



## Mechanisms of Ginseng in Pancreatic Cancer Metastasis: A Network Pharmacology Analysis



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### Keywords

*ginseng;*  
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### Abstract

It has been shown that ginsenosides can inhibit proliferation, migration, and invasion of pancreatic cancer (PC) cells, and promote apoptosis of PC cells. However, the potential mechanisms of ginseng in treating PC metastasis (PCM) have not been fully elucidated. In this study, we employed an integrated bioinformatics approach to network pharmacology analysis. By selecting common targets of diseases and drugs, a drug-component-target-disease network was constructed to analyze the biological functions and signaling pathways involved in the targets. A total of 6 PC samples were included, which were divided into the primary PC group (PANC-1, n=3) and metastatic PC group. A total of 9263 differentially expressed genes (DEGs) and 14 PC target genes were identified. According to the network pharmacology analysis, we found that ginsenoside Rg3 was associated with the treatment of PCM and identified 6 potential targets. Among them, CD44, EGFR, KRAS, and PRNP were the main DEGs related to the treatment of PC by ginsenoside Rg3. These genes were mainly enriched in the Proteoglycans in the Cancer pathway, and KRAS, EGFR, and CD44 were upregulated in the pathway, which may be affected by the ginsenoside Rg3. This provides a new direction for further research on the mechanisms of ginseng in PCM.

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## 1 Introduction

Pancreatic cancer (PC) is a highly malignant digestive tract tumor with a poor prognosis and a very low 5-year survival rate (Li et al., 2022). According to the 2020 global cancer statistics, PC is one of the leading causes of cancer-related deaths worldwide, with the number of deaths almost equaling the number of cases (Sung et al., 2021). Multiple factors, including environmental and lifestyle factors (Rawla et al., 2019) alcohol, high-fat diet, high blood sugar (Li et al., 2012), and genetic mutations (Hu et al., 2019) can promote the occurrence and progression of PC. However, most PC patients are already in advanced stages at the time of diagnosis, and PC patients often have no symptoms in the early stages, making them difficult to detect. Only 5% of PC cases are diagnosed in the early stages (Klein et al., 2013; Lowenfels & Maisonneuve, 2006).

Currently, surgical resection, radiation therapy, and chemotherapy are the main choices for PC treatment. However, due to the complex tumor microenvironment of PC and the high invasiveness and metastasis of PC cells, 80% of PC patients are not suitable for surgery. The pharmacological effects of radiation or chemotherapy are limited and can only prolong the patient's life without curing PC (Wang et al., 2022). Unfortunately, regardless of whether surgery is performed, 80% of PC patients ultimately die from tumor metastasis. The liver is the most common site of PC metastasis (PCM). When diagnosed with liver metastases, the average survival time of patients is only 3-6 months. Currently, interventional therapy is still limited in the treatment range of some liver metastases near large blood vessels, diaphragm, gastrointestinal tract, or gallbladder. Even worse, as first-line treatment, chemotherapy, which includes some effective but rare drugs, may cause systemic damage to patients and even have fatal risks (Philip et al., 2020; Suker et al., 2016). Therefore, there is an urgent need to find new potential therapeutic drugs.

Traditional medicine has a history of thousands of years, and traditional Chinese medicine (TCM) has become a widely accepted mainstream form of beneficial complementary and alternative therapy for cancer patients (Xiang et al., 2019). Some natural plant medicines, such as paclitaxel, vinblastine, and podophyllotoxin, have been successfully used in clinical practice for many years (Fedoros et al., 2018; Zhou et al., 2022). In recent years, natural products have received increasing attention due to their potential anti-cancer functions. Ginseng is a drug with good therapeutic effects and safety in cancer treatment (Nag et al., 2012), and its main active ingredient is ginsenosides. Ginsenoside Rg3 and ginsenoside Rh2 are two very representative monomers of ginsenosides. Studies have shown that ginsenoside Rg3 can increase the sensitivity of gemcitabine to PC by reducing the instability of TSPYL2 mediated by ZFP91 (Pan et al., 2022). In early studies, ginsenoside Rh2 was found to inhibit the proliferation, migration, and invasion of human PC cell line Bxpc-3 and induce apoptosis (Tang et al., 2013). However, the mechanism of action of ginseng drugs in metastatic PC has not been clearly defined.

To determine the mechanism of action of ginseng in PCM, this study used a network pharmacology analysis method to systematically study samples from two groups of PC patients and healthy individuals. Network pharmacology analysis will combine laboratory and clinical queries with data processing to help us find the complex relationship between ginseng and PC and provide a basis for subsequent pharmacological experimental research (Sheng et al., 2014).

## 2 Materials and Methods

### *Retrieval of active ingredients and prediction of drug targets*

Firstly, active ingredients (small molecular compounds) corresponding to ginseng were searched and downloaded from SymMap (<https://www.symmap.org/>) and HERB database (<http://herb.ac.cn/>),

respectively. Then, potential target proteins corresponding to these small molecules were identified from STITCH database (<http://stitch.embl.de/>).

#### *Prediction of disease targets*

Six PC samples were included from the Gene Expression Omnibus (GEO) dataset GSE149103, which were divided into the primary PC group (PANC-1, n=3) and metastatic PC group (Capan-1, n=3). Differential gene expression analysis was performed using a ballgown (Frazee et al., 2014), package based on the grouping information, and differentially expressed genes (DEGs) were screened based on corresponding parameters ( $\log_2|FC| \geq 0.585$ ,  $P \leq 0.05$ ). Corresponding target genes were searched and downloaded from the DisGeNET database (<http://www.disgenet.org/home/>). Finally, gene expression data was downloaded from GEO.

#### *Construction of drug-ingredient-target-disease network*

Firstly, the intersection of small molecules corresponding to ginseng in SymMap and HERB databases, as well as drug-related target genes were identified. Then, the intersection of PC target genes and DEGs was obtained to obtain the final disease-related target genes. Finally, the intersection of drug-related target genes and disease-related target genes was obtained to obtain target genes related to both drug and disease, thus obtaining the drug-ingredient-target-disease relationship pairs, and a network diagram was constructed using Cytoscape (Ernawati et al., 2022).

#### *Functional enrichment analysis of genes*

In this study, we performed functional enrichment analysis of DEGs and target genes based on the Gene Ontology (Ashburner et al., 2000), database and KEGG PATHWAY DATABASE (Kanehisa et al., 2000), of biochemical pathways. Statistical algorithms (Fisher's exact test) were used to identify functional terms that were significantly enriched with a group of genes and had the strongest association with them. Each functional term in the analysis results corresponded to a statistical value (P-value) indicating its significance. The smaller the P-value, the stronger the association between the functional term and the input genes.

#### *Prediction of Protein-Protein Interaction (PPI) network*

The candidate genes were analyzed for protein-protein interaction (PPI) using the STRING (Szklarczyk et al., 2019) online tool. The threshold for protein-protein interaction was set to Required Confidence (combined score) > 0.4. The PPI relationship pairs obtained were then analyzed using Cytoscape to identify the topological structure of the PPI network. Based on the established biological networks, it is known that most biological networks follow the properties of scale-free networks, and therefore the connectivity degree analysis, a statistical measure commonly used in network analysis, was used to identify the hub proteins (He et al., 2006) that play a crucial role in the PPI network.

## **3 Results and Discussions**

### *3.1 Results*

#### *Acquisition of PC target genes*

We conducted a bioinformatics analysis on primary PC and metastatic PC groups, and a total of 9263 DEGs were screened, including 4115 upregulated DEGs and 5148 downregulated DEGs (Figure 1A). As shown in Figure 1B, we presented the heatmaps of the top 20 upregulated and downregulated genes. Compared with primary PC, genes such as *SERPINE1*, *VIM*, *LDHB*, *PPP1R14A*, and *DLL3* were upregulated in metastatic PC, while genes such as *TFF2*, *CXCL5*, *PLAT*, *RNASE1*, and *SPINK1* were downregulated in metastatic PC, and the differences were statistically significant ( $P < 0.001$ ). Then, all DEGs were subjected to GO and KEGG enrichment

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analyses. A total of 2765 entries were obtained in the GO enrichment analysis, including biological process (BP): 2194, cellular component (CC): 255, and molecular function (MF): 316. The top 15 entries for each type of analysis were selected for bioinformatics visualization (Figure 2A). "Positive regulation of cellular metabolic process" and "positive regulation of nitrogen compound metabolic process" were the major biological processes (BP) (Figure 2B). KEGG pathway enrichment analysis identified 128 signaling pathways, and the top 15 pathways were visualized (Figure 2C), mainly involving Hippo signaling pathway, Pathways in Cancer, Hepatocellular carcinoma, TNF signaling pathway, Proteoglycans in Cancer, and so on (Table S1).

#### *Prediction of target genes of ginseng and PC and construction of PPI network*

We performed a Venn diagram analysis of DEGs and the DisGeNET database to obtain 14 target genes for PC (Figure 3). A total of 415 ginseng effective compounds were mined and screened using SymMap and HERB databases. Then, we predicted the target genes of the 415 compounds using the STITCH database and obtained 4394 target genes. Six common target genes of PC and ginseng were selected for GO and KEGG pathway analysis. Furthermore, we constructed a drug-target-disease network using Cytoscape (Figure 4), which demonstrated the correlation between ginsenoside Rg3 and PC, as well as the correlation between six target genes and the major components of ginsenoside Rg3. Among the upregulated DEGs, *EGFR* was correlated with trans-resveratrol, spermidine, and Adenosine Triphosphate (ATP). *KRAS* was correlated with trans-resveratrol, ATP, and citric acid. *NTSR1* was correlated with pentadecylic acid, palmitic acid, and ATP. *CD44* was correlated with glucuronic acid and ATP. *PRNP* was correlated with trans-resveratrol. Among the downregulated DEGs, *GGT1* was correlated with methylselenocysteine in ginsenoside Rg3 (Wei et al., 2012).

The six target genes were imported into the STRING database to construct a PPI network. A total of four nodes and eight edges were found in the PPI network. The larger and darker the node, the greater the degree of the node. The sequence of protein interaction strength between genes and ginsenoside Rg3 was *CD44*, *EGFR*, *KRAS* and *PRNP* (Figure 5, Table 1).

#### *GO and KEGG enrichment analysis of shared target genes*

GO and KEGG enrichment analyses were performed on potential targets of ginseng treatment for metastatic PC in six individuals. The GO enrichment analysis generated a total of 198 entries, including 172 in BP, 25 in CC, and one in MF. The top 15 entries from each type of analysis were selected for visualization in bioinformatics (Figure 6A). The BPs mainly involved in the six target genes were related to learning or memory, cognition, negative regulation of the apoptotic process, negative regulation of programmed cell death, and negative regulation of cell death, which were mainly associated with the membrane raft (Figure 6B). The primary MF was protein heterodimerization activity. KEGG pathway enrichment analysis selected 38 signaling pathways, and the top 15 pathways were visualized (Figure 6C), mainly involving Proteoglycans in Cancer, Bladder cancer, Endometrial cancer, and MicroRNAs in cancer. The Proteoglycans in the Cancer pathway coincided with the enrichment pathway of DEGs in both primary PC and metastatic PC sample groups. Therefore, this pathway was chosen for mapping (Figure 7, Figure S1). The red markers in the figure represented the potential targets of ginseng intervention, including *KRAS*, *EGFR*, and *CD44*, all of which were up-regulated genes.

### *3.2 Discussion*

Currently, due to the uncertain optimal age and screening time for PC screening, at least one-third of PC patients are diagnosed at a locally advanced stage, and about 50% of PC patients already have distant metastasis at diagnosis (Mizrahi et al., 2020). However, current research suggests that PC is a multifactorial and multi-stage continuous process, and no well-established therapeutic mechanism has been established. In this study, we attempted to use network pharmacology analysis to explore the mechanisms of ginseng in treating metastatic PC. Previous studies have demonstrated that rare ginsenoside Rg3 is an effective inhibitor of PC cell invasion and is more likely to inhibit highly metastatic mouse tumor cells (Shinkai et al., 1996). Our results showed that the various components of ginsenoside Rg3 (trans-resveratrol, spermidine, GUP, etc.) might intervene in PCM by mediating the Proteoglycans in the Cancer pathway.

It is well known that the interaction between tumor cells and extracellular matrix (ECM) is the primary step in invasion and metastasis. Proteoglycans, a highly glycosylated glycoprotein, are the major macromolecules that make up the ECM. Many proteoglycans are key macromolecules that promote the biology of various types of cancer, including proliferation, adhesion, angiogenesis, and metastasis, thus affecting the progression of tumors (Wei et al., 2020). Weber et al. found that dimeric chondroitin sulfate is overexpressed in the ECM of PC tissues, inducing G1 arrest and thus inhibiting PC cell proliferation (Weber et al., 2001). Another proteoglycan-decorin has also been shown to have anti-proliferative effects on PC cells (Koninger et al., 2004). Combined with our results, the important role of this pathway in the treatment of PC can be confirmed.

Our results not only confirmed the importance of the Proteoglycans in the Cancer pathway in the treatment of metastatic PC but also suggested the mechanism of action of ginsenoside Rg3 in PCM. Through network pharmacology analysis and KEGG analysis, we identified three DEGs that might be regulated by ginsenoside Rg3 in the Proteoglycans in the Cancer pathway: *CD44*, *KRAS*, and *EGFR*. *CD44* is a complex transmembrane glycoprotein and a recognized marker of cancer stem cells, involved in tumor initiation, progression, and metastasis. Jiang et al. have demonstrated that *CD44* is expressed as a transmembrane glycoprotein in a subset of PC cells and is required for inducing epithelial-mesenchymal transition (EMT) and activation of invasive programs in PC (Jiang et al., 2015). Modulating *CD44* alternative splicing may affect PC occurrence (Lai et al., 2022). Consistent with our results, several studies have shown the regulatory ability of ginsenoside Rg3 on *CD44*, such as its inhibitory effect on the number of *CD44*<sup>high</sup> in breast cancer cells (Oh et al., 2019). We found that this may be associated with Glucuronic acid and ATP in ginsenoside Rg3. Analysis of d-glucuronic acid (GlcUA) in bile has a certain value for detecting PC, and *in vivo*, HMRS detection of GlcUA may help in the noninvasive diagnosis of PC (Bezabeh et al., 2009). However, there is currently no study reporting the specific mechanism of action of glucuronic acid on *KRAS*, and our findings need to be further studied in the future.

*KRAS* is a member of the RAS superfamily of proteins, and its mutations account for 85% of RAS gene mutations, making it a major contributor to cancer development. Nearly 90% of PCs have *KRAS* gene mutations (Liu et al., 2019). Our study suggested that *KRAS* gene expression was upregulated in metastatic PC, indicating that *KRAS* gene mutations promoted the development and metastasis of PC. We hypothesized that pentadecylic acid, palmitic acid, and ATP in ginsenoside Rg3 might be key to treating metastatic PC by targeting *KRAS*. The relationship between pentadecylic acid and PC is still unclear. A recent study showed that palmitic acid significantly decreased in Nudt7-knockout mouse PC models, which may promote the development of KrasG12D-driven colorectal cancer (Song et al., 2020). In PC, *KRAS* mutations alter the conformation of the *KRAS* protein, weaken its affinity to ATP, and affect cell proliferation and metastasis. Some studies are trying to use drugs to enhance the binding between *KRAS* and ATP, such as AMPK activators and ATP synthase activators (Moon et al., 2019).

*EGFR* is upstream of RAS in the regulation of cell growth, and once *KRAS* gene mutations occur, they will directly affect the efficacy of anti-tumor drugs targeting the *EGFR* gene (Boeck et al., 2013; Kim et al., 2011). In our study, *EGFR* was also upregulated in the Proteoglycans in the cancer pathway. The current findings are that *EGFR* is associated with advanced disease, poor survival, and disease metastasis. Yuan et al.'s study provided evidence that ginsenoside Rg3 could inhibit the proliferation of lung cancer cells, possibly by blocking the cell cycle in the G0/G1 phase through the EGFR/Ras/Raf/MEK/ERK pathway (Liang et al., 2021). In PC, the incidence of *EGFR* overexpression ranges from 30% to 89% and is considered a potential target for PC therapy (Verma et al., 2019). Our study results suggested that ginsenoside Rg3 might regulate *EGFR* expression by releasing trans-resveratrol, spermidine, and ATP, thereby affecting the progression of PC. This is a completely new finding and needs to be verified by a large number of trials.

## 4 Conclusion

In summary, our study found that ginseng primarily exerts its effects in metastatic PC through ginsenoside Rg3. Proteoglycans in Cancer might be the main ginsenoside Rg3-mediated pathway. This study provides a new and promising direction for the treatment of PCM and lays a foundation for future research.

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