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Original Article

Using network pharmacology approaches to identify treatment mechanisms for codonopsis in esophageal cancer

Yuan Tian[1], Liang Tang[2]

[1]Public Course Teaching Department, [2]Department of Stomatology, Cangzhou Medical College, Cangzhou 061000, Hebei, China

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Abstract: Objective: We explored codonopsis mechanisms for the treatment of esophageal cancer using a network pharmacology approach. Materials and methods: Using the Laboratory of Systems Pharmacology website, codonopsis compounds and targets were gathered. After identifying esophageal cancer target intersections from the GeneCards website, possible codonopsis targets for esophageal cancer were screened. A protein-protein interaction (PPI) network diagram of protein targets was then constructed using the STRING database. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genome (KEGG) pathway enrichment analyses were performed in R 3.6.0 software. A network diagram of "disease-drug-component-target-pathways" was also constructed using Cytoscape 3.7.1. Results: We screened 21 codonopsis compounds as possible esophageal cancer treatments and 31 drug-disease intersecting targets. GO enrichment analysis identified 778 biological process (BP) components, 15 cellular component (CC) components, and 50 molecular function (MF) components, and KEGG analyses identified 90 signaling pathways. Our analyses showed that p53 and PI3K-Akt signaling pathways (among others) were significant pathways in these processes. Conclusions: Codonopsis may be used to treat esophageal cancer by multiple components, targets, and pathways.

Keywords: Codonopsis, esophageal cancer, network pharmacology, mechanism research

Introduction

By comparison to other cancers, globally, esophageal cancer ranks seventh in terms of incidence and sixth for mortality [1]. Due to non-obvious esophageal cancer symptoms at the early stages, more than half of patients present with unresectable lesions or accompanying distant metastases. Although treatment methods, drug development, and survival rates are improving, the current 5-year survival rate is less than 20% [2, 3]. Therefore, underlying esophageal cancer molecular mechanisms must be identified to explore predictive targets and effective treatments.

Codonopsis is a widely distributed herb across Asia. The plant has antioxidant, anti-cancer, anti-inflammatory, and hypolipidemic activities, and is widely used in traditional Chinese medicine [4]. The plant's phytochemical composition is highly complex. To date, more than 230 compounds have been identified, including alkaloids, alkynes, terpenes, flavonoids, lignins, steroids, and sugars. Of these compounds, alkaloids, polyacetylenes, lignans, flavonoids, and polysaccharides are considered the main active compounds [5]. Consequently, codonopsis exhibits a wide range of pharmacological effects; plant components exert effects on immune function, anti-inflammatory, and anti-tumor cell proliferation and migration activities [6, 7], inhibitory effects against ovarian cancer cell invasion and migration [8-10], suppressing melanoma metastasis [11], and inducing apoptosis in oral cancer [12] and colon cancer cells [13, 14]. Additionally, codonopsis impacts the digestive system, with positive effects on gastric ulcers and chronic gastritis [15], and has poossible applications for the prevention and treatment of acute colitis [16].

While studies have explored the potential therapeutic value of codonopsis for patients with colon tumors and other gastrointestinal diseases, and indeed identified meaningful results, the identified codonopsis compounds are not specific. Therefore, targeted predictions and mechanisms underpinning codonopsis for the treatment of digestive system tumors such as esophageal cancer must be improved, thereby providing more information on codonopsis efficacy and function. To this end, we used bioinformatic and network pharmacology approaches to analyze the targets and mechanisms of codonopsis inesophageal cancer to provide insight for clinical and experimental research.

Materials and methods

Screening effective codonopsis compounds and targets

In the Laboratory of Systems Pharmacology website (http://tcmspw.com/tcmsp.php), active codonopsis compounds and targets were selected from the TCMSP database. Using oral bioavailability (OB) at ≥30% and druglikeness (DL) at ≥0.18 as cutoff values, we further screened codonopsis compounds to identify more active compounds. In this database, we searched for targets corresponding to component names, and deleted components without a target. In the UniProt database (http://www.uniprot.org/), using the species restriction "Homo sapiens", the gene names of collected targets were converted and we established a drug-component-target database.

Sorting esophageal cancer-related target genes

We searched for "esophageal cancer" in the GeneCards database (https://www.genecards.org) to identify related targets and build a disease-target database.

Screening intersecting drug and disease targets

We used the online Venny 2.1.0 program (https://bioinfogp.cnb.csic.es/tools/venny/) to identify codonopsis and esophageal cancer targets, and drug-disease intersecting target genes. We also used this program to draft Venn diagrams.

Building a protein-protein interaction (PPI) network

Using the STRING platform (https://string-db.org/), we set the minimum required interaction score to the highest confidence level (0.900) and assigned intersected codonopsis and esophageal cancer targets to a PPI network to generate protein interaction information.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

We used the clusterProfiler toolkit of R software (version 3.6.0) to convert gene symbols to gene IDs, and performed GO enrichment analysis (biological processes (BP), cellular component (CC), and molecular function (MF)), KEGG pathway enrichment analysis, and drafted barplots and dotplots, respectively.

Building a "disease-drug-component-target-pathway" network diagram

Based on KEGG results, we selected the top 10 pathways and used Cytoscape 3.7.0 software to build a "disease-drug-component-target-pathway" network for visual analysis.

Results

Codonopsis compounds and targets

From the TCMSP database, we identified 134 effective codonopsis compounds. Using OB ≥30% and DL ≥0.18 parameters, 21 high activity compounds were selected (**Table 1**). We then converted target names corresponding to codonopsis compounds into gene names using the Uniprot database and generated 47 hits.

Esophageal cancer targets

We searched GeneCards and identified 1,169 targets related to esophageal cancer, including BRCA2, TP53, and BRCA1 using the ≥10 relevance score.

The intersection of codonopsis targets and esophageal cancer targets

We processed selected codonopsis target genes and esophageal cancer target genes using Venny 2.1.0, and identified 31 codonopsis-esophageal cancer intersecting target

Table 1. Basic information of main components of codonopsis

Mol ID	Molecule Name	OB (%)	DL
MOL001006	Poriferasta-7,22E-dien-3beta-ol	42.98	0.76
MOL002140	Perlolyrine	65.95	0.27
MOL002879	Diop	43.59	0.39
MOL003036	ZINC03978781	43.83	0.76
MOL000449	Stigmasterol	43.83	0.76
MOL003896	7-Methoxy-2-methyl isoflavone	42.56	0.20
MOL004355	Spinasterol	42.98	0.76
MOL004492	Chrysanthemaxanthin	38.72	0.58
MOL005321	Frutinone A	65.90	0.34
MOL000006	Luteolin	36.16	0.25
MOL006554	Taraxerol	38.40	0.77
MOL006774	Stigmast-7-enol	37.42	0.75
MOL007059	3-beta-Hydroxymethyllenetanshiquinone	32.16	0.41
MOL007514	Methyl icosa-11,14-dienoate	39.67	0.23
MOL008391	5alpha-Stigmastan-3,6-dione	33.12	0.79
MOL008393	7-(beta-Xylosyl)cephalomannine_qt	38.33	0.29
MOL008397	Daturilin	50.37	0.77
MOL008400	Glycitein	50.48	0.24
MOL008406	Spinoside A	39.97	0.40
MOL008407	(8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-1,2,4,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one	45.40	0.76
MOL008411	11-Hydroxyrankinidine	40.00	0.66

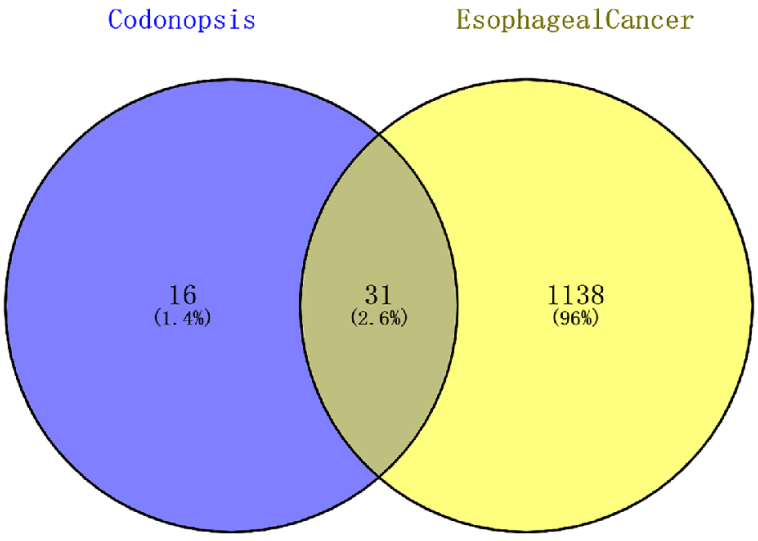


Figure 1. Venn diagram showing the intersection of codonopsis-esophageal cancer targets. Blue circles represent 47 codonopsis targets. Yellow circles represent 1,169 esophageal cancer targets, and the green intersection represents 31 codonopsis-esophageal cancer targets.

genes, including EGFR, ERBB2, and CCND. A Venn diagram was also assembled (**Figure 1**).

From these observations, codonopsis appeared to exert its therapeutic effect on esophageal cancer by influencing these 31 intersecting target genes.

The PPI network

Using a Combined Score >0.9, the STRING database was used to build a PPI network of 31 interesting codonopsis and esophageal cancer targets. There were 31 nodes and 46 edges in the graph, and the average node degree was 2.97 (**Figure 2**). Genes with more interactions had greater roles in this PPI network, and were deemed more important codonopsis targets for esophageal cancer.

GO and KEGG analyses

We used the R software clusterProfiler toolkit to perform GO and KEGG pathway analyses on the 31 intersecting genes. We identified 843 GO items (P<0.05), including 778 BP components, 15 CC components, and 50 MF components. Then, BP, CC, and MF barplots and dotplots were assembled (**Figure 3**). According to GO analyses: the P value top 20 BP components included: response to steroid hormones, cellular response to steroid hormone stimulus, response to UV, response to xenobiotic stimulus, regulation of DNA-binding transcription factor activity, response to light stimulus, response to radiation, response to glucocorticoid, response to vitamins, response to corticosteroids, positive regulation of DNA-binding transcription factor activity, intracellular receptor signaling pathway, response to ketones, reproductive structure development, gland de-

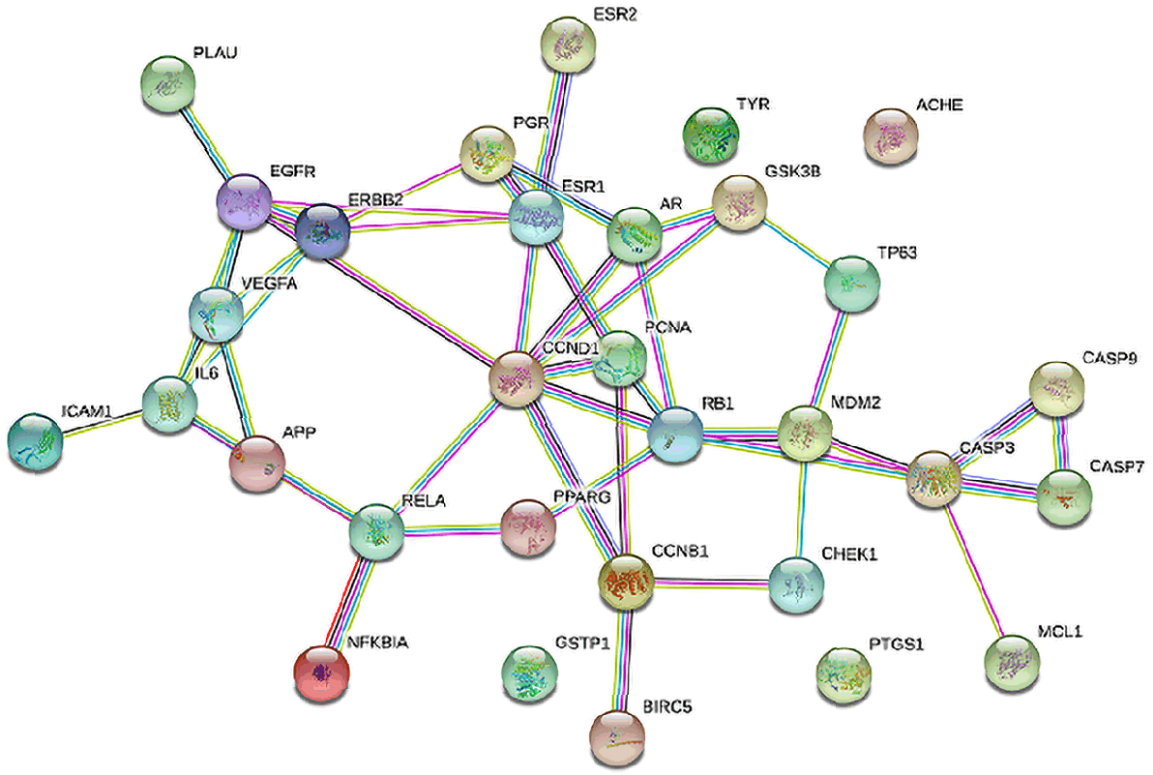


Figure 2. Protein-protein interaction (PPI) network of codonopsis acting on esophageal cancer. Nodes represent proteins, and edges between nodes represent the combination of protein and protein. Colored lines represent different binding relationships between proteins. The blue edge represents the relationship identified from curated databases; the purple side represents experimentally determined relationships, and the above two are known interactions. The green edge is the gene neighborhood relationship; the red edge is the relationship for the gene fusions relationship; the dark blue edge is the gene co-occurrence relationship, and the above three are predicted interactions. In addition, three other relationships are present: the yellow edge represents text-mining, the black edge represents co-expression, and the light blue edge represents protein homology.

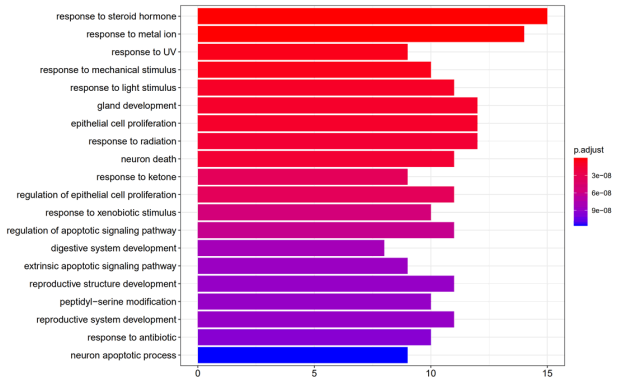
velopment, epithelial cell proliferation, reproductive system development, response to oxidative stress, response to estradiol, and response to nutrients.

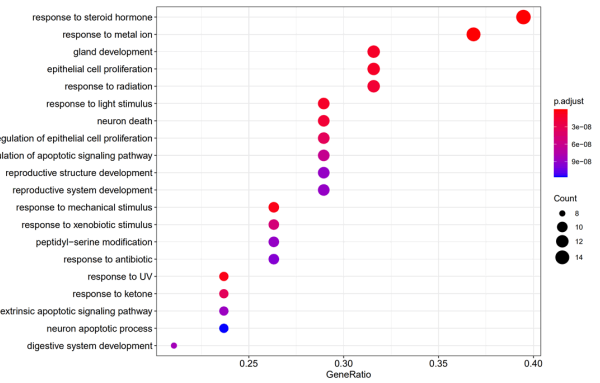
CC components included: cyclin-dependent protein kinase holoenzyme complex, serine/threonine protein kinase complex, protein kinase complex, nuclear chromatin, transferase complex, transferring phosphorus-containing groups, basal plasma membrane, membrane raft, membrane microdomain, membrane region, vesicle lumen, spindle, chromosomal region, basal part of cell, platelet alpha granule lumen, and condensed chromosome.

MF components included: nuclear receptor activity, transcription factor activity, direct ligand regulated sequence-specific DNA binding, steroid hormone receptor activity, ubiquitin-like protein ligase binding, cysteine-type endopeptidase activity involved in apoptotic process, RNA polymerase II transcription factor binding, ubiquitin protein ligase binding, NF-κB binding, steroid hormone receptor binding, steroid binding, estrogen receptor binding, cyclin-dependent protein serine/threonine kinase regulator activity, nuclear hormone receptor binding, p53 binding, hormone receptor binding, ATPase binding, β-catenin binding, histone kinase activity, activating transcription factor binding, and kinase regulator activity. According to dotplots, the order of the gene ratio of GO items in the barplots can be intuitively seen from high to low.

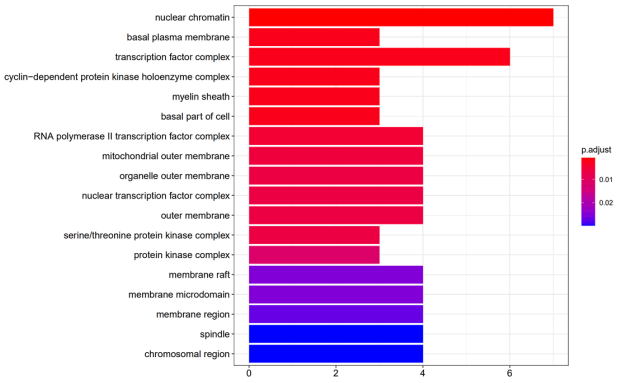
From KEGG pathway analyses: at $P<0.05$, 90 pathways were identified. We screened the most significant top 20 pathways and drafted a barplot and dotplot (**Figure 4**). The intersecting signal pathways implicated as possible codonopsis treatment for esophageal cancer

A BP


response to steroid hormone
response to metal ion
response to UV
response to mechanical stimulus
response to light stimulus
gland development
epithelial cell proliferation
response to radiation
neuron death
response to ketone
regulation of epithelial cell proliferation
response to xenobiotic stimulus
regulation of apoptotic signaling pathway
digestive system development
extrinsic apoptotic signaling pathway
reproductive structure development
peptidyl−serine modification
reproductive system development
response to antibiotic
neuron apoptotic process
0
5
10
15
p.adjust
3e−08
6e−08
9e−08


response to steroid hormone
response to metal ion
gland development
epithelial cell proliferation
response to radiation
response to light stimulus
neuron death
regulation of epithelial cell proliferation
regulation of apoptotic signaling pathway
reproductive structure development
reproductive system development
response to mechanical stimulus
response to xenobiotic stimulus
peptidyl−serine modification
response to antibiotic
response to UV
response to ketone
extrinsic apoptotic signaling pathway
neuron apoptotic process
digestive system development
0.25
0.30
0.35
0.40
GeneRatio
p.adjust
3e−08
6e−08
9e−08
Count
8
10
12
14

B CC


nuclear chromatin
basal plasma membrane
transcription factor complex
cyclin−dependent protein kinase holoenzyme complex
myelin sheath
basal part of cell
RNA polymerase II transcription factor complex
mitochondrial outer membrane
organelle outer membrane
nuclear transcription factor complex
outer membrane
serine/threonine protein kinase complex
protein kinase complex
membrane raft
membrane microdomain
membrane region
spindle
chromosomal region
0
2
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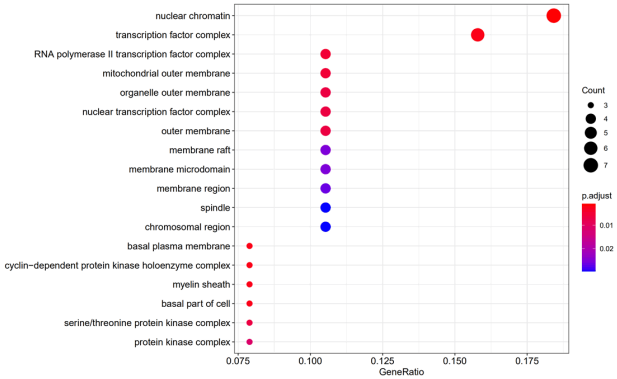
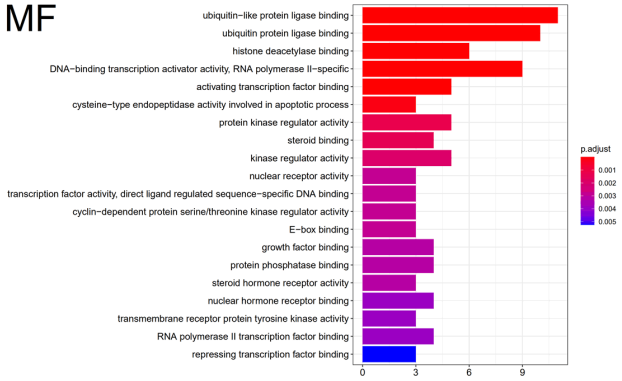
0.02


nuclear chromatin
transcription factor complex
RNA polymerase II transcription factor complex
mitochondrial outer membrane
organelle outer membrane
nuclear transcription factor complex
outer membrane
membrane raft
membrane microdomain
membrane region
spindle
chromosomal region
basal plasma membrane
cyclin−dependent protein kinase holoenzyme complex
myelin sheath
basal part of cell
serine/threonine protein kinase complex
protein kinase complex
0.075
0.100
0.125
0.150
0.175
GeneRatio
Count
3
4
5
6
7
p.adjust
0.01
0.02

C MF


ubiquitin−like protein ligase binding
ubiquitin protein ligase binding
histone deacetylase binding
DNA−binding transcription activator activity, RNA polymerase II−specific
activating transcription factor binding
cysteine−type endopeptidase activity involved in apoptotic process
protein kinase regulator activity
steroid binding
kinase regulator activity
nuclear receptor activity
transcription factor activity, direct ligand regulated sequence−specific DNA binding
cyclin−dependent protein serine/threonine kinase regulator activity
E−box binding
growth factor binding
protein phosphatase binding
steroid hormone receptor activity
nuclear hormone receptor binding
transmembrane receptor protein tyrosine kinase activity
RNA polymerase II transcription factor binding
repressing transcription factor binding
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3
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9
p.adjust
0.001
0.002
0.003
0.004
0.005

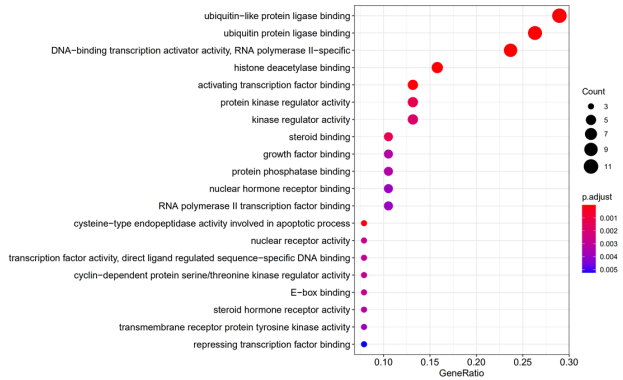
ubiquitin−like protein ligase binding
ubiquitin protein ligase binding
DNA−binding transcription activator activity, RNA polymerase II−specific
histone deacetylase binding
activating transcription factor binding
protein kinase regulator activity
kinase regulator activity
steroid binding
growth factor binding
protein phosphatase binding
nuclear hormone receptor binding
RNA polymerase II transcription factor binding
cysteine−type endopeptidase activity involved in apoptotic process
nuclear receptor activity
transcription factor activity, direct ligand regulated sequence−specific DNA binding
cyclin−dependent protein serine/threonine kinase regulator activity
E−box binding
steroid hormone receptor activity
transmembrane receptor protein tyrosine kinase activity
repressing transcription factor binding
0.10
0.15
0.20
0.25
0.30
GeneRatio
Count
3
5
7
9
11
p.adjust
0.001
0.002
0.003
0.004
0.005

Figure 3. Gene Ontology (GO) analyses. (A) Biologic process, (B) cellular component, and (C) molecular function. Barplots: Y-axis letters represent GO terms. The X-axis shows enriched genes in GO terms. The wider the horizontal bar, the more enriched genes there are, and the redder the dot, the smaller the *P* value. Dotplots: letters on the Y-axis represent GO terms. The X-axis shows gene ratios enriched in GO terms. The larger the dot, the more enriched genes, and the redder the dot, the lower the *P* value.

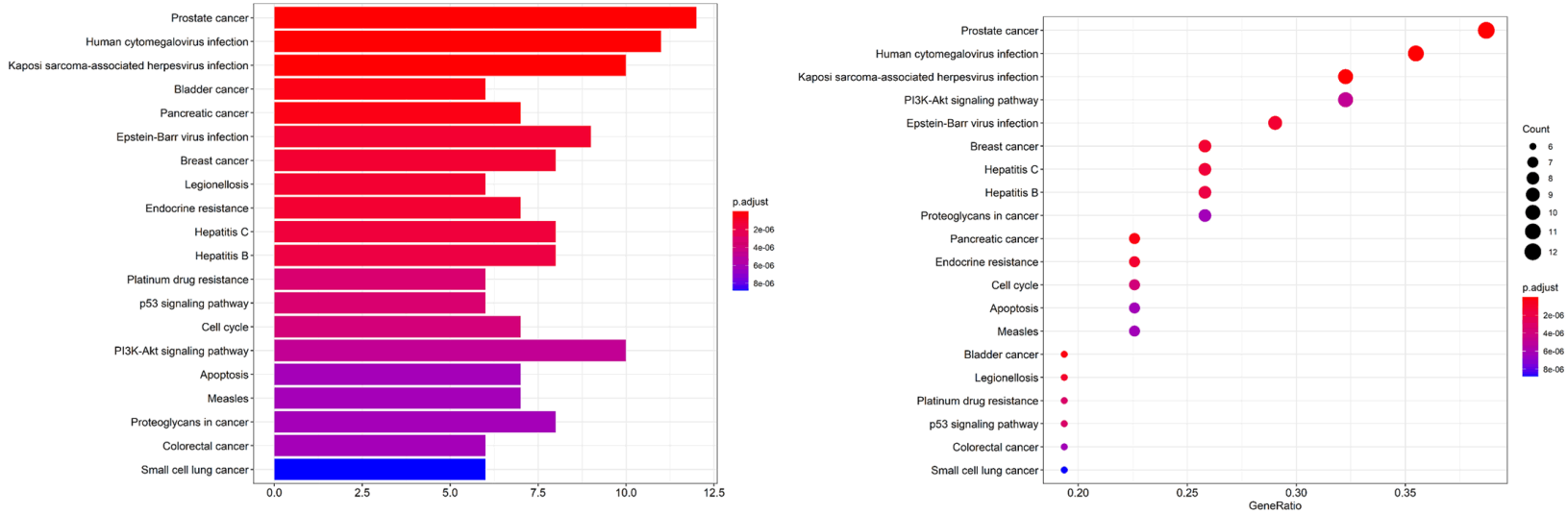

Figure 4. Key codonopsis pathways implicated in potential esophageal cancer treatments. Barplots: Y-axis letters represent Kyoto Encyclopedia of Genes and Genomes (KEGG) names. The X-axis shows the number of enriched KEGG pathways. The wider the horizontal bar, the more enriched genes, and the redder the dot, the lower the *P* value. Dotplots: letters on the Y-axis represent KEGG pathways. The X-axis shows gene ratios enriched in KEGG pathways. The larger the dot, the more enriched genes, and the redder the dot, the lower the *P* value.

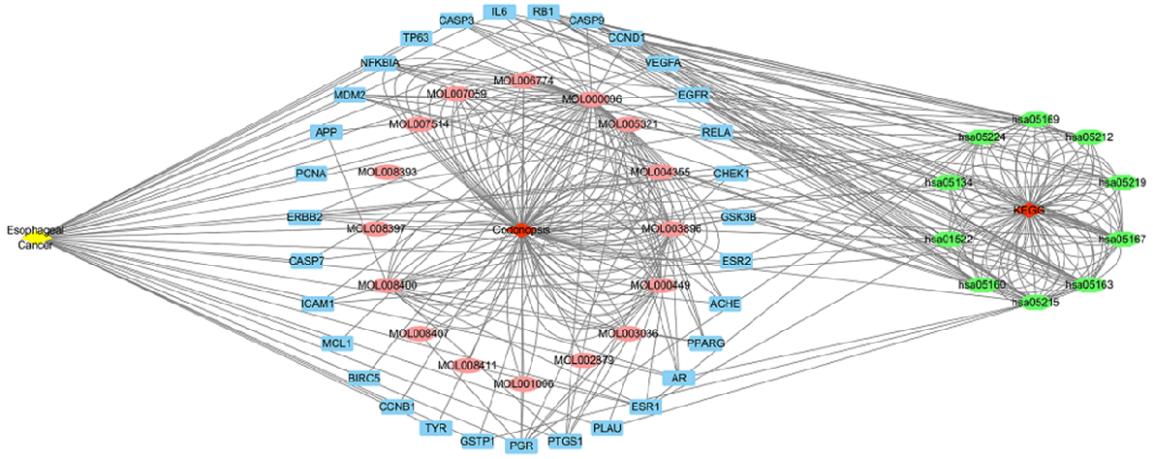

Figure 5. Network diagram of "disease-drug-compound-target-pathways" related to codonopsis and esophageal cancer. The yellow diamond represents esophageal cancer, the red diamond represents codonopsis, and the purple diamond represents KEGG pathways. The pink circles represent codonopsis compounds, blue rectangles represent intersecting gene targets of drugs and disease, and green hexagons represent pathways. The gray lines represent relationships between disease, drugs, compounds, targets, and pathways.

were: prostate cancer, human cytomegalovirus infection, Kaposi sarcoma-associated herpesvirus infection, bladder cancer, pancreatic cancer, Epstein-Barr virus infection, breast cancer, Legionellosis, endocrine resistance, Hepatitis C, Hepatitis B, platinum drug resistance, p53 signaling pathway, cell cycle, PI3K-Akt signaling pathway, apoptosis, measles, proteoglycans in cancer, colorectal cancer, and small cell lung cancer. According to a dotplot, the ranking of the enriched gene numbers of the signal pathways in the barplot can be seen directly.

Constructing a "disease-drug-component-target-pathway" network

We used Cytoscape software to build a "disease-drug-component-target-pathway" network (**Figure 5**). This showed codonopsis related multi-component, multi-target, and multi-pathway mechanisms for esophageal cancer treatment.

Discussion

In recent years, esophageal cancer treatments using innovative clinical drugs have been continuously improving. However, studies have also suggested that medicinal herbs have great potential as treatment [17]. In this study, we used network pharmacology to explore potential mechanisms underlying codonopsis for esophageal cancer. The approach uses genomics, proteomics, bioinformatics and other similar databases, after systematic analyses at the molecular level, to identify targets of the main components in medicinal herbs. Visual analysis of this information also helps clarify and provide insight for medicinal herb mechanisms, and medicinal herb research, respectively.

Using literature-based network pharmacology methods, we identified 21 high activity codonopsis compounds and 31 intersecting codonopsis-esophageal cancer targets. Based on these targets, a PPI network diagram was constructed, GO and KEGG pathway analyses performed, and a "disease-drug-component-target-pathway" network constructed to visually analyze potential codonopsis mechanisms comprising multiple components, multiple targets, and multiple pathways for esophageal cancer treatment.

GO analyses, with respect to therapeutic influences in esophageal cancer, suggested codonopsis was involved in responses to steroid hormones, cellular response to steroid hormone stimulus, response to UV, and response to xenobiotic stimulus. Previously, positive associations between steroid hormone levels and esophageal cancer radiotherapy side effects were identified [18]. Khayer *et al.* proposed that tissue responses to UV-A were

related to the expression of some biomarkers in oral cancer, and that esophageal and oral cancer may have a common set of biomarkers, thereby indirectly associating UV-A reaction processes with esophageal cancer biologic processes [19]. Genetic polymorphisms in xenobiotic metabolizing enzymes were associated with esophageal cancer [20]. From the CC component of GO enrichment analyses, codonopsis exerted regulatory roles on esophageal cancer by the cyclin-dependent protein kinase holoenzyme complex, serine/threonine protein kinase complex, and/or the protein kinase complex. The neddylation inhibitor, MLN4924 induced G2 cell cycle arrest, DNA damage, and sensitized esophageal squamous cell carcinoma cells to cisplatin, and also the cyclin-dependent protein kinase holoenzyme complex affected the development and treatment of esophageal cancer [21]. Zhu *et al.* reported that the recombinase, RAD51, which bound the serine/threonine protein kinase, CHK1, regulated CHK1 stability by autophagy to promote esophageal squamous cell growth [22]. Li *et al.* proposed that the protein kinase complex affected esophageal cancer cell migration and invasion [23]. In the MF component from GO enrichment analyses, codonopsis appeared to have a role in nuclear receptor activity, transcription factor activity, direct ligand regulated sequence-specific DNA binding, and steroid hormone receptor activity with respect to esophageal cancer treatment. Previous studies reported that nuclear receptor activity was related to esophageal cancer cell invasion [24], transcription factor activity, and direct ligand regulated sequence-specific DNA binding were related to esophageal cancer occurrence [25], and steroid hormone receptor activity had regulatory roles during esophageal cancer biologic processes [26].

From KEGG pathway analyses, signal pathways, possibly mediated by the effects of codonopsis on esophageal cancer, included p53 signaling and PI3K-Akt signaling pathways. Xu *et al.* identified SASS6 as a potentially new tumor marker and treatment target for esophageal squamous cell carcinoma, as it promoted esophageal cancer cell proliferation by inhibiting p53 signaling [27]. In recent years, several studies identified aberrant PI3K/Akt signaling in esophageal cancer occurrence, development, and radiosensitivity [28-31].

Using network pharmacology, we identified some of the complex molecular mechanisms underpinning codonopsis as a treatment for esophageal cancer, comprising multiple components, multiple targets, and multiple pathways. Codonopsis may elicit therapeutic effects on esophageal cancer through intrinsic compounds, targets, and pathways that interact with esophageal cancer mechanisms. Our study provides a theoretical basis and new research directions for novel drug development for this disease. However, our data were derived from public databases, which may not have been updated with the most recent advances. Therefore, databases must publish the latest data and experimental results to facilitate a better understanding of plant/herb functions for treating disease.

Disclosure of conflict of interest

None.

Address correspondence to: Liang Tang, Department of Stomatology, Cangzhou Medical College, 39 Jiuhe West Road, Yunhe District, Cangzhou 061000, Hebei, China. Tel: +86-13731735678; Fax: +86-317-5679126; E-mail: tangliang19811-19@163.com

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