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ORIGINAL RESEARCH

# Mechanisms of Panax Ginseng on Treating Sepsis by RNA-Seq Technology

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**Purpose:** To explore the potential active targets and mechanisms of Panax Ginseng in the treatment of sepsis using network pharmacology and RNA-seq technology.

**Patients and Methods:** Patients with sepsis and healthy volunteers were collected according to SEPSIS 3.0, and their peripheral blood was used for RNA-seq analysis. The active ingredients and targets of Panax Ginseng were obtained using the TCMSP database, PPI and GO analysis were performed for disease-drug intersection targets. Then, we used Meta-analysis to screen core genes. Finally, single-cell RNA-seq was used to perform cell localization analysis on core genes.

**Results:** RNA-seq analysis collected 4521 sepsis-related genes, TCMSP database obtained 86 Panax Ginseng active ingredients and their 294 active targets. PPI and GO analysis showed intersection targets were closely linked, and mainly involved in cellular response to chemical stress, response to drug and molecule of bacterial origin, etc. Then, core targets, IL1B, ALOX5, BCL2 and IL4R, were sorted by Meta-analysis, and all four genes have high expression in the sepsis survivor group compared to the sepsis non-survivor group; single-cell RNA-seq revealed that IL1B was mainly localized in macrophages, ALOX5 was mainly localized in macrophages and B cells, BCL2 was mainly localized in natural killer cells, T cells and B cells, IL4R was widely distributed in immune cells. Finally, according to the correspondence between the active ingredients and targets of Panax Ginseng in TCMSP database, we found that Ginsenoside rh2 regulates the expression of IL1B, Ginsenoside rf regulates the expression of IL1B and IL4R, Kaempferol regulates the expression of ALOX5 and BCL2, and β-sitosterol regulates the expression of BCL2.

**Conclusion:** Ginsenoside rh2, Ginsenoside rf, Kaempferol and β-sitosterol may produce anti-sepsis effects by regulating the expression of IL1B, ALOX5, BCL2 and IL4R, thus improving the survival rate of sepsis patients.

**Keywords:** Panax Ginseng, sepsis, RNA-seq, single-cell RNA-seq, network pharmacology

## Introduction

Sepsis is a dangerous complication of severe trauma, shock, burns, major surgery and other critical illness, which seriously threatens human life and health. The organ damage of sepsis involves multi-system and the mechanism is complex, as there is currently no specific effective treatment. Modern Chinese medicine generally agrees that sepsis belongs to the category of "heart disease", drugs with the effects of clearing heat-toxin, promoting blood circulation for removing blood stasis, invigorating qi for relieving desertion are mostly used, and good clinical results have been achieved.[1] Panax Ginseng is the dried root of ginseng of Araliaceae, which has the effect of immunity improvement, fatigue relief, memory improvement, blood circulation improvement, antioxidation.[2] From the perspective of Chinese Medicine, it also has the following effects: strengthening body resistance, invigorating spleen and benefiting lung, promoting production of body fluid and inducing sedation of the mind, it has preventive and control effects on a variety of diseases. The main ingredients of Panax Ginseng are Ginsenosides and Ginseng polysaccharides[3] Modern research has

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confirmed that Panax Ginseng has anti-cancer, anti-aging, antioxidant, hypoglycemic, improve the body's immunity, enhance memory, protect nerves and other medicinal properties.[4,5] In recent years, Panax Ginseng extracts are shown to have both bacteriostatic and bactericidal actions and seem to exert their effects by several mechanisms, including disruption of biofilms, inhibition of quorum-sensing and virulence factors, and altering motility.[6] However, as a Traditional Chinese medicine, Panax Ginseng has multi-component, multi-target and complex action mechanism, which has led to slow progress in the study of the mechanism of Traditional Chinese Medicine. Network pharmacology is an emerging discipline that links the "disease-target-drug" system as a whole, which comprehensively expounds the targets and mechanisms of drug action, adapts to the holistic treatment concept of Traditional Chinese medicine, it makes the material basis, target of action and regulatory path of Traditional Chinese medicine more clear and clear.[7]

In this study, we plan to use network pharmacology and multi-dimensional RNA sequencing, combined with a variety of public database resources, to explore the potential active targets and mechanisms of Panax Ginseng in the treatment of sepsis, and lay a foundation for further research on the mechanism of Panax Ginseng in the treatment of sepsis.

# Materials and Methods

## Clinical Sample Collection

Venous blood samples of 23 patients with sepsis and 10 healthy volunteers were collected from The Affiliated Hospital of Southwest Medical University between January 2019 and December 2020. Each patient and family member voluntarily entered this study and signed informed consent. This research complies with the Helsinki Declaration, and we obtained the approval of the Ethics Committee of The Affiliated Hospital of Southwest Medical University (No. ky2018029), with clinical trial No. ChiCTR1900021261. The included septic cases were diagnosed according to the latest SEPSIS 3.0 criteria. Excluding criteria involved (1) age less than 16 years or older than 80 years, (2) have had organ function failure or immune system disease or blood system disease, (3) patients or families declined to participate in this study. Blood samples were collected by PAXgene tubes according to company manuals, and human blood samples were stored in the biological sample bank of hospital.

## RNA-Seq Analysis

Total RNA was extracted from the peripheral blood using Trizol (Invitrogen, Carlsbad, CA, USA) according to Company Manual. We shaked the venous blood mixture for 15 seconds and then centrifuge at 12,000 rpm for 10 minutes. After centrifugation, we transferred the RNA residual upper aqueous phase to a new tube with an equal volume of solution, then centrifuged at 13,600 rpm for 20 minutes. After leaving the supernatant, we washed the RNA pellet twice with 1 mL 75% ethanol, then centrifuged the mixture at 13,600 rpm for 3 minutes to collect residual ethanol, followed by the pellet air dry for 10 minutes. Finally, we added 50 uL of DEPC-treated water to solubilize the RNA. Fragmented RNA was reversed into cDNA and amplified by polymerase chain reaction (PCR) to create a cDNA library. Subsequently, libraries were qualified and quantified using a Nano Drop and Agilent 2100 bioanalyzer (Thermo Fisher Scientific, MA, USA). Raw data obtained have been uploaded to the China National GeneBank DataBase (CNGBdb, https://db.cngb.org/), under the accession: CNP0002611.

## Screening of Differentially Expressed RNA

The data was filtered and normalized using the online iDEP95 platform[8] (http://bioinformatics.sdstate.edu/idep/), and the normalized data was subjected to box plot and principal component analysis (PCA). In transcriptome analysis, PCA reduces the dimension of large amount of gene expression data to a few unrelated principal components, it can identify outliers samples and screen out sample clusters with high similarity. Subsequently, we screened differentially expressed RNAs under the conditions of Fold Change (FC) $\geq 2$ and False Discovery Rate (FDR) $<0.05$.

## Screening of Active Ingredient and Target of Panax Ginseng

Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platfor[9] (TCMSP, http://tcmspw.com/tcmsp.php) is a commonly used pharmacological analysis tool for traditional Chinese medicine, the database includes information on drug components its oral bioavailability, drug similarity, intestinal epithelial permeability, blood-brain barrier, water solubility of natural compounds and active targets. By setting drug-likeness (DL) $\geq 0.18$, we obtained the active ingredients and targets of

Panax Ginseng from the TCMSP database. The Uniprot database[10] (https://www.uniprot.org/) was used to normalize ingredients and targets for subsequent analysis.

## Constructing of Ingredient-Target Network of Panax Ginseng

In order to further clarify the action targets and mechanism of Panax Ginseng in the treatment of sepsis, the intersection of Panax Ginseng active targets and sepsis differentially expressed RNAs was collected, the intersection targets were defined as potentially active targets of Panax Ginseng antisepsis. Cytoscape 3.8.2 was used to construct the active ingredients-intersection targets network of Panax Ginseng antisepsis to further clarify the relationship between ingredients and targets.

## PPI Analysis

The STRING Database (https://string-db.org/) is a commonly used protein-protein interaction (PPI) analysis platform that contains 14,094 organisms, more than 60 million proteins, and more than 20 billion interactions. We submit the intersection targets to STRING database, select "Homo sapiens" in the Organisms option, set the minimum required interaction score to 0.4, and hide disconnected nodes in the network.

## GO Annotation

Gene Ontology (GO) analysis includes three parts: biological process (BP), cellular component (CC), and molecular function (MF), which is a comprehensive analysis method of genetic big data. In order to visualize the functional enrichment of intersection targets, the first 20 gene sets of BP, CC and MF were enriched by GO analysis using R4.0.5, $p < 0.05$ was considered statistical significance.

## Meta-Analysis

In order to further evaluate the expression of intersecting targets in different groups, and to validate our results with public data. We searched and screened the sepsis datasets GSE54514,[11] GSE63042,[12] GSE95233[13] from GEO database (https://www.ncbi.nlm.nih.gov/geo/), and divided the data into sepsis survivor group (SV) and sepsis non-survivor group (NS).

## Single-Cell RNA-Seq

We collected 5 samples of Peripheral Blood Mononuclear Cell (PBMC) for 10× single-cell RNA-seq, which included 2 healthy volunteers, 1 patient with systemic inflammatory response syndrome, and 2 patients with sepsis. These data were quality controlled by Cell Ranger online platform, which integrates STAR[14] software to compare the reads to reference genome. Single-cell transcriptome sequencing uses transcript sequences combined with Unique Molecular Identifiers (UMI) and Cell Barcode to obtain the absolute value of each transcript molecule within a single cell. The dimensionality reduction algorithms used in this project are Mutual Nearest Neighbors (MNN) and t-distributed Stochastic Neighbor Embedding (t-SNE). The dimensionality reduction results based on MNN were visualized by t-SNE, and finally the optimal cell population was obtained. Marker gene is defined as a gene that is highly expressed in most cells of a given cell population and only a small fraction in the rest of cell population, at the same time the gene is significantly upregulated in this cell population relative to other cells. We artificially identify cell populations using selected marker genes to construct a single cell library associated with sepsis. Subsequently, the four core targets selected in this study, IL1B, ALOX5, BCL2 and IL4R, were submitted to the library to determine the cell line localization.

# Results

## Clinical Information of Samples

We performed a statistical analysis of clinical information from 23 septic patients and 10 normal controls, including sex, age, Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Scale (GCS) score, total number of leukocytes, neutrophil count, monocyte count, urea, total bilirubin, continuous variables are expressed as mean ± standard deviation. Non-paired T-tests were used for statistical analysis (Table 1). The results showed that the inflammatory indicators and organ function impairment indicators were significantly increased in the sepsis group.

**Table 1** Clinical Information of Samples

| Clinic Item | Sepsis (n=23) | Normal (n=10) | P value |
|---|---|---|---|
| Gender (F/M) | 9/14 | 4/6 | – |
| Age (years) | 58.09±2.37 | 51.70±3.69 | 0.15 |
| SOFA score | 5.87±0.63 | 0.00±0.00 | <0.00 |
| GCS score | 11.30±0.83 | 15.00±0.00 | 0.01 |
| WBC ($10^9$/L) | 13.57±2.00 | 6.36±0.55 | 0.03 |
| NEU ($10^9$/L) | 11.82±1.81 | 3,82±0.43 | 0.08 |
| MONO ($10^9$/L) | 1.57±0.51 | 0.36±0.03 | 0.13 |
| Urea (mmol/L) | 9.65±1.34 | 5.30±0.49 | 0.01 |
| TBIL (umol/l) | 51.00±21.47 | 14.30±1.43 | 0.27 |

**Notes**: In the included studies, 23 patients with sepsis and 10 normal controls were statistically analyzed, their sex, age, SOFA score, GCS score, total number of leukocytes, neutrophil count, monocyte count, urea, and total bilirubin levels were expressed as mean ± standard deviation.

## Screening of Differentially Expressed RNA

Box mapping and PCA analysis of mRNA found that the uniformity and intergroup differentiation of normal control samples and sepsis samples were good, and no outliers were found (Figure 1A and B). Then, we performed a differential

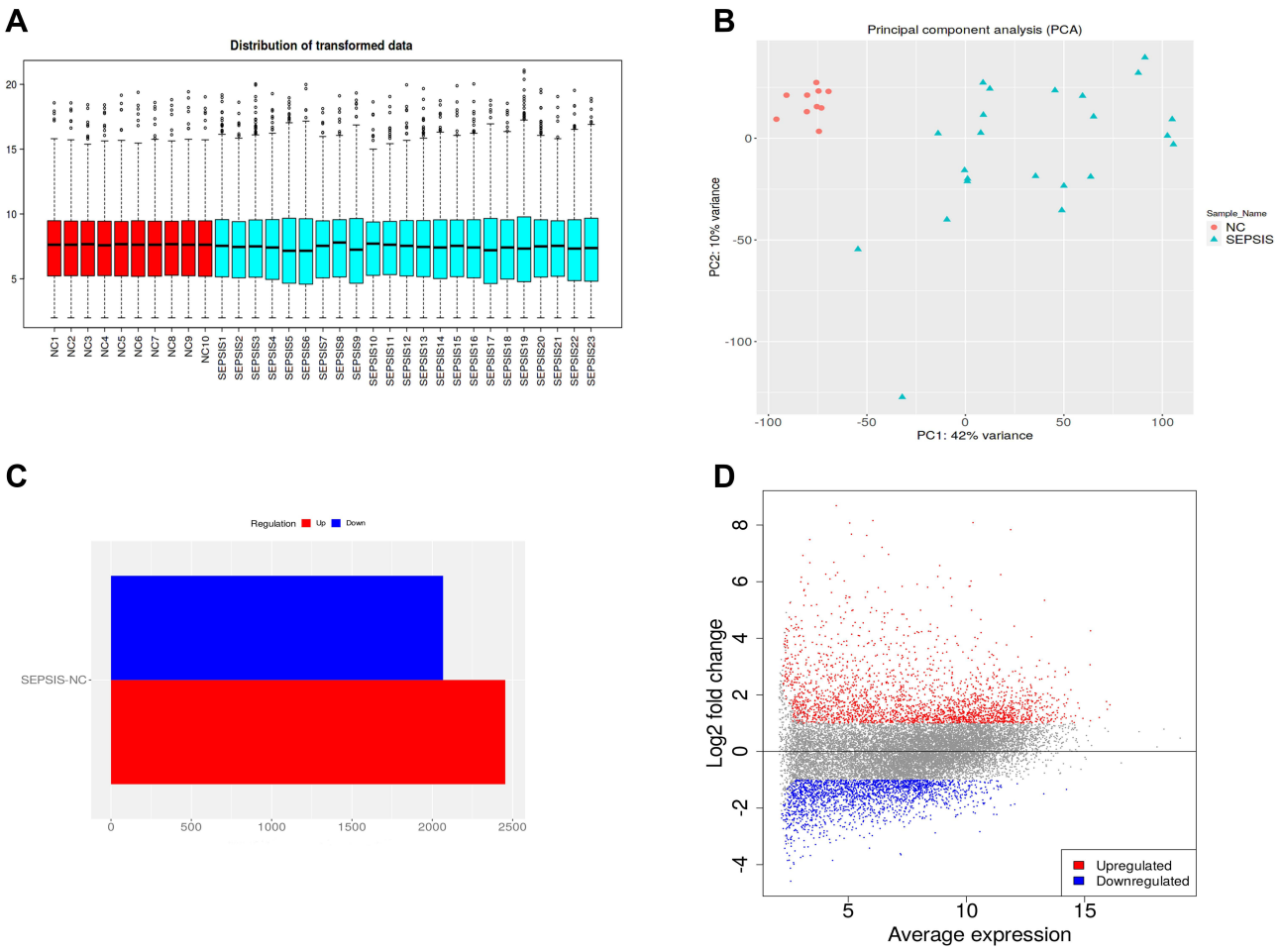


**Figure 1** Data quality control and differentially expressed RNA screening. (**A**) Box plot shows that the data of each sample are distributed at the same level after uniformization, which is comparable. (**B**) PCA analysis shows the two groups could be clearly distinguished, and there were no outlier samples. (**C**) The histogram shows the upregulated (red) and downregulated (blue) genes screened under the conditions of FC≥2 and FDR<0.05, the abscissa is the number of differentially expressed RNA, and the ordinate is the grouping. (**D**) Volcano plot shows differentiating up-regulated (red) and down-regulated (blue) genes, as well as undifferentiated genes (black), with the abscissa being the average expression and the ordinate being log2FC.

expression analysis of two sets of data, and 4521 differential RNAs were screened under the conditions of FC ≥2 and FDR <0.05, among them, 2454 RNAs were high-expressed and 2067 RNAs were low-expressed in sepsis group (Figure 1C and D).

## Screening of Active Ingredient and Target of Panax Ginseng

By setting DL ≥0.18, we obtained 86 active ingredients of Panax Ginseng. After removing non-human and irregular targets, 294 potential targets were obtained by correcting the official genetic abbreviations in Uniprot database. Twenty-seven intersecting targets were obtained from 294 active targets of Panax Ginseng with 4521 differentially expressed genes in sepsis (Figure 2A). These intersection targets correspond to 20 active ingredients of Panax Ginseng (Figure 2B).

## PPI Analysis

After removing the unconnected points, the PPI network consists of 25 nodes, of which IL1B, ALOX5, IL4R, CDK1, NFKBIA, etc. are located in the center of the network (Figure 3A), which may be a key target for Panax Ginseng in the treatment of sepsis. Cluster heat maps show that AR, HTR3A, NR3C2, BCL2, AKR1B1, DPP4 are lowly expressed in sepsis group, and IL1B, ALOX5, BCL2, IL4R, CDK1, MAOB, etc. are highly expressed in sepsis group (Figure 3B).

## GO Annotation

A total of 1033 gene function information were obtained in the GO annotation analysis of the intersection targets, of which 924 were enriched in BP, 16 were enriched in CC and 93 were enriched in MF. Intersecting targets are mainly involved in biological processes such as female pregnancy, cellular response to chemical stress, neurotransmitter catabolic process, multi-multicellular organism process, response to drug, negative regulation of ion transport, extracellular matrix disassembly, etc. (Figure 3C).

## Meta-Analysis

We used the sepsis datasets GSE54514, GSE63042, GSE95233 from GEO public database to conduct Meta-analysis at transcriptional level of the above intersection targets. The results showed that IL1B, ALOX5, BCL2, and IL4R have high expression in sepsis survivor group compared with sepsis non-survivor group, and the difference was statistically significant (Figure 4). The correspondence between the four potential targets and active ingredients of Panax Ginseng is shown in Table 2.

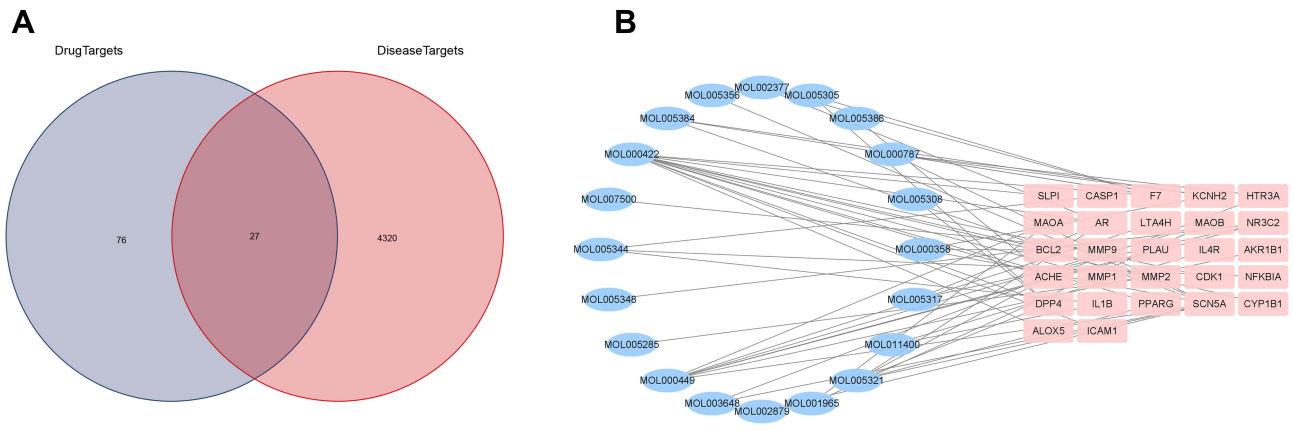


**Figure 2** Screening of active targets of Panax Ginseng for antisepsis. (**A**) Venn diagram shows that blue represent the 103 active targets of Panax Ginseng, pink is the 4347 differentially expressed RNA of sepsis, and 27 intersecting targets in the middle are potential active targets for Panax Ginseng in the treatment of sepsis. (**B**) The □ on the right of the ingredient-target network represent 27 intersection targets, the ○ on the left represent the 20 active ingredients of Panax Ginseng, and the lines represent the interaction of ingredients with targets.

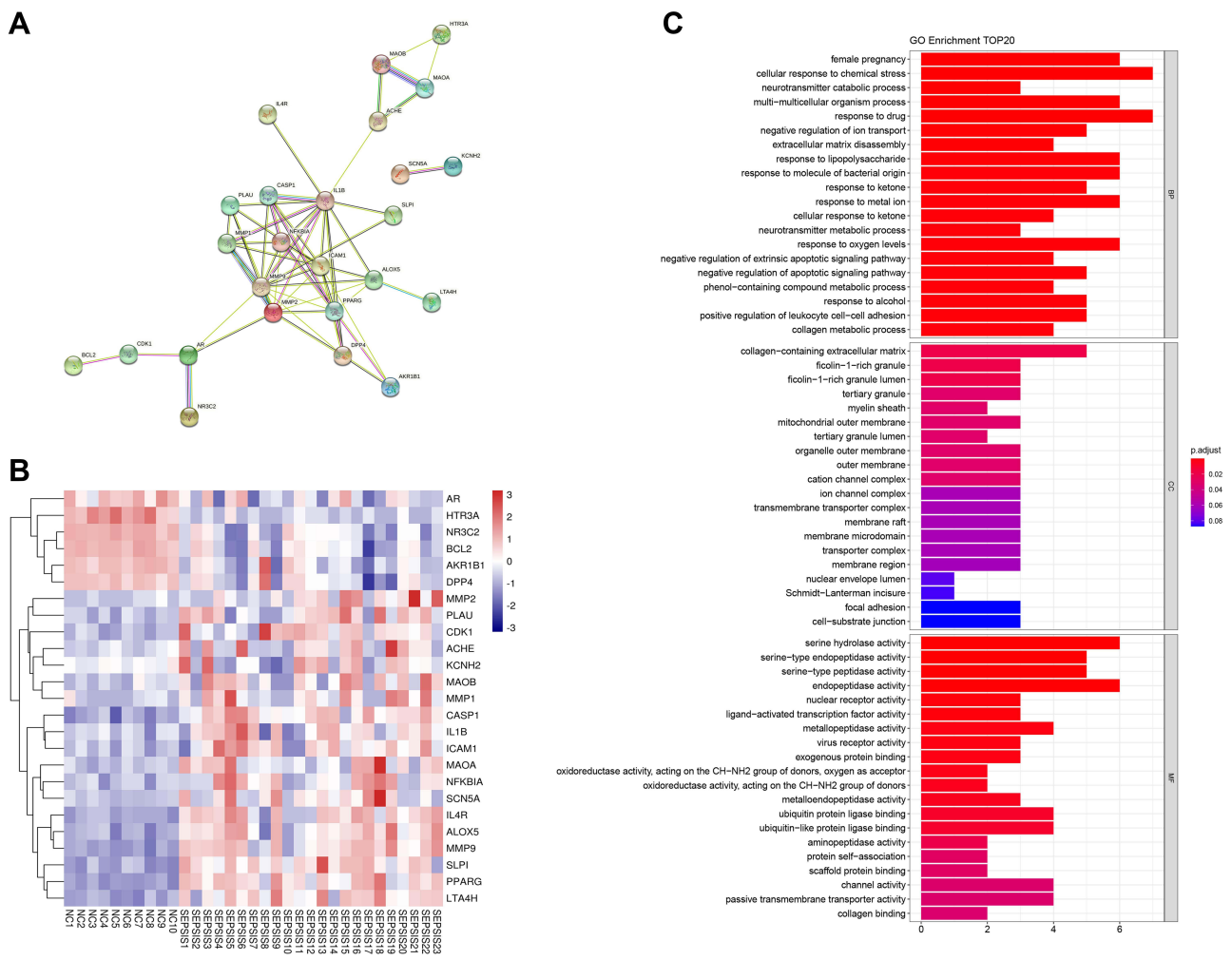


**Figure 3** Analysis of intersection targets. (**A**) PPI network shows that the intersection targets are closely connected, IL1B, ALOX5, IL4R, CDK1, NFKBIA, etc. are located in the center of the network. (**B**) Heat map shows that AR, NR3C2, BCL2, DPP4, etc. have low expression in sepsis group, and IL1B, ALOX5, BCL2, IL4R, etc. have high expression in sepsis group. (**C**) GO annotation shows that the intersection targets are mainly involved in biological processes such as female pregnancy, cellular response to chemical stress, neurotransmitter catabolic process, multi-multicellular organism process, response to drug, negative regulation of ion transport, etc.

## Single-Cell RNA-Seq

A total of 5 samples of single-cell transcriptome sequencing were completed in this analysis. The number of qualified cells for quality control of each sample is distributed in 4000 to 10,000. After dimensionality reduction and clustering, we sorted out 9 groups of cells, which were identified by the immune cell marker gene PTPRC, macrophage marker gene CD14, natural killer cell and T cell marker gene CD3E, and B cell marker gene CD79A (Figure 5A–C). Where 3 and 5 represent macrophages, 4 represent natural killer cells, 1, 2, 6 and 8 represent T cells, 7 represent B cells, and 9 represent platelets (Figure 5D). IL1B is mainly located in 3 and 5 cell groups, that is, macrophage cell lines, ALOX5 is mainly located in 3, 5 and 7 cell groups, namely macrophages and B cell lines, BCL2 is mainly located in the 1, 2, 4, 6, 7 and 8 cell groups, that is, natural killer cells, T cells, B cell lines, IL4R is widely distributed across all immune cells (Figure 6).

# Discussion

Presently, the clinical treatment of sepsis is mainly based on western medicine, long-term treatment has many problems such as antibiotic resistance, hormonal adverse effects, and high costs. With the concept of "holistic concept, treatment based on pattern differentiation, preventing the occurrence, development and recurrence of disease", Traditional Chinese Medicine has gradually exerted its advantages in the prevention and treatment of sepsis.[15] In recent years, the medical

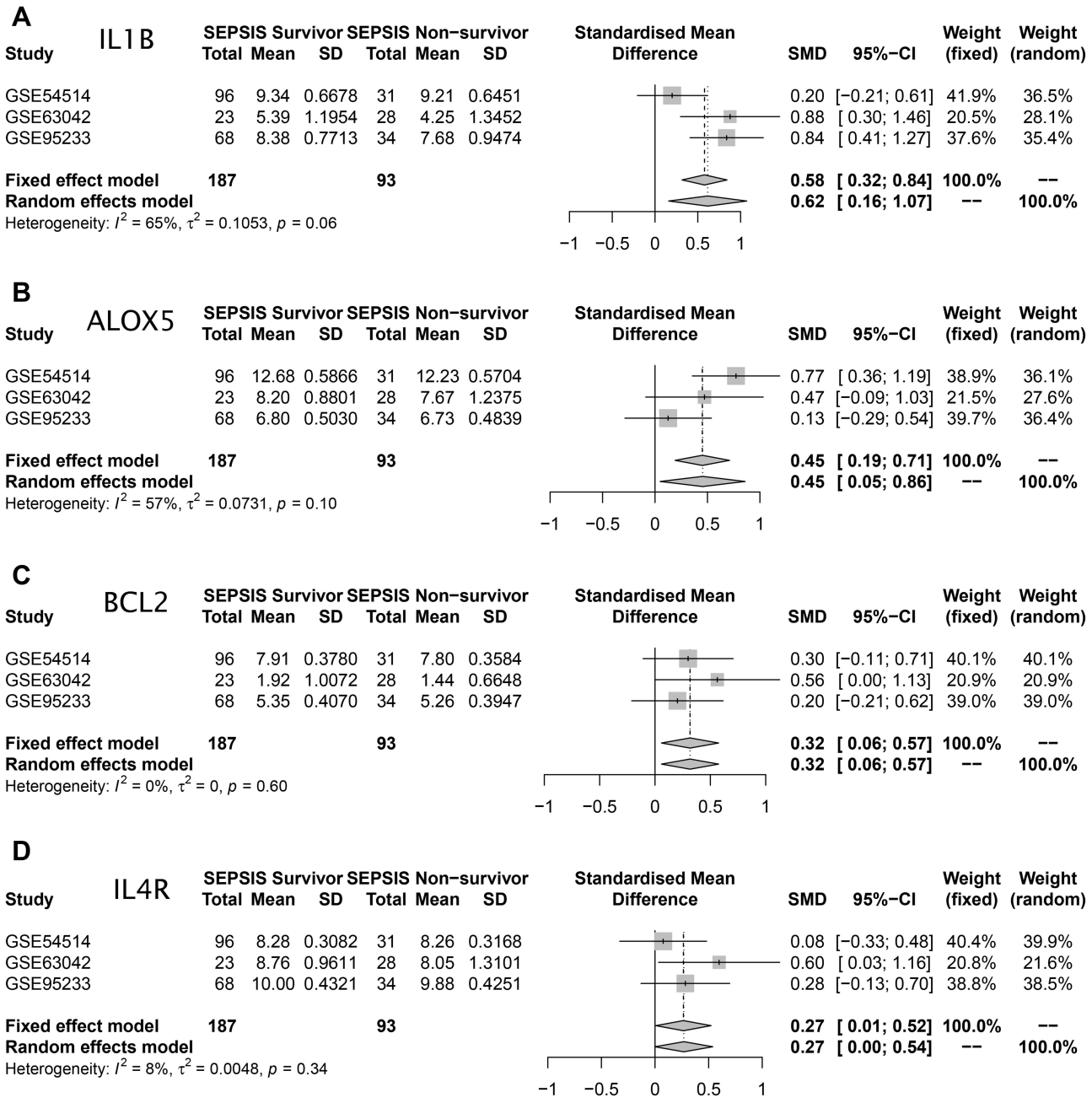


**Figure 4** Meta-analysis. (**A**–**D**), Meta-analysis of IL1B, ALOX5, BCL2 and IL4R based on the datasets GSE54514, GSE63042 and GSE95233 show that the expression of core genes were high in sepsis survivor group and low in sepsis non-survivor group, with a statistically significant difference (P < 0.05).

community has conducted a lot of research on the treatment of septic organ damage in Traditional Chinese Medicine, and has achieved remarkable achievements in both clinical and experimental research, especially some single-flavor Chinese Medicines and their active ingredients.[1] By establishing a mice model of Sepsis-associated encephalopathy (SAE) caused by cecal ligation and puncture (CLP), Li Yinjiao[16] et al found that Ginsenoside Rg1 improved the survival rate and ameliorated cognitive impairments partially through regulating cerebral inflammation and apoptosis, the action mechanism might be noncanonical beclin 1-independent autophagy pathway. By establishing a rat model of sepsis caused by burns, Huang Zengfeng[17] et al concluded that Ginsenosides can restore the activity of CD19 cells and natural killer cells in the peripheral blood of rats, and can also increase the proportion of CD45 cells and IL-2 levels that decline in peripheral blood during sepsis, and significantly improve the state of suppressed cellular immune function in the model

**Table 2** Active Ingredients and Targets of Panax Ginseng

| Ingredients | Mol-ID | MW | OB(%) | DL | Targets |
|---|---|---|---|---|---|
| Ginsenoside rh2 | MOL005344 | 622.98 | 36.32 | 0.56 | IL1B |
| Ginsenoside rf | MOL011400 | 801.14 | 17.74 | 0.24 | IL1B, IL4R |
| Kaempferol | MOL000422 | 286.25 | 41.88 | 0.24 | ALOX5, BCL2 |
| β-sitosterol | MOL000358 | 414.79 | 36.91 | 0.75 | BCL2 |

**Note**: Four active ingredients Ginsenoside rh2, Ginsenoside rf, Kaempferol, β-sitosterol and its Mol-ID.
**Abbreviations**: MW, molecular weight; OB, oral bioavailability; DL, drug-likeness and corresponding targets.

of burn sepsis,[18] but the specific mechanism is not clear. Therefore, through network pharmacology and RNA-seq technology, this study excavates the potential targets of Panax Ginseng for the prevention and treatment of sepsis, IL1B, ALOX5, BCL2 and IL4R. It lays foundation for the subsequent study of mechanism of Panax Ginseng in the treatment of sepsis.

Interleukin (IL) is a key factor in regulating cell signaling pathways and a major contributor to the inflammatory response.[19] Interleukin 1β (IL1B) is a vital mediator of inflammation and plays an important role in memory and emotion regulation, which is thought to be related to the pathogenesis of a variety of psychiatric disorders and cognitive function in normal people.[20] IL-1β has been associated with the elevated levels of inflammatory mediators and multiple inflammatory diseases.[21,22] Through RNA-seq, this study found IL1B have high expression in sepsis group compared to normal group. Meta-analysis found that IL1B have high expression in sepsis survivor group compared to sepsis non-survivor group, it is mainly localized in macrophage lines. Through network pharmacological analysis, it was determined that the important active Ginsenoside rh2 and Ginsenoside rf of Panax Ginseng can act on the target IL1B and produce antiseptic effects.

Arachidonate 5-lipoxygenase gene (ALOX5)-derived leukotrienes and lipoxy regulate immune cell activity and cytokine production play an important role in inflammation regulation.[23] The systemic lymphoid tissue circulating in shock patients is rich in arachidonic acid, which is the substrate for ALOX5 synthesis. ALOX5 is a rate-limiting enzyme in leukotriene synthesis and associated with leukotriene-induced inflammation and post-traumatic lung injury, therefore, ALOX5 can accelerate the development of pulmonary dysfunction.[24] ALOX5 plays a crucial role in mediating inflammatory response to maintain homeostasis, but certain allele variants of ALOX5 may increase the risk of atherosclerosis and coronary heart disease.[25] Through RNA-seq, this study found that ALOX5 have high expression in sepsis group compared to normal group. Meta-analysis found that ALOX5 have high expression in sepsis survivor group compared to sepsis non-survivor group, and ALOX5 is mainly localized in macrophage lines. Through network pharmacological analysis, it was determined that the active ingredient Kaempferol of Panax Ginseng can act on the target ALOX5 and produce antiseptic effects.

B cell lymphoma 2 (BCL2) is an anti-apoptotic protein that inhibits programmed cell death, its overexpression is associated with low sensitivity and low survival rate of chemotherapy in cancer patients.[26] BCL2 regulates mitochondrial integrity and apoptosis,[27] and it is a favorable prognostic factor for breast cancer, negatively correlated with clinical outcomes of breast cancer.[28] Through RNA-seq and bioinformatics analysis, this study found that BCL2 have low expression in sepsis group compared to normal group; Meta-analysis found that BCL2 have high expression in sepsis survivor group compared to sepsis non-survivor group; and mainly located in natural killer cells, T cells, B cell lines. Through network pharmacological analysis, it was determined that the active ingredients Kaempferol and β-sitosterol of Panax Ginseng can act on the target BCL2 and produce antiseptic effects.

Interleukin 4 (IL4) is a Th2 cytokine that signals through Interleukin 4 receptor (IL4R) to regulate lymphocyte proliferation and survival. IL4 also promotes phenotypic conversion of IL4R-positive breast cancer cells to enhance their ability to metastasize. Inhibition of IL4/IL4R signaling by cancer cells may limit the occurrence of metastatic disease.[29] Through RNA-seq, this study found that IL4R have high expression in sepsis group compared to normal group; Meta-analysis found that IL4R have high expression in sepsis survivor group compared to sepsis non-survivor group, and it is

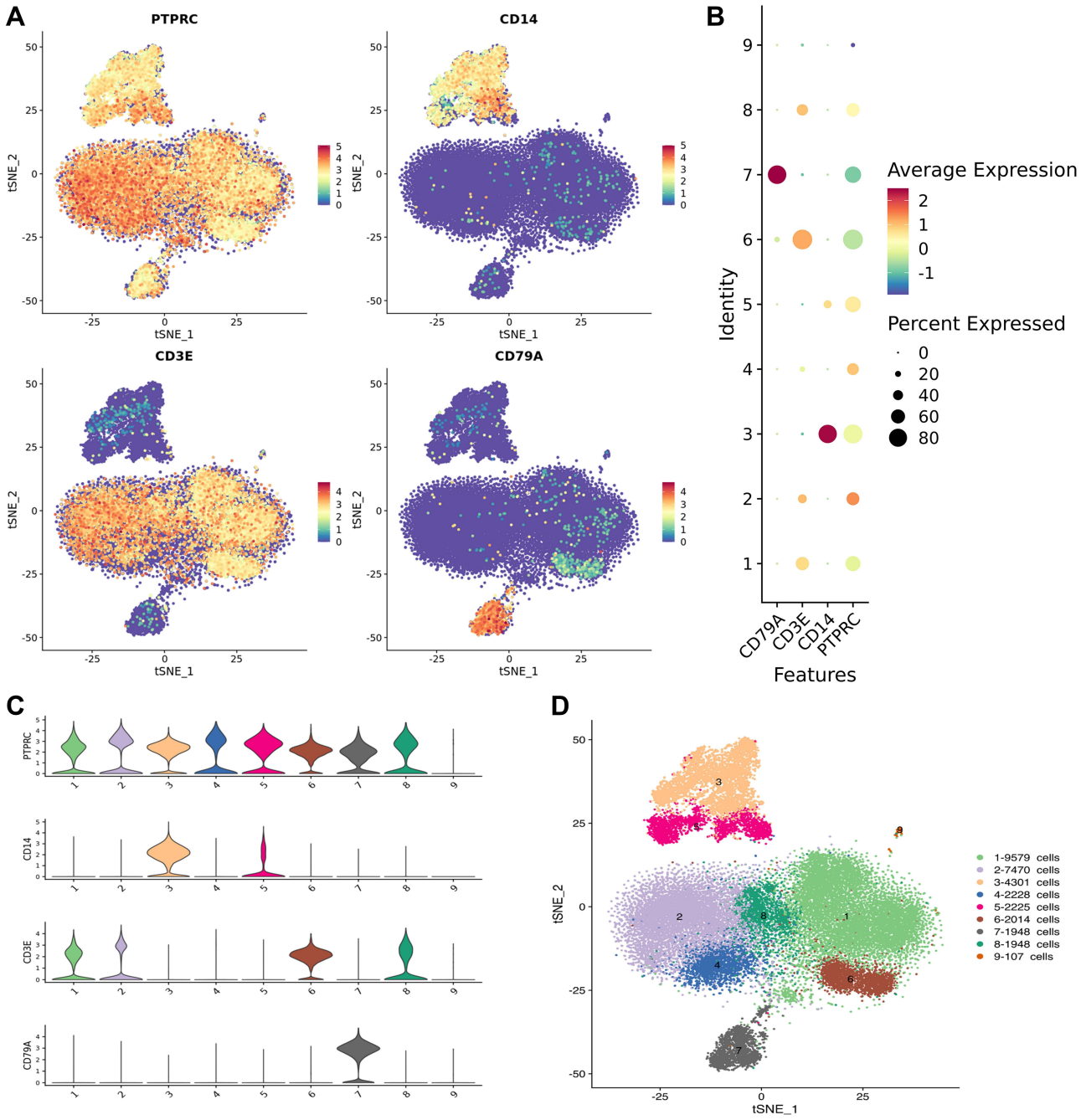


**Figure 5** Single Cell RNA-Seq. (**A**–**C**) Marker gene identification. PTPRC is an immune cell marker, CD14 is a macrophage marker, CD3E is a natural killer cell and T cell marker, CD79A is a B cell marker. (**D**) 9 types of cell populations were obtained by marker gene identification, of which 3 and 5 represent macrophages, 4 represent natural killer cells, 1, 2, 6 and 8 represent T cells, 7 represent B cells, and 9 represent platelets.

widely distributed in various immune cells. Through network pharmacological analysis, it was determined that the active ingredient Ginsenoside rf of Panax Ginseng can act on the target IL4R and produce antiseptic effects.

In summary, we used multidimensional RNA sequencing combined with network pharmacology technology to screen out the important active ingredients Ginsenoside rh2, Ginsenoside rf, Kaempferol and β-sitosterol of Panax Ginseng, which may produce antiseptic effects by regulating the expression of target genes IL1B, ALOX5, BCL2 and IL4R, thereby improving the survival rate of sepsis patients, providing a basis for the development of new drugs and the application of Panax Ginseng, and providing a theoretical foundation for clinical diagnosis and treatment of sepsis. The

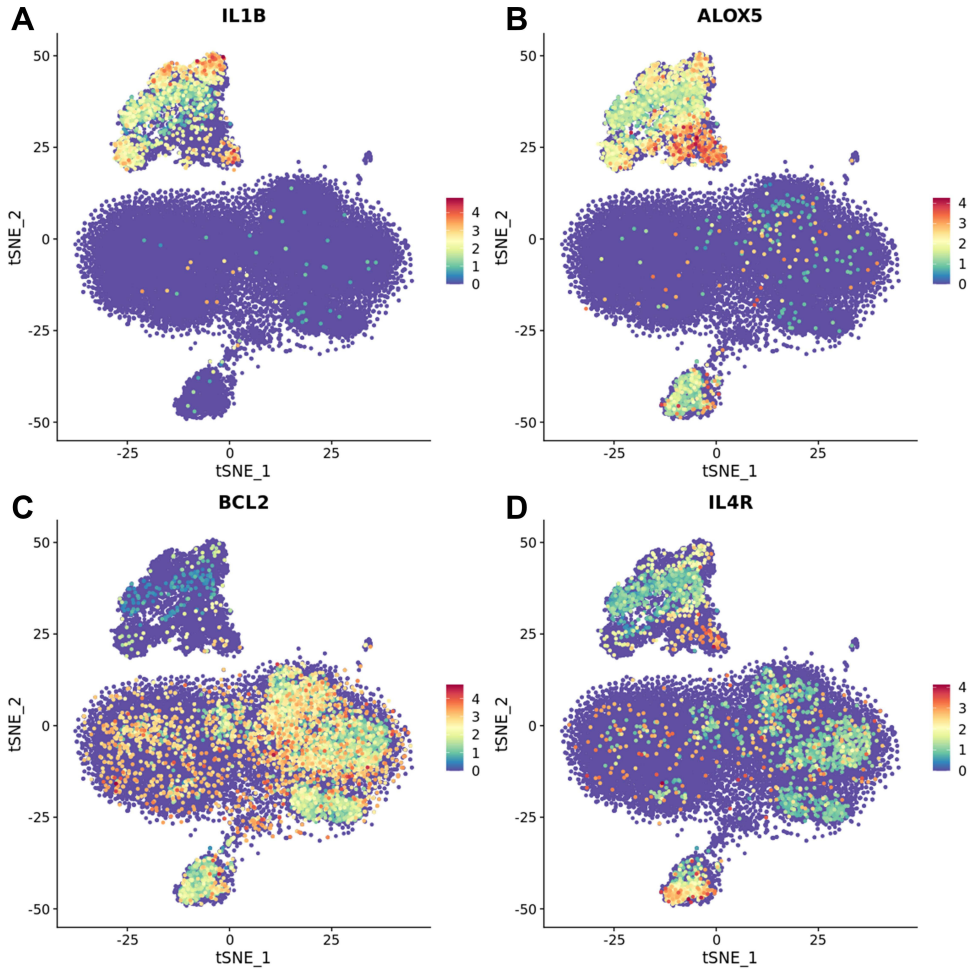


**Figure 6** Cell line localization analysis of target genes. (**A**–**D**) IL1B is mainly located in 3 and 5 cell groups, that is, macrophage cell lines; ALOX5 is mainly located in 3, 5 and 7 cell groups, namely macrophages and B cell lines; BCL2 is mainly located in the 1, 2, 4, 6, 7 and 8 cell groups, that is, natural killer cells, T cells, B cell lines; IL4R is widely distributed across all immune cells.

limitation of this study is that the network pharmacology method is an integrated analysis based on limited information in public database, and in order to further elucidate the pharmacological effects of Panax Ginseng, we need clinical trials and evidence-based medicine to investigate.

## Conclusion

1. High expression of IL1B, ALOX5, BCL2 and IL4R contributes to the survival of septic patients.
2. Ginsenoside rh2, Ginsenoside rf, Kaempferol and β-sitosterol regulate the expression of IL1B, ALOX5, BCL2.
3. Ginsenoside rh2, Ginsenoside rf, Kaempferol and β-sitosterol may improve the survival rate of septic patients and produce anti-sepsis effects.

## Data Sharing Statement

We intend to share individual deidentified participant data. The RNA-seq data from 23 septic patients and 10 healthy volunteers are available in the China National GeneBank

DataBase (CNGBdb) and can be found below: https://db.cngb.org/, under the accession: CNP0002611.

## Acknowledgments

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## Disclosure

The authors report no conflicts of interest in this work.

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