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An Exploration of the Active Ingredients of *Salvia miltiorrhiza* in the Treatment of Gastric Cancer and Its Mechanism Based on Network Pharmacology

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Abstract: BACKGROUND: Danshen, also known as *Salvia miltiorrhiza* or radix salvia in Latin, is an important drug whose main pharmacological effects are vasodilation, promotion of blood circulation, and elimination of stasis. In recent years, it has been reported that danshen also has anti-tumor activity. OBJECTIVE: The aim of this study was to explore the feasibility and potential mechanism of *S. miltiorrhiza* in the treatment of gastric cancer. STUDY DESIGN: We analyzed effective components and target genes of *S. miltiorrhiza* in the Traditional Chinese Medicine System Pharmacology (TCMSP) database and analysis platform. We then searched the GeneCards database for target genes related to gastric cancer and the intersection of these genes with the active components of *S. miltiorrhiza*. Target genes related to gastric cancer were taken as common potential target genes of *S. miltiorrhiza*, which could act on gastric cancer. Using the R programming language, we drew a Venn map of these common potential target genes. The "component–target gene–disease" network of *S. miltiorrhiza* in the treatment of gastric cancer was established using Cytoscape software version 3.7.1; the protein–protein interaction (PPI) network was constructed in the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database. With the help of R and Perl languages, we performed gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses of potential target genes of *S. miltiorrhiza* in the treatment of gastric cancer. RESULTS: We extracted a total of 65 active components from *S. miltiorrhiza*, including dihydrotanshinone I and miltionones I and II, as well as 102 potential target genes for gastric cancer. According to the Degree ranking in Cytoscape3.7.1 software, the top 10 potential target genes were protein kinase B1 (*AKT1*), interleukin-6 (*IL-6*), vascular endothelial growth factor A (*VEGFA*), epidermal growth factor receptor (*EGFR*), *Fos*, mitogen-activated protein kinase 1 (*MAPK1*), *Myc*, *JUN*, Caspase-3 (*CASP3*), and signal transducer and activator of transcription 3 (*STAT3*). Pathway enrichment mainly involved signaling pathways such as phosphoinositide 3-kinase (PI3K)–Akt, hypoxia-inducible factor 1 (HIF-1), and IL-17. CONCLUSION: Based on network pharmacology, *S. miltiorrhiza* is expected to be mined as a candidate Traditional Chinese Medicine (TCM) for the treatment of gastric cancer. Its mechanism for treating this cancer operates via multiple components and pathways. This study provides the basic theory and the basis for further research.

Keywords: *Salvia miltiorrhiza*, Gastric Cancer, Network Pharmacology, Target Gene, GO Function Enrichment Analysis, KEGG Pathway Enrichment Analysis

1. Introduction

Gastric cancer is the second-leading cause of cancer-related deaths worldwide, with more than half of cases occurring in East Asia [1]. In the United States, about 28,000 new cases and 10,960 deaths occurred in 2017 [2]. In China, gastric cancer is the second-leading cause of cancer-related deaths, with an estimated 500,000 deaths per year [3]. Despite improvements in diagnosis and treatment, the long-term survival rate of many gastric-cancer patients is still very low, and the 5-year survival rate is < 20% [4]. Most patients with gastric cancer already had tumor metastasis at diagnosis; the high rate of tumor metastasis leads to the low survival rate [5]. The etiology and pathogenesis of gastric cancer have

not been fully elucidated. Therefore, it is urgent for doctors to find strategies to improve the survival rate of gastric-cancer patients.

In recent years, Traditional Chinese Medicine (TCM) has played an increasingly important role in the prevention and treatment of diseases for Chinese people, Asians in general, and even people in other countries [6]. This is because it has good therapeutic effects and a low rate of side effects. Therefore, TCM has attracted more and more attention worldwide. However, the lack of reliable evidence for its effectiveness and safety might be an important reason for its difficulties in being recognized as legitimate treatment in Europe and the US [7].

The network pharmacology method, which integrates system biology with computer technology, could provide strategies for research into the mechanisms of TCM [8]. In the past few years, hundreds of network pharmacology studies have confirmed the molecular mechanisms of TCM [9-11]. Danshen, also known as *Salvia miltiorrhiza* or radix salvia in Latin, is an important TCM drug. Its main pharmacological effects are vasodilation, promotion of blood circulation, and elimination of stasis [12]. One meta-analysis of high-quality randomized controlled trials found that *S. miltiorrhiza* could improve the clinical prognosis of gastric-cancer patients [13], but the molecular mechanism by which this occurred has not been clarified. In this study, we used network pharmacology to elucidate the feasibility and potential pharmacological mechanism of *S. miltiorrhiza* in the treatment of gastric cancer.

2. Materials and Methods

All researches were approved by the Research Committee of Zhuhai People's Hospital (Zhuhai Hospital Affiliated with Jinan University), and carried out in accordance with the approved guidelines.

2.1. Searching Effective Components of S. miltiorrhiza

We input the keyword "*Salvia miltiorrhiza*" into the Traditional Chinese Medicine System Pharmacology (TCMSP) database and analysis platform and retrieved *S. miltiorrhiza*'s active ingredients. According to recommendations in the literature, we regarded compounds with oral bioavailability (OB) >30% and drug-likeness (DL) >0.18 as effective components.

2.2. Searching Potential Target Genes of S. miltiorrhiza

We searched all target genes of *S. miltiorrhiza* and then extracted the target genes of its effective components. We imported 102 potential target genes of *S. miltiorrhiza*'s active components into the UniProt database (https://www.uniprot.org/), selected "human" as the species, and obtained names of target genes and their corresponding acronyms.

2.3. Searching for Gastric-cancer–related Genes

The GeneCards database (http://www.genecards.org/) is a 1-stop database for human-gene annotation that covers nearly 90% of human protein-coding genes. We input the keyword "gastric cancer" into GeneCards and then exported the retrieval results.

2.4. Intersection of Potential Target Genes of S. miltiorrhiza and Gastric-cancer–related Genes

We considered genes that were both potential target genes of *S. miltiorrhiza* and gastric-cancer-related genes to be the genes of interaction between *S. miltiorrhiza* and gastric cancer.

2.5. Constructing a Component–target Gene–disease Network

We deleted effective components that could not act on gastric-cancer–related target genes. Then we imported the remaining effective components and potential target genes for gastric-cancer treatment into Cytoscape software version 3.7.1 (US National Institute of General Medical Sciences [NIGMS], Bethesda, Maryland, US; https://cytoscape.org/) to build an effective component–target gene–disease network.

2.6. Constructing a Protein–protein Interaction (PPI) Network

We input potential target genes of *S. miltiorrhiza* in the treatment of gastric cancer into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org/) and selected "*Homo sapiens*" as the species. We obtained the PPI network in tab-separated values (.tsv) file format; the PPI network picture was saved in Portable Network Graphics (.png) format.

2.7. Screening Core Genes of PPI Network

Using the R programming language, we calculated a genes.tsv file and selected the top 30 target genes of degree value as the core genes.

2.8. Gene Ontology (GO) Function and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analyses

Using R language, we analyzed our GO function enrichment analysis of potential target genes and our KEGG pathway enrichment analysis, including biological processes, molecular functions, and cell components. We selected the path whose kinase insert domain receptor (KDR) value (i.e., *Q*-value) was <0.05, and then we ranked the paths with the 20 highest KDR values in order to draw a histogram and bubble chart.

3. Results

3.1. Acquisition of Effective Components and Potential Target Genes of S. miltiorrhiza

From the TCMSP database we obtained 65 active components of *S. miltiorrhiza*, such as dihydrotanshinone I

and miltionones I and II, using the screening conditions of OB>30% and DL>0.18 (Table 1). At the same time, we converted target genes corresponding to active components of *S. miltiorrhiza* in the UniProt database.

Table 1. *Active components of Salvia miltiorrhiza.*

No.	molID	molName	MW	OB (%)	DL
01	MOL001601	1,2,5,6-Tetrahydrotanshinone	280.34	38.75	0.36
02	MOL001659	Poriferasterol	412.77	43.83	0.76
03	MOL001771	Poriferast-5-en-3beta-ol	414.79	36.91	0.75
04	MOL001942	Isoimperatorin	270.3	45.46	0.23
05	MOL002222	Sugiol	300.48	36.11	0.28
06	MOL002651	Dehydrotanshinone II A	292.35	43.76	0.4
07	MOL002776	Baicalin	446.39	40.12	0.75
08	MOL000569	Digallate	322.24	61.85	0.26
09	MOL000006	Luteolin	286.25	36.16	0.25
10	MOL006824	α-Amyrin	426.8	39.51	0.76
11	MOL007036	5,6-Dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	298.41	33.77	0.29
12	MOL007041	2-Isopropyl-8-methylphenanthrene-3,4-dione	264.34	40.86	0.23
13	MOL007045	3α-Hydroxytanshinone II a	310.37	44.93	0.44
14	MOL007048	(E)-3-[2-(3,4-Dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	312.29	48.24	0.31
15	MOL007049	4-Methylenemiltirone	266.36	34.35	0.23
16	MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	356.4	62.78	0.4
17	MOL007051	6-o-Syringyl-8-o-acetyl shanzhiside methyl ester	628.64	46.69	0.71
18	MOL007058	Formyltanshinone	290.28	73.44	0.42
19	MOL007059	3-beta-Hydroxymethyllenetanshiquinone	294.32	32.16	0.41
20	MOL007061	Methylenetanshinquinone	278.32	37.07	0.36
21	MOL007063	Przewalskin a	398.49	37.11	0.65
22	MOL007064	Przewalskin b	330.46	110.32	0.44
23	MOL007068	Przewaquinone B	292.3	62.24	0.41
24	MOL007069	Przewaquinone c	296.34	55.74	0.4
25	MOL007070	(6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	312.34	41.31	0.45
26	MOL007071	Przewaquinone f	312.34	40.31	0.46
27	MOL007077	Sclareol	308.56	43.67	0.21
28	MOL007079	Tanshinaldehyde	308.35	52.47	0.45
29	MOL007081	Danshenol B	354.48	57.95	0.56
30	MOL007082	Danshenol A	336.41	56.97	0.52
31	MOL007085	Salvilenone	292.4	30.38	0.38
32	MOL007088	Cryptotanshinone	296.39	52.34	0.4
33	MOL007093	Dan-shexinkum d	336.41	38.88	0.55
34	MOL007094	Danshenspiroketallactone	282.36	50.43	0.31
35	MOL007098	Deoxyneocryptotanshinone	298.41	49.4	0.29
36	MOL007100	Dihydrotanshinlactone	266.31	38.68	0.32
37	MOL007101	Dihydrotanshinone I	278.32	45.04	0.36
38	MOL007105	Epidanshenspiroketallactone	284.38	68.27	0.31
39	MOL007107	C09092	286.5	36.07	0.25
40	MOL007108	Isocryptotanshi-none	296.39	54.98	0.39
41	MOL007111	Isotanshinone II	294.37	49.92	0.4
42	MOL007115	Manool	304.57	45.04	0.2
43	MOL007118	Microstegiol	298.46	39.61	0.28
44	MOL007119	Miltionone I	312.39	49.68	0.32
45	MOL007120	Miltionone II	312.39	71.03	0.44
46	MOL007121	Miltipolone	300.43	36.56	0.37
47	MOL007122	Miltirone	282.41	38.76	0.25
48	MOL007123	Miltirone II	272.32	44.95	0.24
49	MOL007124	Neocryptotanshinone II	270.35	39.46	0.23
50	MOL007125	Neocryptotanshinone	314.41	52.49	0.32
51	MOL007127	1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	280.29	34.72	0.37
52	MOL007130	Prolithospermic acid	314.31	64.37	0.31
53	MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	360.34	109.38	0.35
54	MOL007140	(Z)-3-[2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid	314.31	88.54	0.26
55	MOL007141	Salvianolic acid g	340.3	45.56	0.61

No.	molID	molName	MW	OB (%)	DL
56	MOL007142	Salvianolic acid j	538.49	43.38	0.72
57	MOL007143	Salvilenone I	270.40	32.43	0.23
58	MOL007145	Salviolone	268.38	31.72	0.24
59	MOL007149	NSC 122421	300.48	34.49	0.28
60	MOL007150	(6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone	312.34	75.39	0.46
61	MOL007151	Tanshindiol B	312.34	42.67	0.45
62	MOL007152	Przewaquinone E	312.34	42.85	0.45
63	MOL007154	Tanshinone iia	294.37	49.89	0.4
64	MOL007155	(6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	310.37	65.26	0.45
65	MOL007156	Tanshinone VI	296.34	45.64	0.30

There are 65 active components of S. miltiorrhiza. molID=molecular identification number; molName=molecular name; MW=molecular weight; OB=oral bioavailability; DL=drug-likeness.

3.2. Predicting Potential Target Genes of S. miltiorrhiza in the Treatment of Gastric Cancer

We retrieved a total of 18,221 gastric-cancer-related genes from the GeneCards database and compared them with target genes corresponding to each effective component of *S. miltiorrhiza*. We selected 102 common target genes (Table 2) as potential target genes of *S. miltiorrhiza* in the treatment of gastric cancer (Figure 1).

Table 2. *Potential target information of S. miltiorrhiza.*

No.	Uniprotkb	Target	No.	Uniprotkb	Target	No.	Uniprotkb	Target
1	P22303	*ACHE*	35	P21918	*DRD5*	69	P01106	*MYC*
2	Q08462	*ADCY2*	36	P42892	*ECE1*	70	Q15788	*NCOA1*
3	P35348	*ADRA1A*	37	P14138	*EDN3*	71	P25963	*NFKBIA*
4	P35368	*ADRA1B*	38	P25101	*EDNRA*	72	P60321	*NOS2*
5	P08913	*ADRA2A*	39	P00533	*EGFR*	73	P06748	*NPM1*
6	P18089	*ADRA2B*	40	P04626	*ERBB2*	74	O75469	*NR1I2*
7	P18825	*ADRA2C*	41	P03372	*ESR1*	75	P04150	*NR3C1*
8	P07550	*ADRB2*	42	Q92731	*ESR2*	76	P08235	*NR3C2*
9	O95433	*AHSA1*	43	P08709	*F7*	77	Q9BZD4	*NUF2*
10	P15121	*AKR1B1*	44	P49327	*FASN*	78	P41143	*OPRD1*
11	P31749	*AKT1*	45	P01100	*FOS*	79	P35372	*OPRM1*
12	P05067	*APP*	46	P78334	*GABRE*	80	Q9UKK3	*PARP4*
13	P10275	*AR*	47	P49841	*GSK3B*	81	P12004	*PCNA*
14	P10415	*BCL2*	48	P09211	*GSTP1*	82	P06401	*PGR*
15	Q07817	*BCL2L1*	49	P09601	*HMOX1*	83	P37231	*PPARG*
16	O15392	*BIRC5*	50	P46098	*HTR3A*	84	P07477	*PRSS1*
17	P30988	*CALCR*	51	P05362	*ICAM1*	85	O14684	*PTGES*
18	P42574	*CASP3*	52	P01579	*IFNG*	86	P23219	*PTGS1*
19	P55210	*CASP7*	53	P22301	*IL10*	87	P35354	*PTGS2*
20	P55211	*CASP9*	54	P60568	*IL2*	88	P06400	*RB1*
21	P20248	*CCNA2*	55	P05112	*IL4*	89	Q04206	*RELA*
22	P14635	*CCNB1*	56	P05231	*IL6*	90	P19793	*RXRA*
23	P24385	*CCND1*	57	P06213	*INSR*	91	Q14524	*SCN5A*
24	P29965	*CD40LG*	58	P05106	*ITGB3*	92	P14672	*SLC2A4*
25	P38936	*CDKN1A*	59	P05412	*JUN*	93	P23975	*SLC6A2*
26	O14757	*CHEK1*	60	Q12809	*KCNH2*	94	Q01959	*SLC6A3*
27	P11229	*CHRM1*	61	P28482	*MAPK1*	95	P31645	*SLC6A4*
28	P08172	*CHRM2*	62	Q16539	*MAPK14*	96	P40763	*STAT3*
29	P20309	*CHRM3*	63	Q07820	*MCL1*	97	O95150	*TNFSF15*
30	Q15822	*CHRNA2*	64	Q00987	*MDM2*	98	P11387	*TOP1*
31	P04798	*CYP1A1*	65	P08581	*MET*	99	P11388	*TOP2A*
32	P05177	*CYP1A2*	66	P03956	*MMP1*	100	Q9H3D4	*TP63*
33	P08684	*CYP3A4*	67	P08253	*MMP2*	101	P14679	*TYR*
34	P14416	*DRD2*	68	P14780	*MMP9*	102	P15692	*VEGFA*

There are 102 target genes corresponding to active components of *S. miltiorrhiza* in the UniProt database.

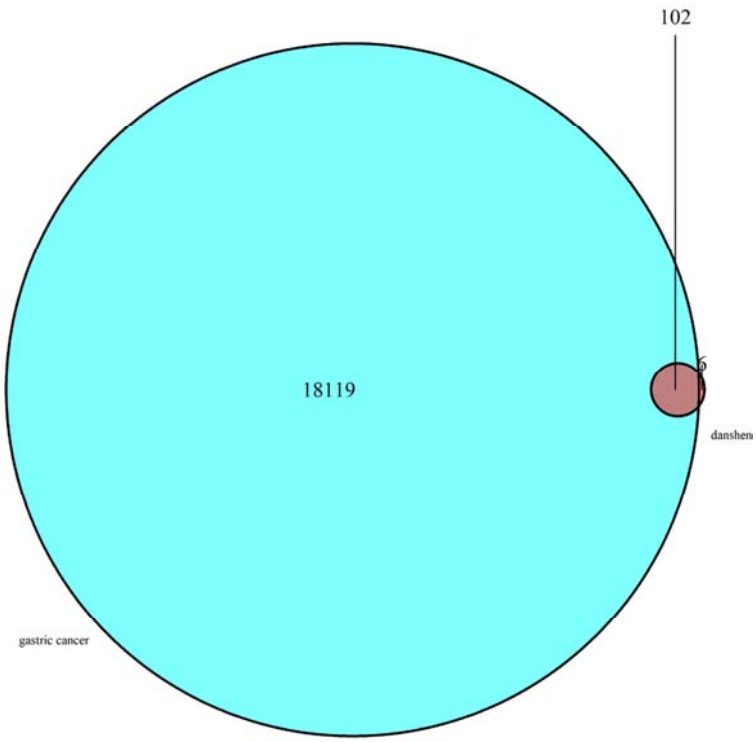

Figure 1. *The target genes in common between S. miltiorrhiza and gastric cancer.*

3.3. Constructing a Component–target Gene–disease Network

We introduced potential target genes of *S. miltiorrhiza* for gastric-cancer treatment into Cytoscape to construct a component–target gene–disease network (Figure 2). The network had 102 nodes and 1190 strip edges. In Figure 2, the blue octagonal shape represents *S. miltiorrhiza*, the purple triangle represents the active-component molecule, the green circle represents the target gene, and the red diamond represents the disease. As the figure shows, the same active ingredient can correspond to different target genes, and different active ingredients can correspond to the same target gene. This suggested that the potential mechanism of *S. miltiorrhiza* in the treatment of gastric cancer is mediated by multi-component and multi-target genes.

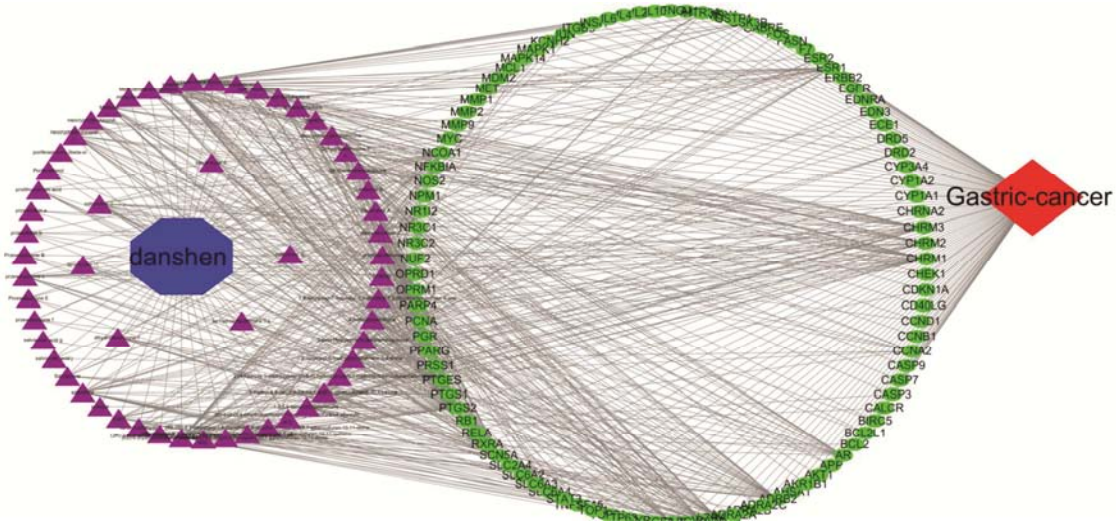

Figure 2. *Construction of component–target gene–disease network.*

3.4. Constructing a PPI Network and Screening Core Target Genes

We imported potential target genes of *S. miltiorrhiza* in gastric-cancer treatment into the STRING database and obtained a PPI network (Figure 3) and TSV file. With the help of R language, we calculated a genes.tsv file and obtained the top 30 target genes of degree value (Figure 4).

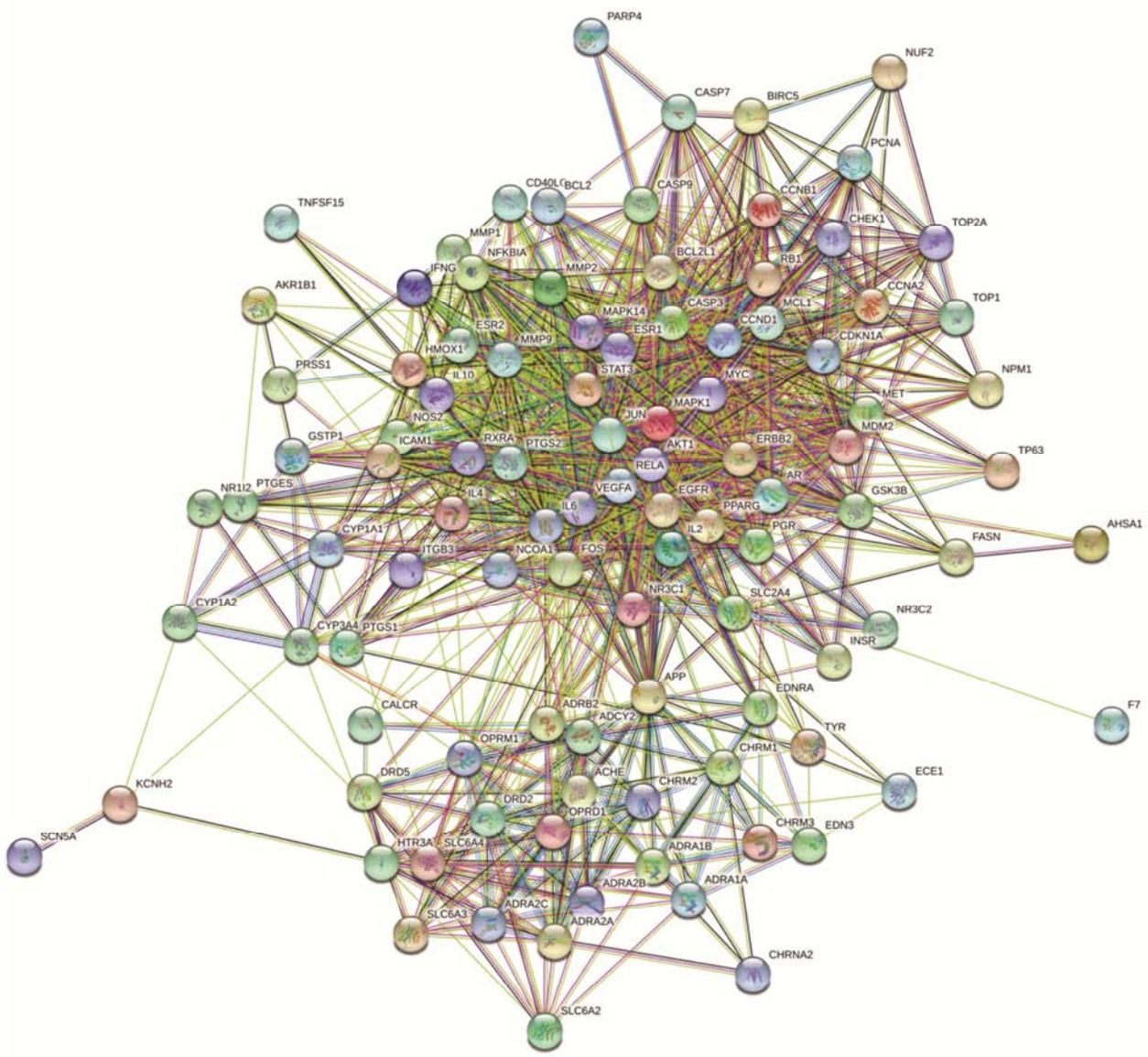

Figure 3. *Construction of PPI network.*

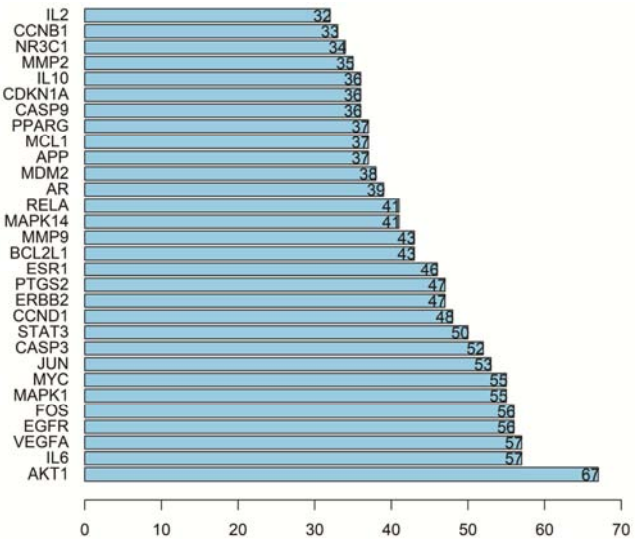

Figure 4. *Top 30 core target genes.*

3.5. GO Function and KEGG Pathway Enrichment Analyses

Using R language, we performed GO function and KEGG pathway enrichment analyses of potential target genes of *S. miltiorrhiza* in gastric-cancer treatment. The results of GO function enrichment analysis (Figures 5 and 6) showed that the biological processes were mainly those such as transcription factor activity, direct ligand-regulated sequence-specific DNA binding, and activating transcription factor binding. The cell components were mainly those such as nuclear receptor activity and chromatin binding, while the molecular functions were mainly those such as steroid hormone receptor activity and catecholamine binding. The results of KEGG pathway enrichment analysis (Figures 7 and 8) showed that potential target genes of *S. miltiorrhiza* in the treatment of gastric cancer were mainly enriched in signaling pathways such as PI3K–Akt, HIF-1, and IL-17.

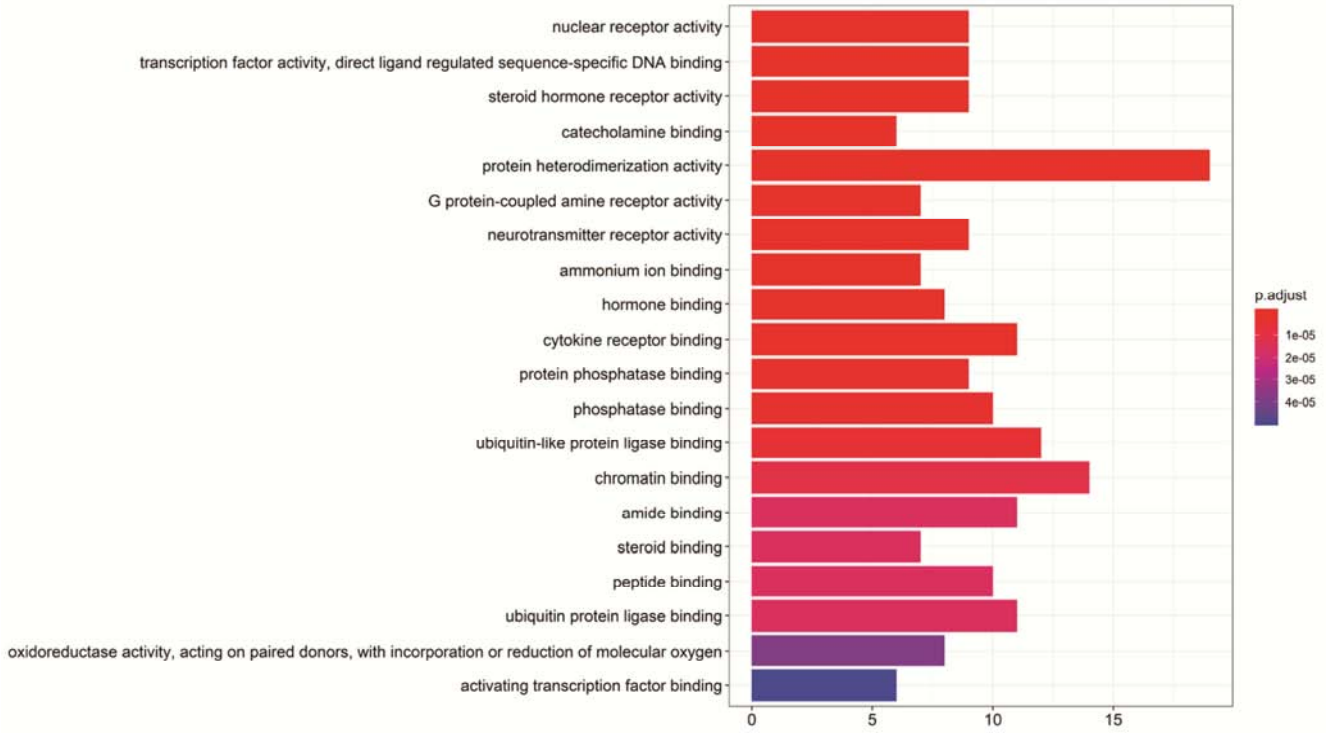

Figure 5. *GO functional enrichment analysis (histogram).*

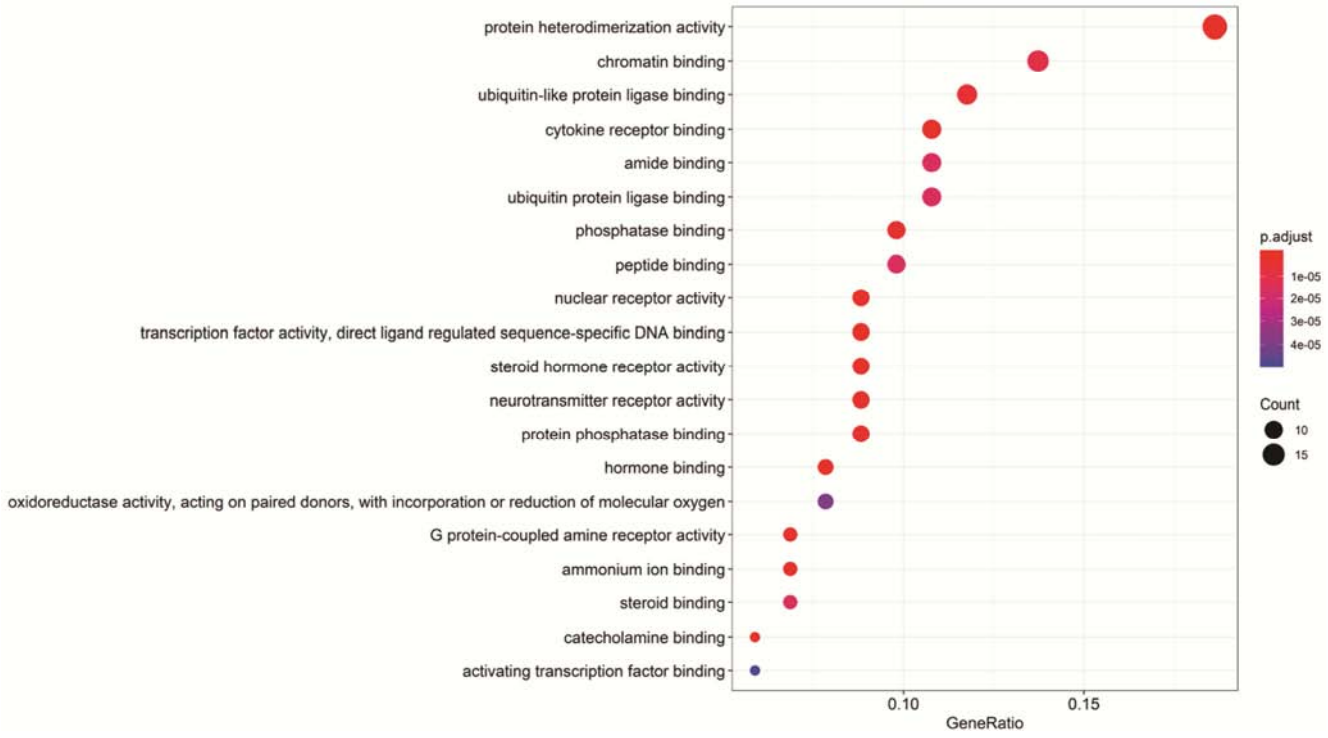

Figure 6. *GO functional enrichment analysis (bubble chart).*

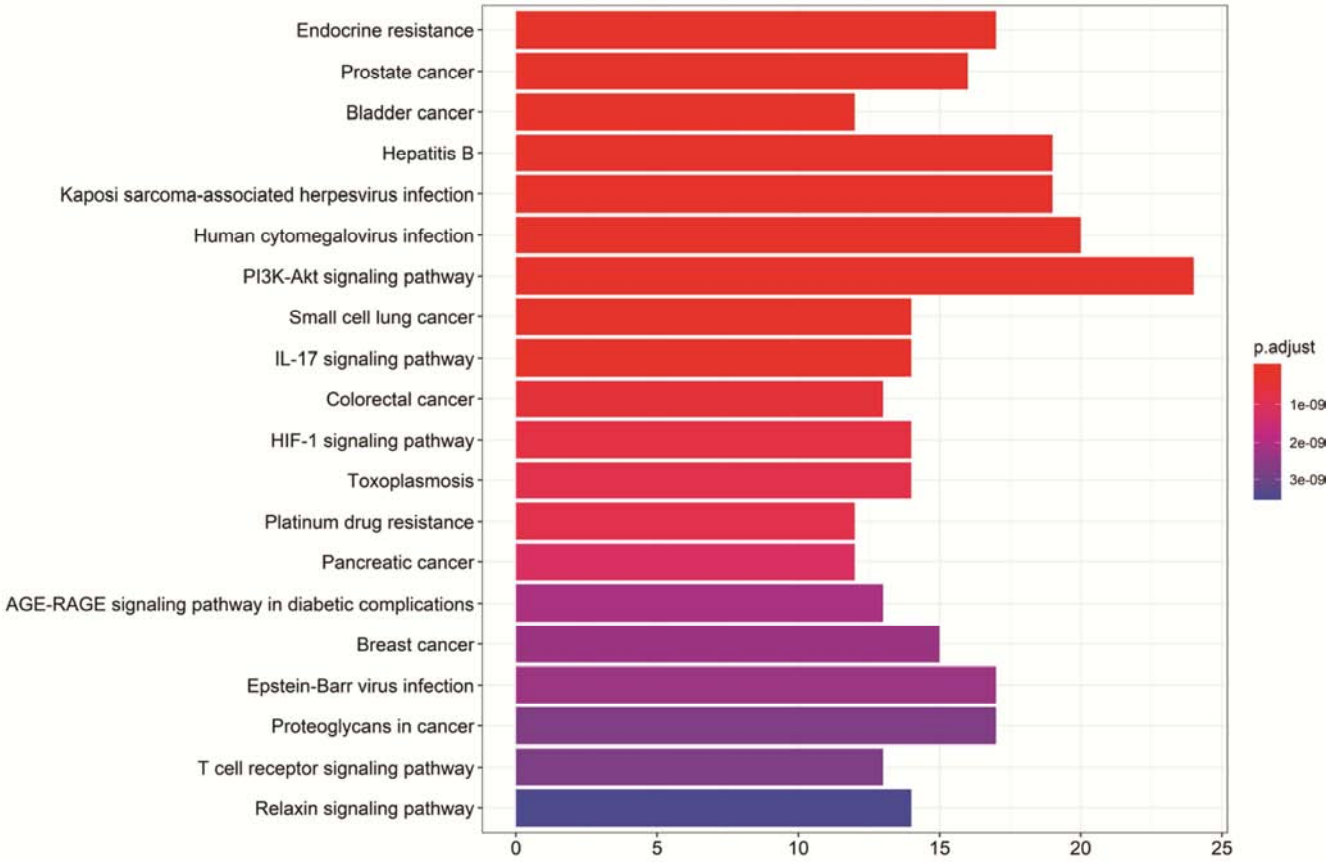

Figure 7. *Results of KEGG pathway enrichment analysis (histogram).*

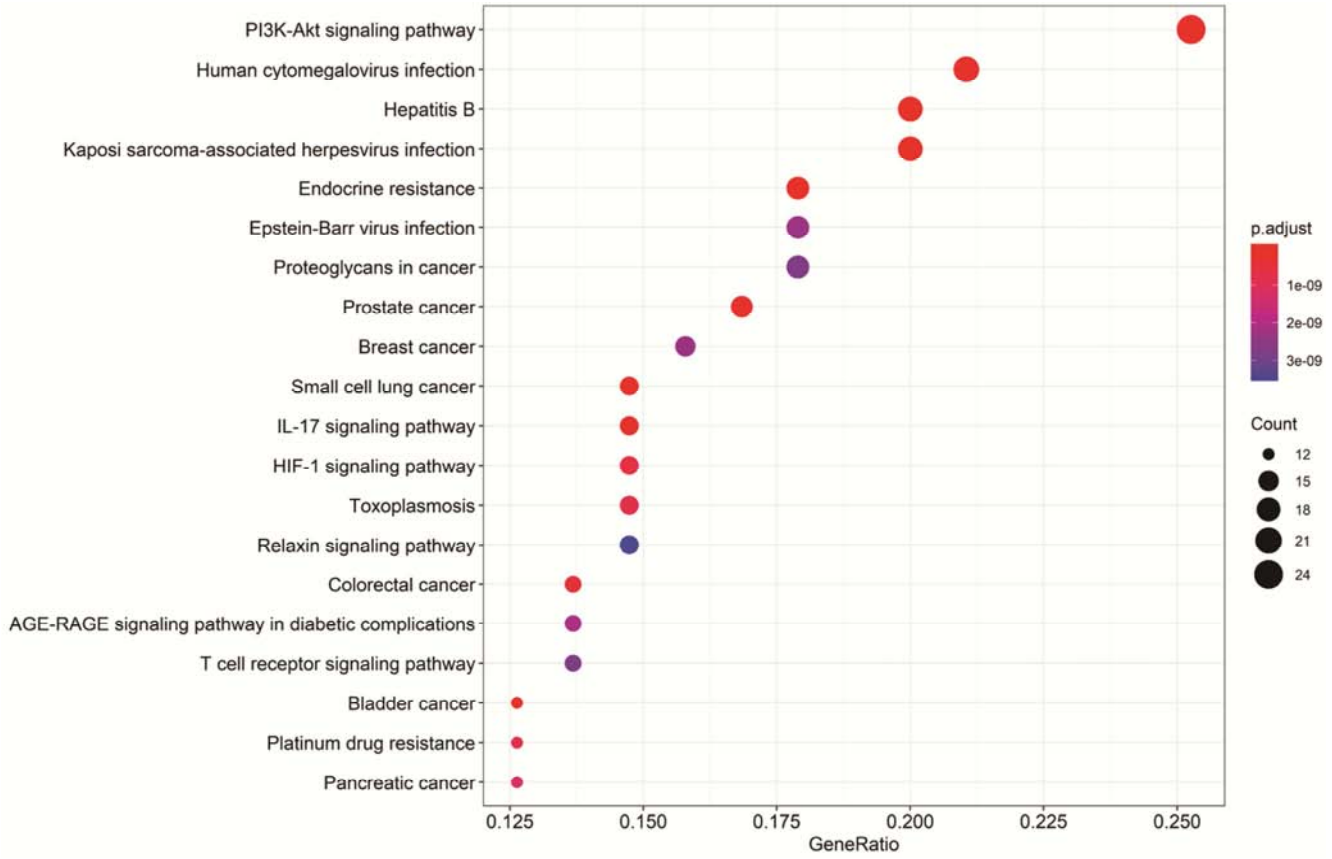

Figure 8. *Results of KEGG pathway enrichment analysis (bubble chart).*

4. Discussion

TCM, an important auxiliary and alternative medical method [14], has a history dating back thousands of years and has been popularized in many countries. Modern research shows that the effective ingredients in TCM could become candidates for anti-tumor drugs. TCM has unique advantages [15]: it employs compound drugs with multi-target and multi-component effects. Such drugs play anti-tumor roles by regulating the overall function of the body and have been widely reported as having low toxicity, good efficacy, and high specificity [16]. Some TCM drugs have been used in clinical treatment for cancers such as liver cancer [17].

In our study, we used computational tools and multiple relational databases to explore the pharmacological-action network of *S. miltiorrhiza* in the treatment of gastric cancer and to predict its active components and potential protein targets and pathways. The Traditional Chinese Medicine System Pharmacology (TCMSP) database and analysis platform is a database that is often used in conjunction with both modern and traditional medicine; it includes 29,384 components, 3311 targets, and 837 related diseases and is helpful for revealing the mechanisms of TCM action [18]. The GeneCards database, including GeneCards (human genes), MalaCards (human diseases), and PathCards (human pathways), has also come to play a key role in clinical research [19]. We searched 18,221 gastric-cancer-related genes in GeneCards.

In this study, we found 102 potential target genes of *S. miltiorrhiza* in the treatment of gastric cancer, mainly involving protein kinase B1 (*AKT1*), interleukin-6 (*IL-6*), vascular endothelial growth factor A (*VEGFA*), epidermal growth factor receptor (*EGFR*), *Fos*, mitogen-activated protein kinase 1 (*MAPK1*), *Myc*, *JUN*, Caspase-3 (*CASP3*), and signal transducer and activator of transcription 3 (*STAT3*). GO function and KEGG signaling pathway enrichment analyses suggested that the signaling pathway by which *S. miltiorrhiza* exerts its effect in the treatment of gastric cancer is closely related to the PI3K–Akt, HIF-1, and IL-17 signaling pathways.

The PI3K–Akt signaling pathway plays an important role in invasion, proliferation, and apoptosis of gastric-cancer cells. Some studies show that activation of this pathway can enhance invasion and proliferation of such cells [20], as well as inhibit the expression of downstream proteins and promote development of gastric cancer [21]. Inhibiting the PI3K–Akt signaling pathway can induce autophagy of gastric-cancer cells [22]. A chronically hypoxic environment greatly promotes the proliferation, migration, and invasion of these cells [23]. In a hypoxic environment, AKT1 expression was upregulated in cells downstream of the PI3K–Akt signaling pathway, while VEGF expression was upregulated, both of which processes were involved in tumor neovascularization, enhanced cell tolerance to hypoxic environment, and promoted tumor formation [24]. Therefore, activation of the PI3K–Akt or HIF-1 signaling pathway is an important mechanism for the development of gastric cancer. Inflammation has been reported to be associated with gastric-cancer development. IL-6 is a common cytokine that is closely related to gastric-cancer pathogenesis. Cytokines such as adipocytokines can mediate the IL-17 signaling pathway and become important factors in tumor development [25]. Inflammatory factors can play direct roles in immunosuppression, stimulate angiogenesis in gastric cancer, and promote tumor cell formation. *CASP3* is a gene that controls apoptosis. Apoptosis is controlled by many intracellular or extracellular signals, including Caspase and B-cell lymphoma 2 (Bcl-2) family proteins. The literature shows that *CASP3* is involved in the occurrence and development of gastric cancer, inhibiting the proliferation of gastric-cancer cells and promoting apoptosis [26]. Mitochondria plays a key role in mediating apoptosis through various apoptotic proteins such as cytochrome c (*Myc*) [27]. The main functions of *Myc* are to control cell metabolism and apoptosis and to induce Caspase cascade [28]. Caspase is the main executor of apoptosis [29] as a transcription-related protein, and c-Jun is an important cell cycle regulator [30]. In gastric-cancer patients, transcription activity of c-Jun is significantly enhanced and expression of cyclin D1 is activated, which accelerates the transformation of tumor cells from G0/G1 to S phase and promotes the proliferation of tumor cells [31].

It can be seen that *S. miltiorrhiza* is a feasible means of treating gastric cancer, and that its potential mechanisms are as follows: (1) inhibiting the PI3K–Akt signaling pathway and regulating proteins downstream thereof so as to inhibit proliferation and promote apoptosis of gastric-cancer cells; (2) reducing the tolerance of gastric-cancer cells to hypoxia in the tumor environment and inducing apoptosis of these cells; and (3) regulating immune system function and inhibiting both inflammation and anti-inflammation in the gastric-cancer tumor environment (it should be infiltrated with inflammation, so as to inhibit the local angiogenesis of gastric cancer); (4) activating the *CASP3* gene and the activity of apoptotic protease so as to promote apoptosis of gastric-cancer cells; and (5) inhibiting gastric-cancer-related factors so as to inhibit the proliferation of gastric-cancer cells.

Although we have obtained some important new findings based on network pharmacology, there are still limitations to our study. We explored only the feasibility and potential mechanism of *S. miltiorrhiza* in the treatment of gastric cancer at the molecular level, which still needs to be confirmed in the later stage.

In conclusion, this study showed that 65 main active components of *S. miltiorrhiza*, such as dihydrotanshinone I and miltonones I and II, could be used in the treatment of gastric cancer. These active components could play a pharmacological role in such treatment by acting on the target genes *AKT1*, *IL-6*, *VEGFA*, *EGFR*, *Fos*, *MAPK1*, *Myc*, *Jun*, *CASP3*, and *STAT3*, as well as by regulating signaling pathways such as PI3K–Akt, HIF-1, and IL-17. However,

this study provided only a preliminary prediction of the molecular mechanism by which *S. miltiorrhiza* treats gastric cancer, and did so at the molecular level of network pharmacology. It lacked further verifications such as polymerase chain reaction testing. In the future, we will do more in-depth research.

5. Conclusion

Based on network pharmacology, *S. miltiorrhiza* is expected to be mined as a candidate Traditional Chinese Medicine (TCM) for the treatment of gastric cancer. Its mechanism for treating this cancer operates via multiple components and pathways. This study provides the basic theory and the basis for further research.

Data Availability

The original data used to support this study can be available from the corresponding author upon request.

Conflict of Interest

The authors declare that they have no competing interests.

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