contained in "*Treatise on the Spleen and Stomach*", can not only treat digestive system diseases, but also treat cough, irregular menstruation, enuresis and many other diseases whose

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cause and mechanism of disease are spleen-*qi* deficiency or insufficiency of middle *qi* (L. Wang, Ouyang, & Liang, 2016). Banxia Xiexin Decoction is derived from "*Treatise on Cold Damage Diseases*", which has been clinically proven to be effective for digestive system ulcers and inflammations that belong to insufficiency of middle *qi* and cold-heat complex pattern/syndrome (Yuan & Li, 2009). However, the internal mechanism of "Same treatment for different diseases" was still uncleared.

In the theory of traditional Chinese medicine, the spleen governs transportation and transformation, and the stomach governs food and drink receiving. The body's intake of nutrients from diet depends on the spleen and stomach's transport and acceptance functions. When food enters the stomach, it is first accepted and digested preliminarily by the stomach, then digested further in the small intestine. At this time, the spleen transforms the food into cereal essence which is transported upward to the lungs later to inject *qi*. Then the lungs transport *qi* to heart meridian and form blood. *Qi* and blood are transported throughout the body to nourish organs and limbs and maintain normal life activities. It is known that spleen is the foundation of the acquired and the source of *qi* and blood generation (Chen & Xu, 2018). Particularly, the spleen is closely associated with the stomach in function. Gastric diseases such as gastric ulcers, gastritis, and gastric cancer can damage the receiving and digestive functions of stomach, and weaken the spleen's ability to transport, resulting in spleen-*qi* deficiency which will aggravate the gastric disease. Drugs with the spleen-fortifying effect can relieve the spleen-*qi* deficiency and help the recovery of gastric diseases. Gastric ulcer refers to an inflammatory injury of the gastric mucosa caused by factors such as stress, infection, drugs, smoking, and drinking, the defending and repairing functions of the gastric mucosa cannot maintain the integrity of the mucosa and promote the healing of ulcers, and then the lesion penetrates the mucosal muscle layer or reaches a deeper level (Ge, Xu, & Wang, 2018; YW Kim et al., 2012). Gastritis is the inflammatory response of the gastric mucosa to various stimulating factors in the stomach, including acute gastritis, chronic gastritis and special types of gastritis (Ge et al., 2018). Gastric cancer is one of the common malignant tumors of the digestive system, and its high morbidity and high mortality seriously endanger human health (Zuo, Zheng, Zeng, Zhang, & Chen, 2017). Both gastric ulcer and gastritis have recurrent and long-term characteristics, which easily lead to the occurrence of gastric cancer. These three kinds of gastric diseases belong to different types of diseases, but spleen-*qi* deficiency always occurs during their occurrence and development. Based on the effects of spleen-fortifying, they can be treated with the strategy of "Same treatment for different diseases".

Codonopsis Radix (*Codonopsis pilosula* (Franch.) Nannf., Dangshen in Chinese) is one of the long-term applied herbals, recorded in the 2015 edition of *Chinese Pharmacopoeia*, entered to the Campanulaceae. It has mild characteristics and sweet taste, belongs to the spleen meridian and lung meridian, and has the effects of fortifying the spleen and lungs and nourishing the blood. Accord effect to the "*New Records of the Materia Medica*" (Bencao Congxin, by Yi-luo Wu in Qing Dynasty), Dangshen has the functions of tonifying the middle *qi* and harmonizing the spleen and stomach. Actually, the function of spleen is transformation and absorbing the essence from food and drink in traditional Chinese medicine, which is performed by the stomach in western medicine. It is worth mentioning that Dangshen is often used as a substitute for *Panax ginseng* in traditional formulas for gastric diseases such as Four Gentlemen Decoction (Sijunzi Tang) and Buzhong Yiqi Decoction, according to its mild and *qi*-blood-nourishing characteristics. Hence, we want to expound the unique Dangshen's spleen-fortifying effects from the perspective of stomach disease (Zou, Qiu, Liu, Wan, & Zhu, 2017). Searching and screening the formula using Dangshen as the principal medicine in the National Scientific Data Sharing Platform for Population and Health (http://dbcenter.cintcm.com/), we found that the main pharmaceutical effects of these formulas are all based on their spleen-fortifying effect, such as protecting the digestive system through regulating gastrointestinal movement, anti-ulcer effect, promoting hematopoiesis and regulating immunity. Moreover, some formulas have the effects of anti-inflammatory and anti-tumor. Consistently, most of the search results on the CNKI (https://cnki.net/) with the theme keywords "*Codonopsis pilosula*" and "Disease" are related to gastric diseases. With the spleen-fortifying effect, Dangshen has significant advantages in spleen-*qi* deficiency and is beneficial for the treatment of gastric diseases such as gastric ulcer, gastritis and gastric cancer.

Network pharmacology is an emerging research tool that can illustrate the pharmacological mechanism from the perspective of multiple targets and multiple pathways (Li et al., 2019). However, most of network-pharmacology studies focused on a single disease, but fewer studies on multiple diseases. Yet, in our opinion, network pharmacology might be a potential tool contributing to explaining the scientific connotation of "Same treatment for different diseases", because of its systematic and holistic perspective. In this study, we used the spleen-fortifying effect of Dangshen as an example to reveal its common mechanism of treating gastric diseases including gastric ulcer, gastritis and gastric cancer via network pharmacology research. It's an attempt and may provide a scientific basis for understanding the strategy of "Same treatment for different diseases" in traditional Chinese medicine.

2. Materials and methods

2.1. Acquisition of active components of Dangshen and screening their target proteins

The TCMSP (http://tcmspw.com/tcmsp.php) database was used to collect and screen the chemical constituents of Dangshen based on oral bioavailability (OB $\geq$ 30%) and drug-like properties (DL $\geq$ 0.18). At the same time, combined with the filtering results of Score $\geq$ 20 and P value $\leq$ 0.05 in the BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/) database and the results of literature mining, the active components of Dangshen was preliminary determined. The target proteins corresponding to the active components were acquired through these two databases. Then, the gene names of the target proteins were united by the Uniprot (http://www.uniprot.org/) database, in which the non-human target and unfound ones were eliminated. Finally, the active components of Dangshen and its target proteins were identified.

2.2. Screening of targets for gastric ulcer, gastritis and gastric cancer

Enter keywords "gastric ulcer", "gastritis", "gastric cancer" in the GeneCards (https://www.genecards.org/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed), TTD (http://db.idrblab.net/ttd/), DisGeNET (http://www.disgenet.org/) databases to collect disease-related targets. In the GeneCards database, the targets were confirmed with the relevance score greater than the median. By combining and deleting the duplicates, the targets related to gastric ulcer, gastritis and gastric cancer were obtained. Respectively imported the related targets of gastric ulcer, gastritis, and gastric cancer into the STRING (http://stringdb.org/) database, used the Multiple Proteins tool, limited the species to human (Homo sapiens), and selected "highest confidence (0.900)", to construct the protein–protein interaction (PPI) network. Then the degree value of each target was calculated with excel, and then we selected the targets that are greater than the average degree value and imported it into the KEGG database for analysis. The top path-

ways (*P*-value < 0.1) and the targets enriched in these pathways were defined as important pathways and important targets related to gastric ulcer, gastritis, and gastric cancer.

2.3. Construction of pharmacodynamic network for treating gastric ulcer, gastritis and gastric cancer of Dangshen

The target proteins of Dangshen were respectively mapped to the important targets related to gastric ulcer, gastritis and gastric cancer, to obtain the predicted targets of Dangshen for treating gastric ulcer, gastritis and gastric cancer. After importing the predicted target into the STRING database, Multiple Proteins tool was employed to construct a protein–protein interaction (PPI) network, with species to humans (Homo sapiens) and "highest confidence (0.900)". We defined the key target for Dangshen to treat diseases as these targets with high degree value and involving in at least three pathways.

At the same time, the chemical components corresponding to the predicted targets were sorted according to the number of targets. The top-ranked chemical components acted on the key targets were defined as the key components of Dangshen for treating diseases.

2.4. Pathway analysis and GO analysis

By KEGG pathway analysis and GO analysis from the predicted targets, we can know the main pathways and biological processes of Dangshen in treating diseases. A Dangshen-key components-key targets-important pathways-disease network map was constructed by Cytoscape.

3. Results

3.1. Screening of active components and target proteins

A total of 84 Dangshen components were screened by TCMSP and BATMAN-TCM databases, and 1, 316 target proteins were screened after UniProt standardized protein names (Fig. 1).

3.2. Disease target screening results

3.2.1. Gastric ulcer

GeneCards, PubMed, TTD and DisGeNET databases were employed to collect 877 targets related to gastric ulcer. After importing these targets into the STRING database to build a protein

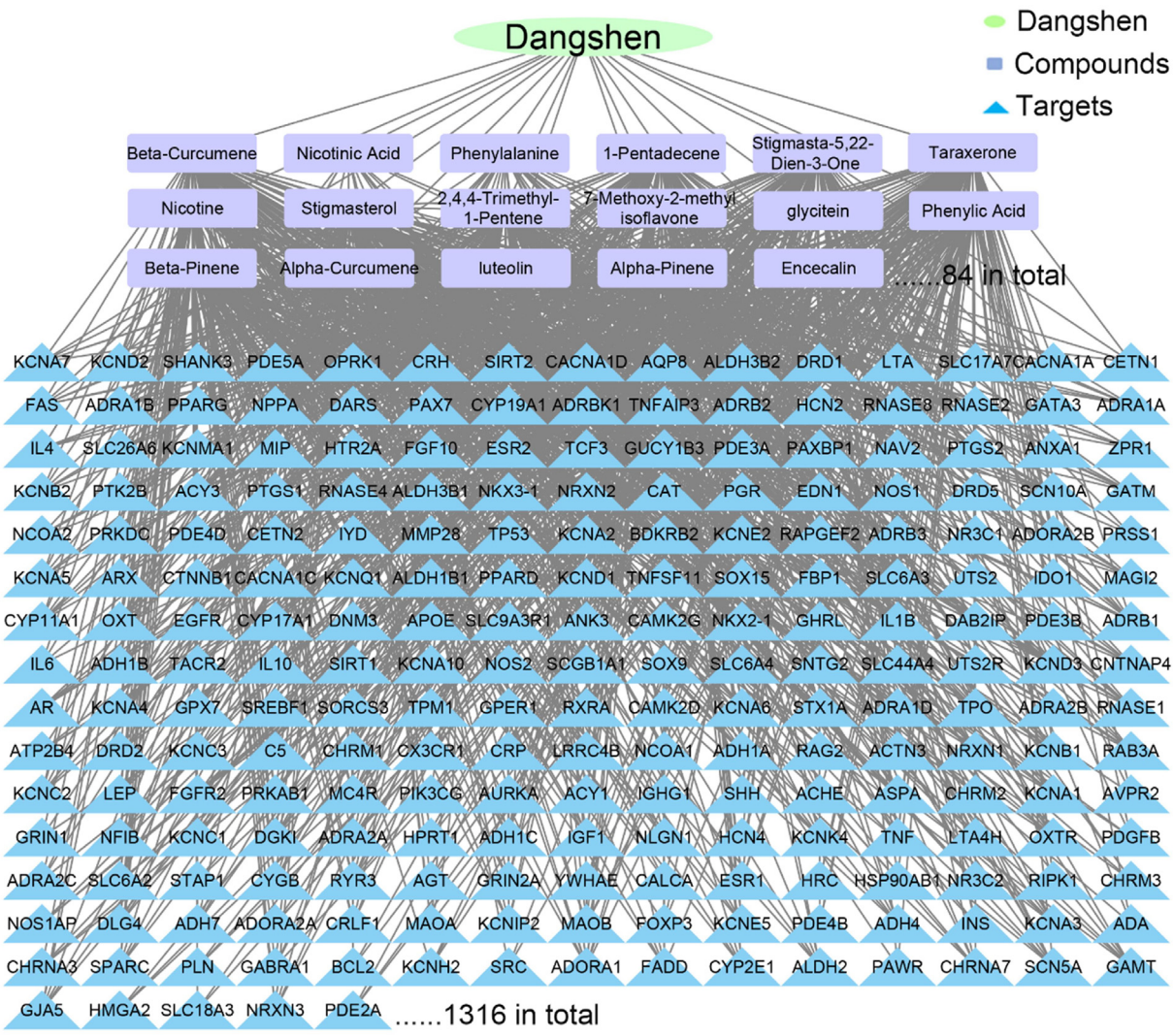


Fig. 1. Compound-target network of Dangshen.

interaction network, the result revealed 309 targets with greater degree value than the average. According to the KEGG pathway analysis, 176 targets enriched in the top 10 pathways were defined as key targets for gastric ulcer.

3.2.2. Gastritis

GeneCards, PubMed, TTD and DisGeNET databases were employed to collect 650 targets related to gastritis. After importing these targets into the STRING database to build a protein interaction network, the result revealed 221 targets with greater degree value than the average. According to the KEGG pathway analysis, 109 targets enriched in the top 10 pathways were defined as key targets for gastritis.

3.2.3. Gastric cancer

GeneCards, PubMed, TTD and DisGeNET databases were employed to collect 1301 targets related to gastric cancer. After importing these targets into the STRING database to build a protein interaction network, the result revealed 443 targets with greater degree value than the average. According to the KEGG pathway analysis, 119 targets enriched in the top 10 pathways were defined as key targets for gastric cancer.

3.3. Construction and analysis of pharmacodynamic network of Dangshen

3.3.1. Gastric ulcer

One hundred and seventy-six important targets related to gastric ulcer were mapped with 1316 components of Dangshen. Then 71 predicted targets of Dangshen for treating gastric ulcer were obtained. We imported the predicted targets into the STRING database to construct a protein–protein interaction (PPI) network, drew the PPI network (Fig. 2) with Cytoscape software, and calculated the degree value. The key targets and the key components for Dangshen to treat gastric ulcer were shown in Tables 1 and 2.

3.3.2. Gastritis

One hundred and nine important targets related to gastritis were mapped with 1316 components of Dangshen. Then 43 predicted targets of Dangshen for treating gastritis were obtained. We imported the predicted targets into the STRING database to construct a protein–protein interaction (PPI) network, drew the PPI network (Fig. 3) with Cytoscape software, and calculated the degree value. The key targets and the key components for Dangshen to treat gastritis were shown in Tables 3 and 4.

Table 1
Key targets of Dangshen in treatment of gastric ulcer.

Key targets	Pathway numbers	Degree values
AKT1	10	31
PIK3CA	9	38
PIK3R1	9	37
PIK3CB	9	16
RELA	7	26
EGFR	7	20
NFKB1	7	18
MAPK14	5	18
IGF1	5	15
SRC	4	31
VEGFA	4	24
JUN	3	27
IL6	3	19
FOS	3	17
RPS6KB1	3	15

Table 2
Key components of Dangshen in treatment of gastric ulcer.

Key components	Key targets numbers	Predict targets numbers
luteolin	6	18
Stigmasta-5,22-dien-3-one	4	28
Taraxerone	4	28
Nicotinic acid	2	11
Phenylalanine	2	7
Phenylic acid	2	15
Alpha-curcumene	2	7
Nicotine	2	8
Encecalin	1	5
7-Methoxy-2-methyl isoflavone	1	6
Glycitein	1	5
Alpha-pinene	1	5
Stigmasterol	1	5

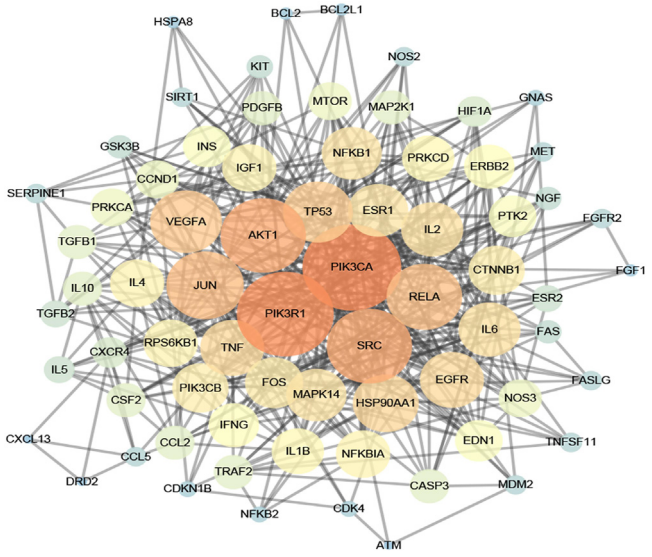


Fig. 2. PPI network of Dangshen in treatment of gastric ulcer.

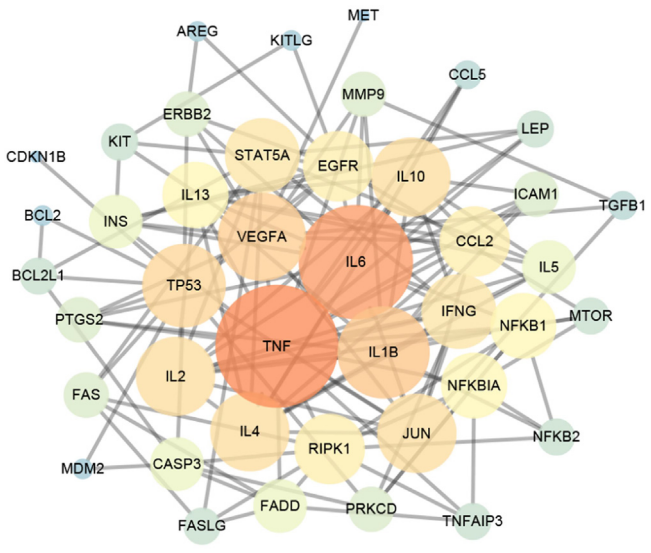


Fig. 3. PPI network of Dangshen in treatment of gastritis.

Table 3
Key targets of Dangshen in treatment of gastritis.

Key targets	Pathway numbers	Degree values
NFKB1	7	8
IL6	6	19
NFKBIA	6	8
TNF	5	21
IL1B	4	14
JUN	4	11
IL10	3	11
IL2	3	11
IL4	3	11
CCL2	3	9
RIPK1	3	9
EGFR	3	9

Table 4
Key components of Dangshen in treatment of gastritis.

Key components	Key targets numbers	Predict targets numbers
Phenylic acid	7	12
luteolin	6	17
Stigmasta-5,22-dien-3-one	4	13
Taraxerone	4	13
Nicotinic acid	2	11
1-Pentadecene	1	5
2,4,4-Trimethyl-1-pentene	1	5
Alpha-pinene	1	5
Beta-pinene	1	5
Stigmasterol	1	6
Beta-curcumene	1	5

3.3.3. Gastric cancer

One hundred and nineteen important targets related to gastric cancer were mapped with 1316 components of Dangshen. Then 53 predicted targets of Dangshen for treating gastric cancer were obtained. We imported the predicted targets into the STRING database to construct a protein–protein interaction (PPI) network, drew the PPI network (Fig. 4) with Cytoscape software, and calculated the degree value. The key targets and the key components for Dangshen to treat gastric cancer were shown in Tables 5 and 6.

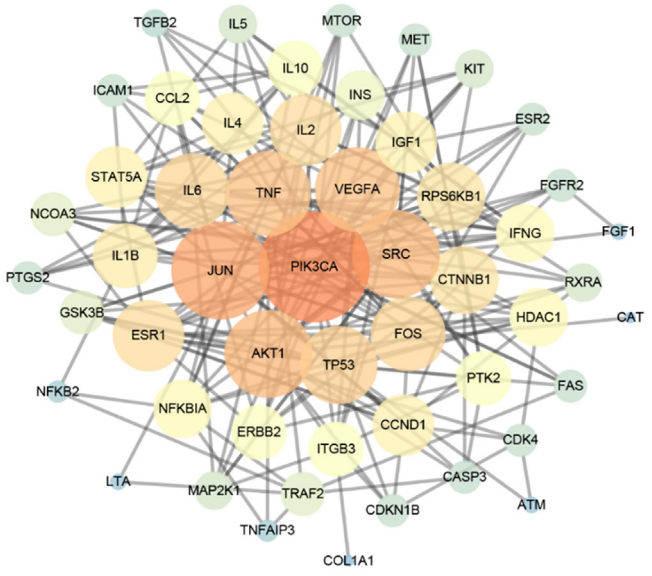


Fig. 4. PPI network of Dangshen in treatment of gastric cancer.

Table 5
Key targets of Dangshen in treatment of gastric cancer.

Key targets	Pathway numbers	Degree values
AKT1	10	19
PIK3CA	9	26
JUN	4	22
SRC	4	19
IL6	4	15
FOS	4	15
IGF1	4	11
CCND1	4	11
TNF	3	18
VEGFA	3	18
TP53	3	16
RPS6KB1	3	13
ITGB3	3	9

Table 6
Key components of Dangshen in treatment of gastric cancer.

Key components	Key targets numbers	Predict targets numbers
Luteolin	6	16
Stigmasta-5,22-dien-3-one	4	18
Taraxerone	4	18
Phenylalanine	3	5
Nicotinic acid	4	9
Phenylic acid	2	14
Nicotine	2	6
Alpha-pinene	1	5
Stigmasterol	1	7
Encecalin	1	6
Alpha-curcumene	1	5

3.4. Pathway analysis and GO analysis

3.4.1. Gastric ulcer

By conducting KEGG and GO analysis on 71 predicted targets, the main pathways and biological processes of Dangshen in treating gastric ulcer were obtained. An efficacy network map of Dangshen-key components-key targets-important pathways-gastric ulcer was constructed by Cytoscape (Figs. 5 and 6).

The results revealed that the FoxO signaling pathway is the main pathway of Dangshen for treating gastric ulcer, suggesting that Dangshen may reduce gastric mucosal damage through the antioxidant mechanism to facilitate the healing of gastric ulcer. Several studies showed that Dangshen can increase the activity of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and reduce the content of malondialdehyde (MDA). It is indicated that Dangshen can clear free radicals in organism, inhibit the formation of lipid peroxides and remove the generated lipid peroxides, which can break the vicious cycle of cell damage mediated by oxygen free radicals and protect the integrity of cell membrane structure and function (Guo, Zhu, Zhang, & Xiao, 1995; Jiang, 2013; Zhang et al., 2005, 2006). Inulin-type fructans extracted from Dangshen was reported to increase the activity of SOD and GSH-Px, reduce the content of MDA and raise the level of NO in ethanol-induced gastric ulcer model (Li et al., 2017). Methanol extracts and absolute ethyl alcohol extracts of Dangshen can also increase the activity of antioxidant enzymes to protect the gastric mucosa and resist ethanol-induced acute gastric mucosal injury (Wang, Ge, Yang, & Gao, 2015).

Dangshen protects the gastric mucosa through regulating the secretion of gastric mucosa-related factors. It has been reported

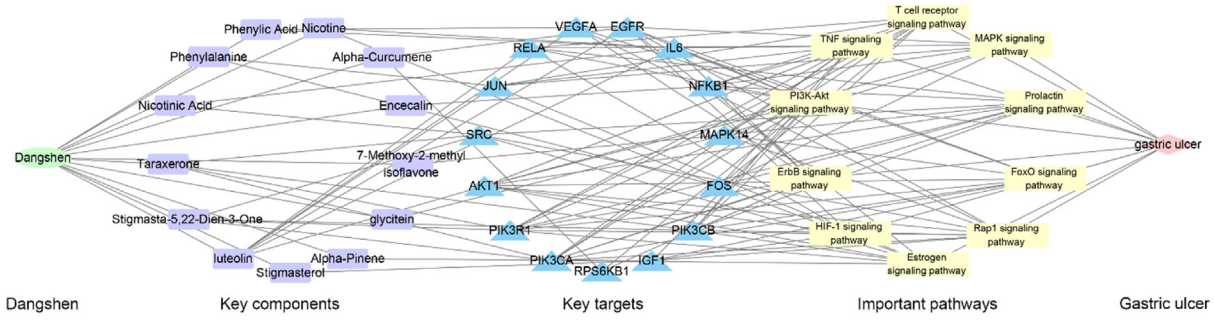


Fig. 5. Network of Dangshen – key components – key targets – important pathways – gastric ulcer.

that the level of PGE can be increased by activating the MAPK signaling pathway (Choudhury, McKay, Flower, & Croxtall, 2000; Yousif et al., 2018). Prostaglandin E (PGE) is a well-known mucosal protective molecule that can promote blood circulation of mucosa and secretion of mucus and bicarbonate (Ge et al., 2018). It is reported that under various stimuli such as ethanol, aspirin, stress and other damage to the gastric mucosa, Dangshen can increase the PGE content, strengthen the defense force of the gastric mucosa, and repair the damaged gastric mucosa (Cui, Zhang, Zhang, & Xu, 1988; Han, Jiang, & Xu, 1990; Liu, Wang, Hou, Hu, & Chen, 1990; Sun & Liu, 1995). Epidermal growth factor (EGF) and gastrin (Cas) are also involved in the complex regulation of gastric mucosal barrier function. EGF promotes cell growth, inhibits gastric acid and pepsin secretion, which can help gastric mucosa repair. Cas promotes gastric acid secretion and promotes digestion, but can aggravate gastric mucosal damage. Dangshen could significantly increase the content of prostaglandins (PG) and EGF in rat serum and reduce the content of Gas, which can inhibit gastric acid secretion, increase gastric mucus secretion and gastric mucosal blood flow, ultimately protect the gastric mucosa of gastric ulcer rats (Jing, Song, & Dou, 2017; Liu, Chen, & Wang, 1997; Song, Wang, Li, & Zhong, 2008). The mucosa at the edge of the ulcer forms a characteristic "healing zone", where epidermal growth factor receptors (EGFR) expression increases and cells actively proliferate. These cells migrate from the edge of the ulcer to the granulation tissue and reform the mucosal epithelium, which is essential for ulcer healing (Tarnawski, 2005). Dangshen can increase the expression of EGFR in the marginal tissue of ulcer, which helps to promote the proliferation and migration of epithelial cells, cover the bottom of the ulcer, and help the ulcer heal (Li & Ma, 2008).

In addition, Dangshen may have an anticholinergic effect. Acetylcholine from the enteric nervous system comprehensively regulates gastric acid secretion by affecting the functional status of parietal cells, G cells and D cells through neuroendocrine. Under stress, cholinergic nerve hyperfunction leads to the strong contraction of gastric smooth muscle, blood supply disorder of gastric mucosal and increased gastric acid secretion, which promote the formation of ulcer. Studies have found that CPN can reduce gastric mucosal damage in rats with gastric ulcer induced by water-immersion restraint stress, and inhibit the basic electrical rhythm disorder and hyperactivity of its stomach. This is similar to the atropine group (Hou, Jiang, He, & Jiang, 1985). Furthermore CPN can significantly antagonize the gastric emptying delay caused by atropine (Chen et al., 2006; Zheng et al., 2000). It is speculated that the above pharmacological mechanism of CPN may be related to the anticholinergic effect.

3.4.2. Gastritis

By conducting KEGG and GO analysis on 43 predicted targets, the main pathways and biological processes of Dangshen in treating gastritis were obtained. An efficacy network map of Dangshen-key components-key targets-important pathways-gastritis was constructed by Cytoscape (Figs. 7 and 8).

Currently, the formula with Dangshen as the principle medicine, such as Sijunzi Decoction and Buzhong Yiqi Decoction, has good effects on gastritis. With mild and nontoxic characteristics, Dangshen is considered to be suitable for the treatment of chronic diseases (Qiu et al., 2012; Xu, 2017). Through data mining, we found that Dangshen was one of the core Chinese medicines for the treatment of chronic atrophic gastritis, which is consistent with the knowledge of TCM and clinical practice experience (Liu, 2014; Ma, 2017; Qin, 2019).

In this work, Dangshen was found to target a series of inflammation-related factors, such as TNF, IL6, IL1B, IL10, IL2, IL4, CCL2 and BCL2. And the KEGG pathway analysis revealed that TNF signaling pathway, NF-κB signaling pathway, NOD-like receptor signaling pathway, T cell receptor signaling pathway and Toll-like receptor signaling pathway, which are inflammation-related pathways luteolin, are closely associated with Dangshen's efficacy. And active compounds of Dangshen, such as luteolin, curcumin and stigmasterol, have been reported to have anti-inflammatory activity (Kim, Li, Kang, Ryu, & Kim, 2014; Panda, Jafri, Kar, & Meheta, 2009; Pandith et al., 2013). This suggested that Dangshen could achieve the purpose of treating gastritis by reducing inflammatory factors and relieving the inflammatory damage.

In summary, it has been proved in clinic that the formula contained Dangshen as the principle medicinal is effective for the treatment of chronic gastritis. And the modern pharmacological studies have shown that Dangshen has good anti-inflammatory activity. At the same time, data mining has found that Dangshen was one of the core traditional Chinese medicines for treating gastritis. The network pharmacology research in this paper also showed the extensive effect of Dangshen on inflammatory factors and pathways in gastritis.

3.4.3. Gastric cancer

By conducting KEGG and GO analysis on 53 predicted targets, the main pathways and biological processes of Dangshen in treating gastric cancer were obtained. An efficacy network map of Dangshen-key components-key targets-important pathways-gastric cancer was constructed by Cytoscape (Figs. 9 and 10).

According to statistics, Dangshen is one of the high-frequency representative drugs for treating gastric cancer (Liu, Li, & Liang, 2017; Liu et al., 2016). The study found that the total polysaccharide of Dangshen inhibited the proliferation of gastric cancer BGC-823 cells, which may be related to the induction of tumor cell apoptosis (Qiu et al., 2019). In the results of this network-pharmacology research, TNF signaling pathway and MAPK signaling pathway were related to apoptosis, while Rap1 signaling pathway could regulate cell adhesion. Some researchers claimed that inhibiting SRC and down-regulating the expression of MMPs could

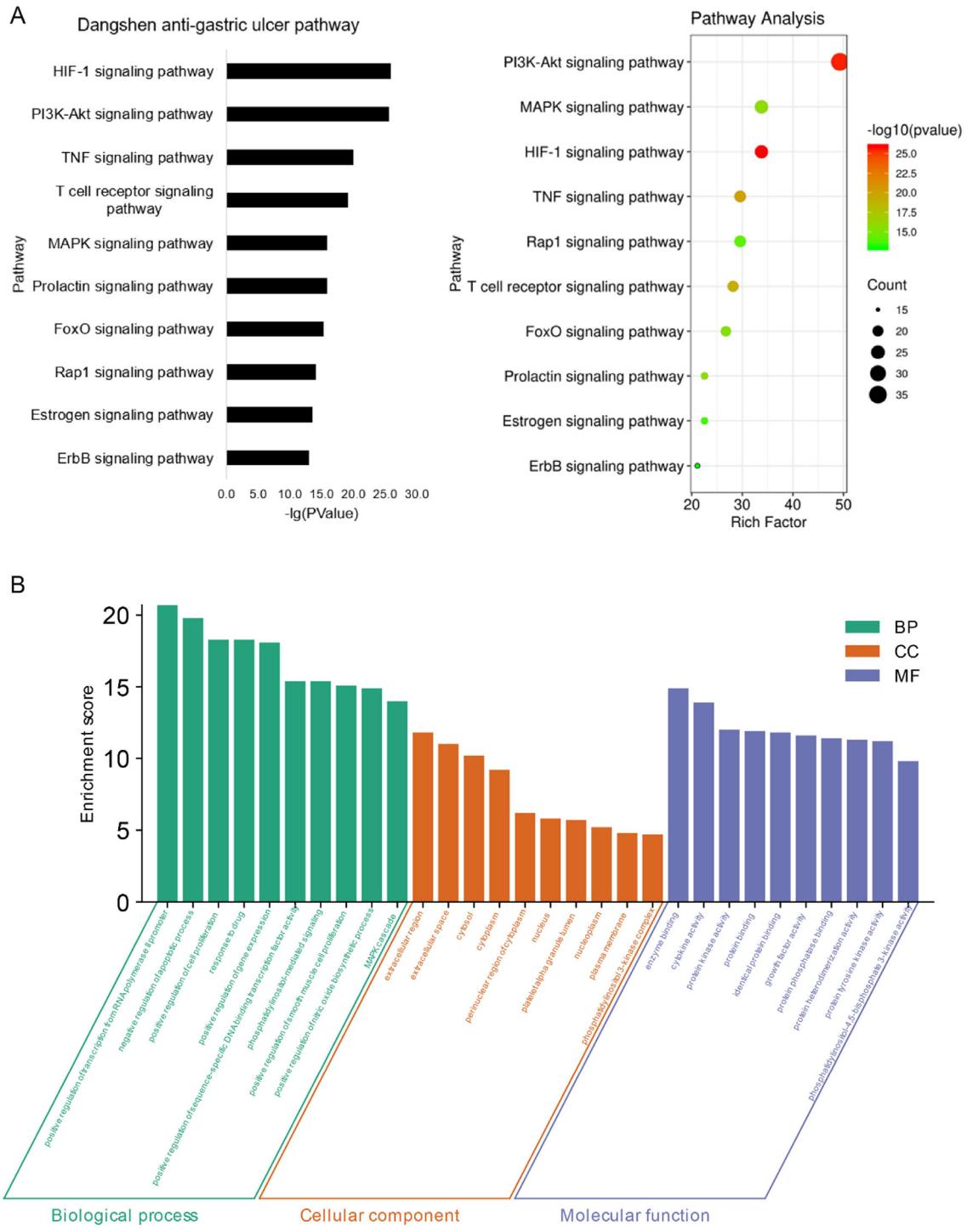


Fig. 6. Targets prediction of Dangshen in gastric ulcer by pathway analysis (A) and GO analysis (B).

block the adhesion and survival of gastric cancer cells, and reduce its migration and invasion (Qi et al., 2018; Quan, Chen, Li, Chen, & Huang, 2019). Through literature research, it is found that the anti-tumor mechanism of Dangshen always is via promoting apoptosis and reducing adhesion.

It is worth mentioning that the formula "Weikang Granules" containing Dangshen can induce autophagy in human gastric cancer cell SGC-7901, including the formation of intracellular vacuoles, the transformation of microtubule-associated protein 1 light chain 3 (LC3), which is not common apoptosis (Huo et al., 2013). Other studies reported that the total saponins of Dangshen presented the inhibitory effect on the proliferation of human hepatoma cells in a concentration dependent manner. It could up-regulate the activity of Caspase-8 and Caspase-9, promote the increase of p53 protein by activating the p38MAPK pathway, which synergistically activates Caspase-3 to promote cancer cell apoptosis (Fang, Li, Yang, & Leng, 2015). The water-soluble polysaccharides of Dangshen can induce apoptosis of HepG2 cells. The mechanism was reported to increase the Bax/Bcl-2 ratio and activate Caspase-3 (Bai et al., 2018). Therefore, the activation of

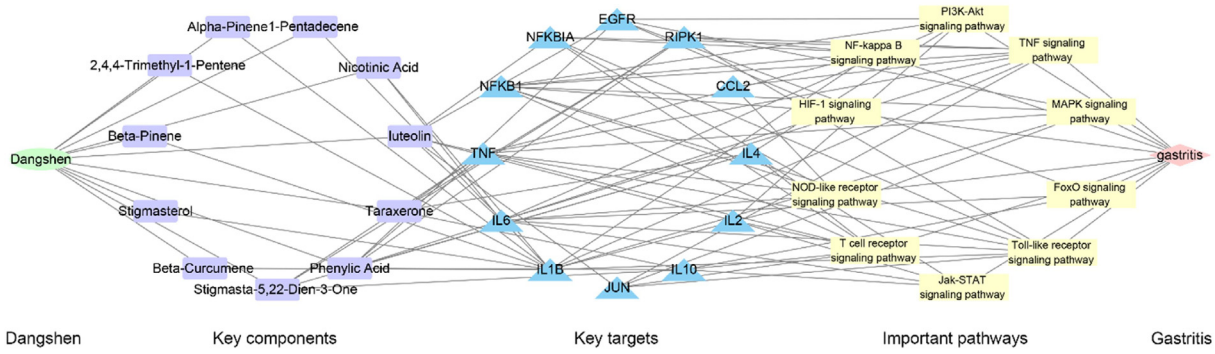


Fig. 7. Network of Dangshen-key components-key targets-important pathways-gastritis.

Caspase-3 may be the key to the mechanism of Dangshen to promote tumor cell apoptosis. Furthermore, codonolactone, one of the active compounds in Dangshen, inhibits the epithelial-mesenchymal transition of breast cancer cells by inhibiting the ability of TGF-β signaling and Runx2 phosphorylation, thereby inhibiting cancer cell metastasis (Fu et al., 2016). And codonolactone inhibits the ability of invasion and migration in metastatic breast cancer cells, which can be attributed to the down-regulation of Runx2 transcriptional activity and the inhibition of MMPs (Wang et al., 2014). Therefore, the mechanism of codonolactone inhibiting cancer cell metastasis may be related to the down-regulation of TGF-β and the inhibition of Runx2 and MMPs expression. In addition, the acid polysaccharide of Dangshen can inhibit the growth, invasion and migration of ovarian cancer cell HO-8910, which may be related to the inhibition of CD44 expression (Xin et al., 2012).

4. Discussion

In traditional Chinese medicine, "Same treatment for different diseases" is a unique treatment strategy under the guidance of the principle of "Syndrome differentiation and treatment". A lot of formulas, such as Sijunzi Decoctions (Qiu et al., 2012; Xu, 2017), Buzhong Yiqi Decoction (Wang, Ouyang and Liang, 2016), and Banxia Xiexin Decoction (Yuan and Li, 2009), exert their definite effects in different diseases. It is a supplement to mainstream medical treatment strategies that focus on disease, and beneficial for the expansion of new treatment options and the secondary development of existing Chinese patent medicine. However, the unclear mechanism hinders the further clinical application of this strategy.

Researchers and scientists of TCM have taken many attempts to unveil the mechanism of one formula/herbal on specific disease. As the complexity of diseases' mechanism and formulas' components, it hinders people from conducting systematic research on "Same treatment for different diseases". Fortunately, network pharmacology, an emerging research tool, shows potential to unveil pharmacological mechanism via multiple-targets perspective. It could build the connection between complex formula/herbal's components and thousands of diseases' targets. This is an opportunity to explain the scientific connotation of "Same treatment for different diseases". Different from previous researches, which always focus on one formula/herbal for one disease, it will be a beneficial attempt to elucidate the common mechanism of one formula/herbal for a series of diseases by network pharmacology.

In TCM, gastric diseases, such as gastric ulcer, gastritis and gastric cancer, can damage the stomach's receiving and digestive functions, and weaken the ability of spleen to transport, resulting in spleen-*qi* deficiency. Actually, these gastric diseases always show some common characteristics or associations in clinic. According to the Correa model (Correa, Haenszel, Cuello, Tannenbaum, & Archer, 1975), the occurrence of gastric cancer often goes through the following process: normal gastric mucosa-inflammation-atrophy-metaplasia-dysplasia-gastric cancer. Firstly, short-term large-scale stimulation including stress responses, drug and alcohol stimulation may also directly cause inflammatory defects on the gastric mucosa, even leading to gastric ulcer. In addition, *Helicobacter pylori* infection makes patients more susceptible to ulcer disease by destroying mucosal integrity (Gonciarz et al., 2019). If gastric ulcer is not treated in time, gastric bleeding, perforation, obstruction and even ulcer will occur. Due to long-term stimulation by various factors such as inflammation, metaplasia and dysplasia occur in gastric cells. Over time, repetitive damage and repair lead to excessive proliferation, increased mitotic errors, and eventually normal gastric cells become tumor cells (Lv et al., 2011). Studies have shown that patients with gastric ulcer have a higher risk of developing gastric cancer, especially in the first two years after diagnosis (Lee et al., 2015). It is worth mentioning that the symptoms of gastric ulcers are similar to those of gastric cancer, and endoscopy often diagnoses early malignant ulcers as benign diseases, making it difficult to distinguish gastric ulcers from gastric cancer, which leads to a delay in the early diagnosis of gastric cancer (Jing et al., 2018). This shows that there are some commonalities and relevancies among gastric ulcer, gastritis and gastric cancer, which might provide the pathological basis for "Same treatment for different diseases".

Actually, because of the spleen-fortifying effect, Dangshen is one of the most common herbals which are clinically used to treat gastric diseases such as gastric ulcer, gastritis and gastric cancer. However, the common mechanism of Dangshen in these three gastric diseases is unknown. In our results, PI3K-Akt signaling pathway, HIF-1 signaling pathway, TNF signaling pathway, T cell receptor signaling pathway, FoxO signaling pathway, and MAPK signaling pathway run through the entire process of Dangshen's treatment on these three gastric lesions. Among them, PI3K-Akt signaling pathway and MAPK signaling pathway are related to basic cell functions, T cell receptor signaling pathway and TNF signaling pathway are related to immunity and inflammation, HIF-1 signaling pathway is related to hypoxia stress, Foxo signaling pathway is related to oxidative stress. Therefore, we speculate that Dangshen is involved in the treatment of gastric ulcers, gastritis, precancerous gastric lesions through regulating cellular basic functions, fighting inflammation, anti-hypoxia and anti-oxidative. Among them, the PI3K-AKT signaling pathway and the downstream HIF-1 signaling pathway were considered to be important in Dangshen's efficacy after literature mining.

PI3K-Akt signaling pathway attracted our attentions, as it achieved a high ranking on Dangshen's intervened pathways for

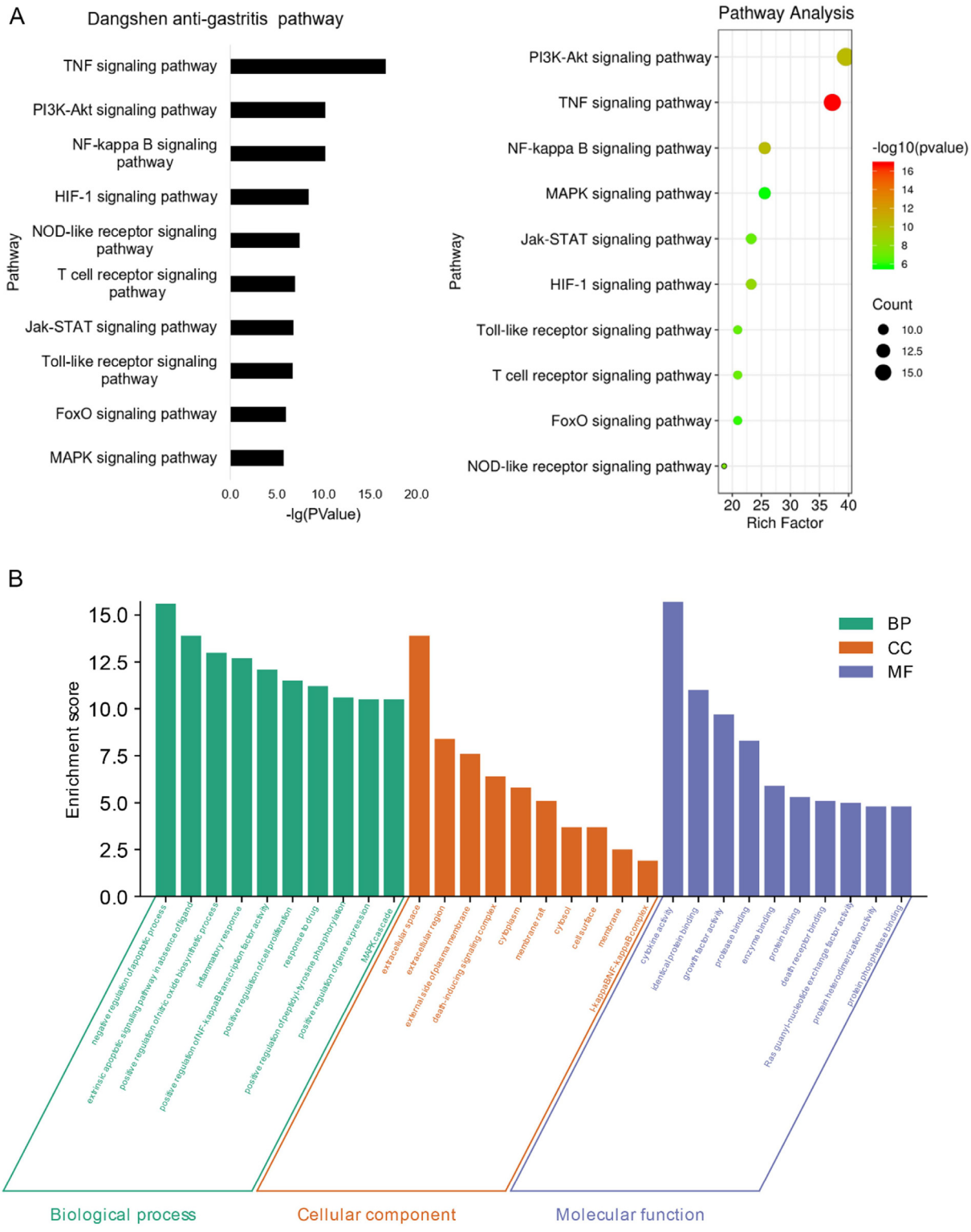


Fig. 8. Targets prediction of Dangshen in gastritis by pathway analysis (A) and GO analysis (B).

the three gastric diseases. The PI3K-Akt signaling pathway is an important node in mammalian cells to control cell growth, migration, proliferation and metabolism (Haddadi et al., 2018). It is reported that the activation of the PI3K-AKT pathway played a vital role in reducing gastric mucosal damage caused by alcohol, such as promoting the proliferation and migration of gastric epithelial cells and accelerating the healing of ulcers (Arab, Salama, Eid, Kabel, & Shahin, 2019). Dangshen may activate the PI3K-AKT signaling pathway of gastric epithelial cells to fight with gastric-mucosa damage and slow down the development of ulcer marginal cells (Aziz, Kim, & Cho, 2018; Imran et al., 2019; Kang et al., 2017). Furthermore, it has been reported that activation of the PI3K-AKT sig-

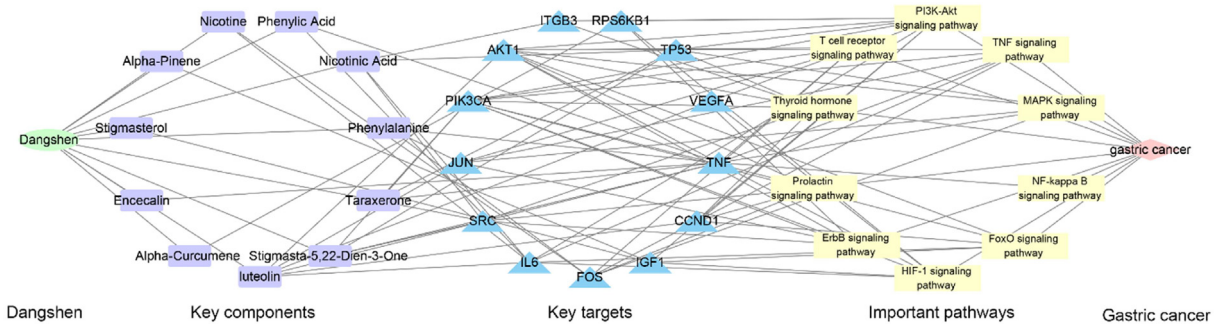
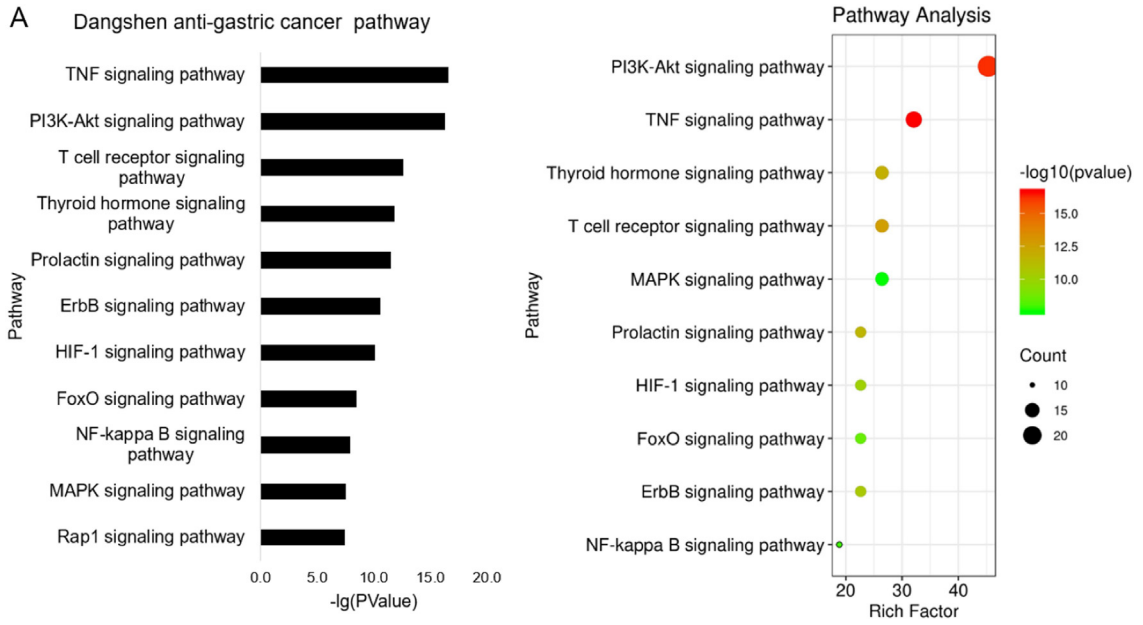


Fig. 9. Network of Dangshen-key components-key targets-important pathways-gastric cancer.



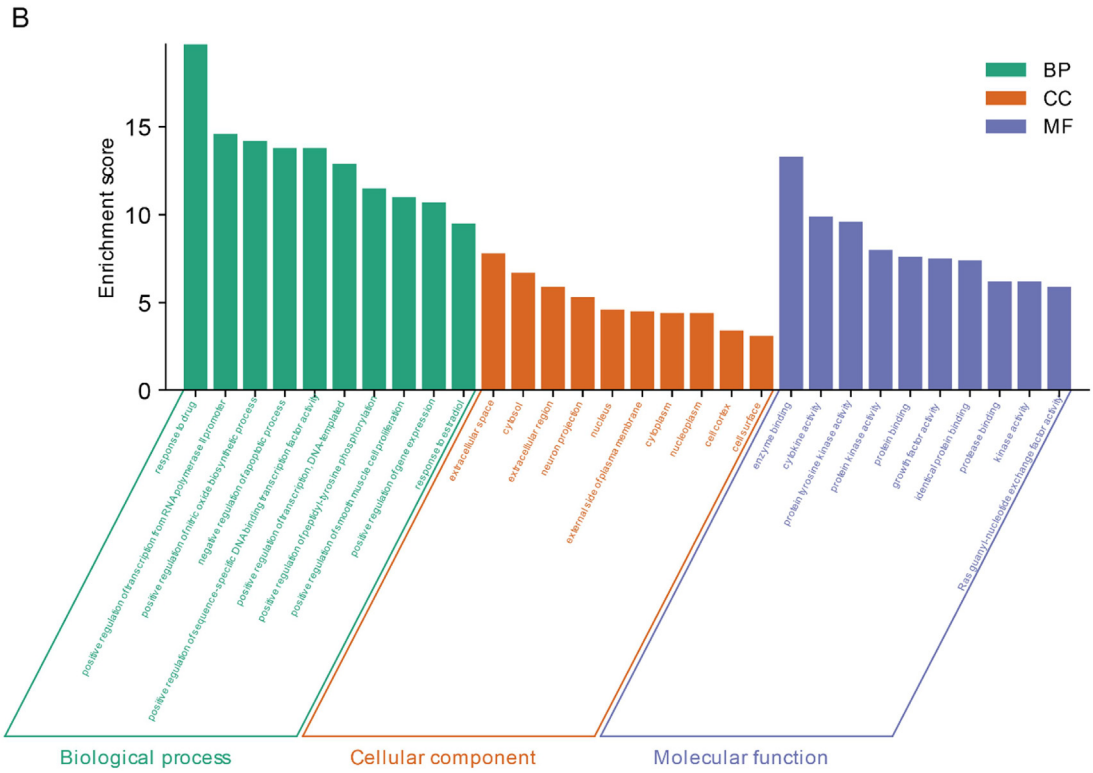


Fig. 10. Targets prediction of Dangshen in gastric cancer by pathway analysis (A) and GO analysis (B).

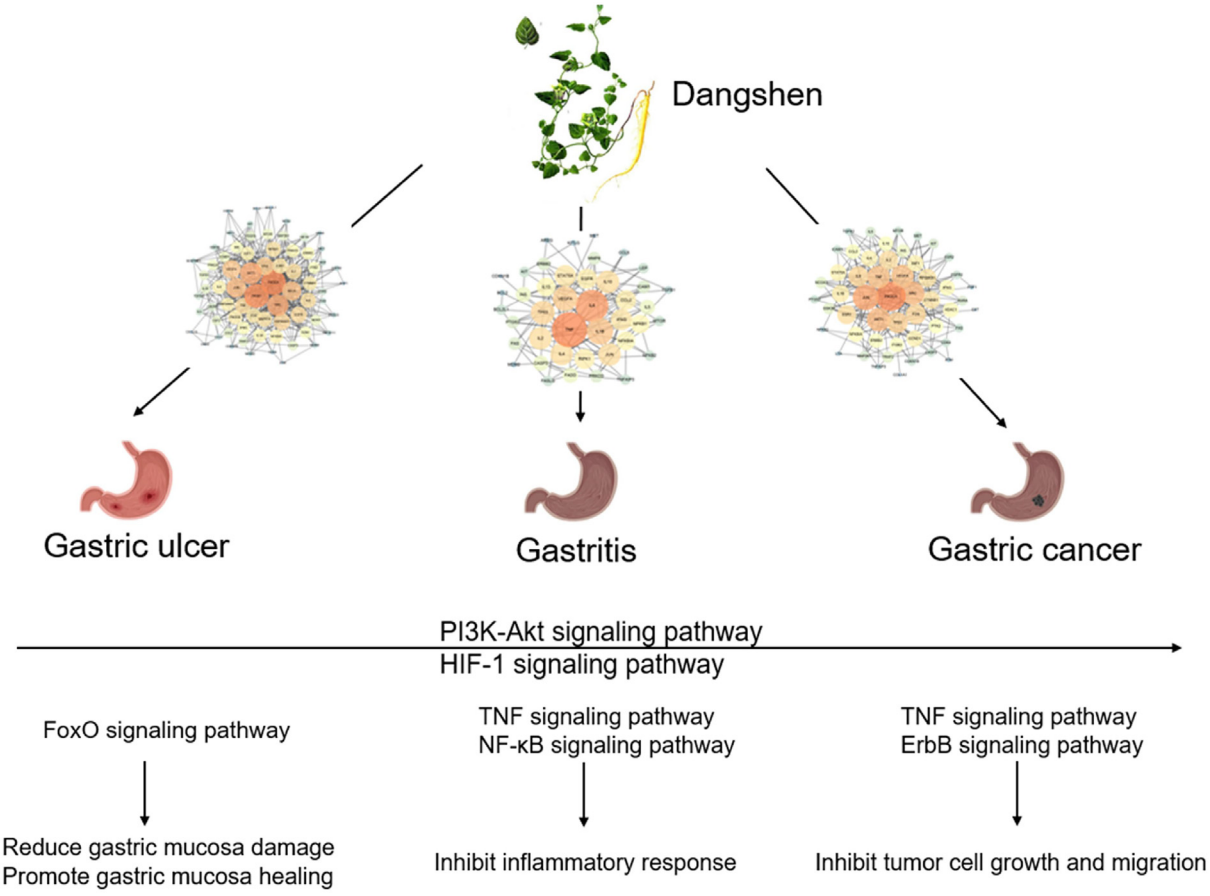


Fig. 11. Schematic diagram of spleen-fortifying effect of Dangshen on three gastric lesion.

naling pathway can promote gastric mucosa to produce IFN-γ and T cell responses (Kong et al., 2020). Therefore, we supposed that the role of Dangshen in treating gastritis mainly depends on inhibiting the production of inflammatory-related factors to relieve the inflammatory responses. At the same time, the down-regulation of the phosphorylation level of the PI3K-AKT signaling pathway can inhibit the proliferation and migration of gastric cancer cells (Lin et al., 2019). Dangshen polysaccharide has been proven to down-regulate the phosphorylation activation of the PI3K-AKT signaling pathway, which could inhibit the proliferation, invasion and migration ability of cancer cells cultured *in vitro*, and promote its apoptosis (Liu, Cai, & Wang, 2020).

In addition, gastric ulcers, gastritis, and gastric cancer all have a hypoxic microenvironmental state caused by broken capillaries and injured gastric tissue. HIF-1 signaling pathway plays a very important role in hypoxic cells. And the key protein, HIF-1α, can activate vascular endothelial growth factor (VEGF) (Zimna & Kurpisz, 2015), glucose transporter-1 (GLUT1) (Lu et al., 2016), lactate dehydrogenase (LDHA) (Kim, Tchernyshyov, Semenza, & Dang, 2006), erythropoietin (EPO) (Lappin & Lee, 2019), etc., which help cells to survive under hypoxic condition by promoting angiogenesis, activating glucose transportation, increasing glycolysis and inducing erythropoiesis. When inflammation occurs, macrophages aggregate to take phagocytosis effect, and at the same time induce the expression of inflammatory factors. If the inflammatory factors are not eliminated in time, it will cause inflammation damage. Some studies have shown that the stability of HIF-1α in macrophages not only depend on oxygen (Peyssonnaux et al., 2005). LPS (Blouin, Page, Soucy, & Richard, 2004) and TNF-α (Albina et al., 2001) can induce the accumulation of HIF-1α protein in macrophages, which is helpful for macrophages to move from hyperoxic blood to hypoxic inflammation or tumor areas. By inhibiting the production of inflammatory factors such as IL-6, TNF and reducing the activation of HIF-1α (Brouet & Ohshima, 1995; Ruby, Kuttan, Babu, Rajasekharan, & Kuttan, 1995), Dangshen may inhibit the aggregation of macrophages and inhibit the expression of pro-inflammatory factors to relieve inflammatory damage in gastric ulcer, gastritis, and gastric cancer. Furthermore, it is reported that Dangshen could reduce gastric acid secretion, protect gastric mucosa, and restrain gastric ulcer via inhibiting HIF-1 signaling pathway (Jing et al., 2017; Song et al., 2008). Through literature research and network pharmacology research, we proposed that Dangshen could inhibit the synthesis of Cas to avoid the activation of the HIF-1 signaling pathway (Tang, Wang, Liu, & Yan, 2019). Then it could weak the resistance of inflammatory damaged cells under hypoxic condition, and reduce the angiogenesis and invasion of gastric cancer cells.

In one word, Dangshen with spleen-fortifying effect was employed to understand the strategy of "Same treatment for different diseases" based on its common mechanism in the treatment of gastric diseases including gastric ulcer, gastritis and gastric cancer via network pharmacology research. It makes an attempt to reveal the scientific connotation of "Same treatment for different diseases" and may provide new revelation for the study of spleen-fortifying effect.

5. Conclusion

In this study, we used the spleen-fortifying effect of Dangshen as an example to understand the "Same treatment for different dis-

eases" strategy in traditional Chinese medicine. The therapeutic effect of Dangshen on gastric ulcer, gastritis and gastric cancer is mainly achieved through the overall regulation of PI3K-AKT signaling pathway and HIF-1 signaling pathway, but it has a different emphasis on different degrees of lesions. The treatment of gastric ulcer mainly depends on the regulation of mucosal protective factors secretion, which increases the defensive force of the gastric mucosa and promotes the healing of ulcers. The treatment of gastritis tends to rely on the regulation of TNF, NF-κB and other inflammation-related signaling pathways, which alleviates inflammatory damage and blocks the transformation from gastritis to cancer. The treatment of gastric cancer mainly bases on inhibiting the proliferation and metastasis of tumor cells through the ErbB signaling pathway, and at the same time strengthening the inhibition of inflammation (Fig. 11). Based on the conclusions, we will establish animal models to evaluate the efficacy of Dangshen, and then explore whether the treatment of these three gastric diseases by Dangshen is related to these pathways through proteomics and metabolomics research. The results showed that Dangshen achieved the effect of "Same treatment for different diseases" through complicated regulation of multiple targets and multiple pathways, which could provide some revelations for the research of spleen-fortifying effect and mechanism in traditional Chinese medicine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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