Application of network pharmacology and bioinformatics to study the effective components and mechanisms of Xuebijing in the treatment of acute pancreatitis

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Research Article

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Abstract

Xuebijing injection (XBJ), a traditional Chinese medicine, has been widely used in the treatment of acute pancreatitis (AP). However, the chemical composition and potential therapeutic mechanism is still unclear. Here, we used network pharmacology, bioinformatics analysis and molecular docking to investigate the main effective components, potential therapeutic targets and the molecular mechanisms of XBJ in treating AP. TCMSP and HERB database were used to identify components and potential targets of XBJ. GEO database were used to identify the differentially expressed genes (DEGs) between AP and normal samples. Genecards, DisGeNet, NCBI and CTD databases were used to search AP-related therapeutic targets. Then, the overlapped genes between potential targets of XBJ, DEGs and therapeutic targets of AP were selected and conducted for bioinformatics analysis. Finally, the binding activity between XBJ's main effective components and the core potential therapeutic targets of AP were analyzed by molecular docking. As a result, 122 potential therapeutic targets of XBJ for AP treatment were selected. Bioinformatics analysis revealed that the mechanism of XBJ in AP treatment might be associated with IL-17 and TNF signaling pathway. Molecular docking demonstrated that the effective components of XBJ had the good binding activity to the 5 core potential therapeutic targets of AP. Further studies found that quercetin and luteolin were the main effective components of XBJ in AP treatment. In conclusions, our outcomes demonstrate that XBJ treated AP depending on quercetin and luteolin, and mainly through IL-17 and TNF signaling pathways.

1. Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases in the world [1]. The global incidence of AP is about 34 cases per 100,000 population per year [2]. Among them, about 20% of AP cases are moderate severe and severe [3]. The total mortality rate of AP is about 5%, while the mortality rate of severe AP is as high as 30% [4]. More and more evidence shows that alcohol, cholelithiasis, metabolic disorders and obesity are the main causes of AP. Studies also indicate that complex intra-acinar events including zymogen activation, autophagy, oxidative stress, mitochondrial dysfunction and ER stress are related to the occurrence of AP [5]. At present, the main therapeutic approaches for AP are symptomatic treatment including pain relief, and the correction of fluid, electrolyte, and pH balances [6, 7]. Although those therapeutics can relieve the physiological symptoms of AP, they cannot ultimately cure the disease. Therefore, there is an urgent need to develop more effective and safer drug treatments for AP.

Traditional Chinese medicine (TCM) has been clinically used in China for thousands of years. Based on the holistic concept, syndrome differentiation, systemic modulation and less side effects, TCM therapy shows its advantages in the treatment of AP [8].

Xuebijing injection (XBJ), as a traditional Chinese medicine, is developed by Professor Jinda Wang based on the ancient blood-regulating formula. It contains mainly of extracts from Carthamus tinctorius L. (Honghua), Salvia miltiorrhiza Bunge (Danshen), Paeonia lactifora Pal. (Shaoyao), Ligusticum chuanxiong hort (Chuanxiong) and Angelica sinensis (Dangguai) [9]. At present, XBJ has been widely used
in the clinical treatment of AP in China, and has been proved to have good clinical with low side effects [10]. However, the active components, potential therapeutic targets and molecular mechanisms of XBJ in treating AP are still unclear.

Network pharmacology has become popular all over the world recently. By constructing a "drug-targets-disease" network, it provides a holistic perspective of the relationship between drugs and diseases. Because of its integrity and systematic characteristics, it is widely used to predict the potential effective components in TCM and further study their mechanism of action on disease targets [11, 12]. Molecular docking, an important virtual drug screening method, is of great significance in modern pharmacological research. By calculating the interaction and binding energy between small-molecule ligands (drugs) and protein receptors (targets), the binding affinity between drugs and targets can be predicted [13, 14]. At present, the combination of network pharmacology and molecular docking has been successfully applied in the study to discover the potential pharmacological mechanism of TCM.

In this study, network pharmacology, bioinformatics analysis and molecular docking were applied to reveal the effective components, potential therapeutic targets and molecular mechanisms of XBJ in treating AP.

2. Materials And Methods

2.1. Screen the effective components and potential targets of XBJ

Based on the TCMSP database (https://old.tcmsp-e.com/tcmsp.php), the effective components in XBJ were screened according to oral bioavailability (OB) >= 30% and drug likeness (DL) >= 0.18 [15]. According to HERB database (http://herb.ac.cn/), the potential targets of XBJ were found out. Then, the network between the effective components and their corresponding potential targets of XBJ were constructed using the Cytoscape 3.9.1 software.

2.2. Collect therapeutic targets of AP

The databases of Genecards (https://www.genecards.org/), DisGeNet (https://www.disgenet.org/), NCBI (https://www.ncbi.nlm.nih.gov/) and CTD (http://ctdbase.org/) were used to identify therapeutic targets of AP with the keyword "acute pancreatitis".

2.3. Screen AP-related targets

AP-related datasets (GSE194331) from the Gene Expression Omnibus database (GEO) was used and further screened out differentially expressed genes (DEGs) between AP samples and normal samples with thresholds of log 2-fold change(FC) > 1 and adjusted p value < 0.05.

2.4. Screen potential therapeutic targets of XBJ in treating AP
Genecards, DisGeNet, NCBI and CTD databases and DEGs from GEO database were used to obtain the therapeutic targets of AP. All therapeutic targets were identified in at least two databases. Then, these therapeutic target were crossed with XBJ potential targets to determine the prospective XBJ potential therapeutic targets for AP.

**PPI network, GO and KEGG analysis**

Protein-protein interactions between potential therapeutic targets of XBJ in treating AP were obtained through the STRING database (https://cn.string-db.org/). Then, PPI network was constructed by using the Cytoscape software, the degree value was calculated and the core therapeutic targets were selected according to the degree value. Besides, Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were used to investigate the molecular mechanisms of XBJ in the treatment of AP.

### 2.5. Molecular docking

The main effective components that correlate to XBJ's core targets in the treatment of AP were identified. Next, the two-dimensional structure of the main effective components were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The three-dimensional crystal structures of the core potential therapeutic targets were downloaded from the UniProt database (https://www.uniprot.org/). The water molecules and excess ligands were removed by PyMOL software. Finally, we used the "autodock4" software to dock these molecules and the docking results were displayed by PyMOL software.

### 2.6. Determine the core and important components of XBJ for AP treatment

We analyzed the potential therapeutic targets of all active components in XBJ for AP treatment. The active component with the most potential therapeutic targets was considered as the core component of XBJ. The active component with the second number of potential therapeutic targets was considered to be an important component of XBJ. The potential therapeutic targets of the core and important components were further carried out for PPI network, GO and KEGG analysis.

### 2.7. Determine the main signaling pathways of XBJ for AP treatment

We collected the common GO and KEGG enrichment signaling pathways of the core and important components of XBJ in treating AP. The most overlapping signaling pathways were considered to be the main signaling pathways of XBJ for AP treatment and presented by KEGG Mapper (https://www.kegg.jp/kegg/mapper/).

### 3. Results

#### 3.1. The effective components and potential targets of XBJ
According to the selection conditions, 115 effective components and 314 potential targets of XBJ were obtained from TCMSP database and HERB database (Supplement Table 1 and Supplement Table 2). Then, the network of XBJ's effective components and their potential target genes was constructed by Cytoscape software. As shown in Fig. 1, circles with different colors inside were the effective components of XBJ; the purple triangles represented the common effective components shared by various TCM in XBJ; and blue rectangles represented the potential targets; the label size represented the degree value which is a count of the number of edges incident with a node, and high degree values indicate a large number of connections to a node. According to the degree values, the top 5 core components of XBJ were selected, including quercetin, kaempferol, baicalein, luteolin and cryptotanshinone.

3.2. The therapeutic targets for AP

Using "acute pancreatitis" as the keyword, we obtained 773, 435, 317 and 879 therapeutic targets from Genecards, DisGeNet, NCBI and CTD databases, respectively (Supplement Table 3).

3.3. Targets related to AP

Using log 2-fold change(FC) > 1 and adjusted p value < 0.05 as cutoff criteria, we found 2304 DEGs in the AP-related GEO dataset (GSE194331) (Supplement Table 3). Figure 2A showed the distribution of the DEGs, the blue dot on the left represented under-expressed genes, and the red dot represented over-expressed genes. The heatmap showed the expression pattern of the top 20 DEGs between AP and healthy controls (Fig. 2B).

3.4. Potential therapeutic targets of XBJ for the treatment of AP

Therapeutic targets were combined with AP-related DEGs, and the target genes appearing in at least two databases were screened. Subsequently, the screened targets were overlapped with XBJ potential targets, and 122 potential therapeutic targets of XBJ for the treatment of AP were selected (Fig. 3 and Supplement Table 4).

3.5. The results of GO, KEGG analysis and PPI networks of potential therapeutic targets of XBJ for the treatment of AP

To better understand the mechanisms of XBJ for AP treatment, we applied GO, KEGG enrichment analysis and PPI network analysis on 122 potential therapeutic targets.

Through GO enrichment analysis, from the perspective of biological processes, the potential therapeutic targets were mainly enriched in Reactions with positive regulation of calcidiol 1-monoxygenase activity, Regulation of nitrogen utilization, Angiotensin-activated signaling pathway involved in heart process, Smooth muscle hyperplasia, Glial cell apoptotic process, Positive regulation of transcription from RNA polymerase ii promoter in response to hypoxia, Wound healing involved in inflammatory response, Negative regulation of primary miRNA processing, etc. From the perspective of cell components, the targets were mainly enriched in Cyclin A2-CDK2 complex, Transcription factor AP-1 complex, Bcl-2 family...
protein complex, I-kappaB/NF-kappaB complex, Lipopolysaccharide receptor complex, Death-inducing signaling complex, Phosphatidylinositol 3-kinase complex, etc. From the perspective of molecular function, the targets were mainly enriched in Nitric-oxide synthase activity, Histone deacetylase regulator activity, Tetrahydrobiopterin binding, Superoxide dismutase activity, phosphatidylinositol-3,4-bisphosphate 5-kinase activity, Cysteine-type endopeptidase activity involved in apoptotic signaling pathway, phosphatidylinositol-4,5-bisphosphate 3-kinase activity, etc. (Fig. 4A)

The results of KEGG enrichment analysis showed that the potential therapeutic targets were mainly enriched in Apoptosis-multiple species, IL-17 signaling pathway, TNF signaling pathway, p53 signaling pathway and so on. (Fig. 4B).

PPI network of 122 potential therapeutic targets was showed in Fig. 5A and Supplement Table 5. The higher the degree value, the larger the node area, and the darker the color, the greater the connectivity and importance. In addition, according to the degree values, the top 5 core potential therapeutic targets of XBJ for AP treatment were selected, including AKT1, ALB, TNF, TP53 and IL6 (Fig. 5B).

3.6. Molecular docking results

According to the network between effective components and potential target genes of XBJ, the corresponding active components of 5 core potential therapeutic targets of XBJ for AP treatment were selected. Based on the molecular docking steps, molecular docking of the core potential therapeutic targets and its corresponding active components was carried out to verify the binding activity between components and targets. The molecular docking data were showed in Supplement Table 6. The molecular docking results indicated that all binding energies were less than −5.0 kcal/mol. As showed in Fig. 6, the core effective compounds of XBJ (quercetin, luteolin, kaempferol and baicalein) had the lowest binding energy with the core potential therapeutic targets of AP.

3.7. Quercetin was the core component of XBJ for AP treatment

Through screening the potential targets of core effective component in XBJ for AP treatment (Fig. 7A and Supplement Table 7), we found that quercetin had the most potential therapeutic targets of AP. Analysis and statistics showed that quercetin had 84 potential therapeutic targets compared with 122 potential therapeutic targets of XBJ for AP treatment (Fig. 7B). Therefore, we identified quercetin as the core component of XBJ in treating AP.

In addition, we analyzed PPI network of these 84 targets and found that 3 core targets (AKT1, TNF and TP53) were the same as XBJ (Fig. 7C and Supplement Table 8). GO and KEGG enrichment analysis results showed that the potential therapeutic targets of quercetin for AP mainly correlated with IL-17 signaling pathway, TNF signaling pathway, p53 signaling pathway (Fig. 7D-E).

3.8. Luteolin was an important component of XBJ in the treatment of AP
Simultaneously, we found that luteolin had the second number of potential therapeutic targets for AP treatment. Analysis and statistics showed that luteolin had 46 potential therapeutic targets compared with 122 potential therapeutic targets of XBJ for AP treatment (Fig. 8A). Therefore, we identified luteolin as an important component of XBJ in treating AP.

Besides, we analyzed PPI network of these 46 targets and found that 2 core targets (AKT1 and TP53) were the same as XBJ (Fig. 8B and Supplement Table 9). GO and KEGG enrichment analysis results showed that the potential therapeutic targets of luteolin for AP mainly focused on IL-17 signaling pathway, TNF signaling pathway, p53 signaling pathway (Fig. 8C-D).

### 3.9. IL-17 and TNF signaling pathway were the main signaling pathways of XBJ in the treatment of AP

By collecting the common KEGG enrichment signaling pathways of XBJ, quercetin and luteolin in treating AP, we found that 24 potential therapeutic targets of XBJ, 21 potential therapeutic targets of quercetin and 14 potential therapeutic targets of luteolin were enriched in IL-17 signaling pathway (Supplement Table 10); 27 potential therapeutic targets of XBJ, 22 potential therapeutic targets of quercetin and 13 potential therapeutic targets of luteolin were enriched in TNF signaling pathway (Supplement Table 11).

Therefore, we finally determined that XBJ treated AP mainly depending on quercetin and luteolin, and focused on IL-17 and TNF signaling pathways (Fig. 9 and Fig. 10).

### 4. Discussion

Clinical studies found that XBJ cured AP by improving microcirculation, increasing blood flow, decreasing inflammation and capillary permeability, reducing inflammatory exudation, promoting inflammation absorption and inhibiting the formation of inflammatory granulomas [16]. At present, many TCM have been used in the clinical treatment of AP [17]. However, with the characteristics of muti-component and muti-target, TCM is difficult to be studied at molecular level. Fortunately, the emergence of network pharmacology makes it possible to systematically study TCM. Therefore, based on network pharmacology, molecular docking and bioinformatics, this study explored the effective components, potential therapeutic targets and molecular mechanisms of XBJ in treating AP.

By crossing XBJ's potential targets and AP-related therapeutic targets, 122 potential therapeutic targets of XBJ for AP treatment were obtained. Then, we used potential therapeutic targets to construct PPI network and 5 core potential therapeutic targets of XBJ (AKT1, ALB, TNF, TP53 and IL6) were screened out. AKT1, as a powerful promoter of the G1-S checkpoint transition, is a major candidate factor to promote pancreatic acinar cell proliferation [18]. Studies showed that AKT1 signaling pathway had been proved to play an important role in the pathogenesis of inflammatory diseases, including AP [19, 20]. Chen et al. found that the use of AKT activators may be beneficial to promote pancreatic regeneration and organ function recovery [21, 22]. Albumin (ALB), as a negative acute-phase protein synthesized by the liver, decreases rapidly in acute infection. Previous studies showed that ALB was negatively correlated with inflammation severity, disease prognosis and mortality of AP [23]. At present, there are some therapy
aimed at ALB having been used on AP patients [24]. TP53, as a tumor suppressor, is usually expressed at a low level under normal physical conditions, but it can accumulate rapidly after DNA damage, and cause signal cascade, which leads to cell cycle arrest, DNA repair or apoptosis [25]. In clinical practice, pancreatic tissues from AP patients always exhibit apoptotic nuclei and increased p53 expression [26]. Consistently, Zhou et al. found that down-regulation of TP53 significantly inhibited apoptosis of pancreatic acinar cell and inflammation of AP induced by LPS in mouse [27]. IL6, as a pro-inflammatory cytokine, is significantly increased and positively correlated with the severity of AP [28] [29]. IL6 can bind to IL6Rα and gp130 to form a complex. And the complex activates JAK/STAT3 signaling pathway by phosphorylation [30]. Phosphorylated and activated STAT3 dimerizes and translocates to the nucleus to regulate its target genes, including STAT3, IL6 and SOCS3, and forms a positive feed-back loop. Then, this positive feed-back loop amplifies the progression of systemic inflammatory cascade [31]. Previous studies showed that neutralization of IL6 by antibody effectively suppressed the activation of STAT3 in the pancreatic acinar cells, inhibited the positive feed-back loop and consequently reduced the severity of AP [32].

Through KEGG enrichment analysis of potential therapeutic targets, including quercetin, luteolin and XBJ in treating AP, we found that the molecular mechanism of XBJ in treating AP was mainly related to IL-17 and TNF signaling pathway. Interleukin 17 (IL-17) is an important pro-inflammatory cytokine mainly secreted by T-helper 17 (Th17) cells [33]. In AP, cell damage caused by pancreatic self-digestion can cause immune cells including Th17 cells to gather. The aggregation of immune cells leads to releases more multiple pro-inflammatory cytokines and further damage of pancreatic acinar cells [34]. So far, many studies confirmed the correlation between IL-17 and AP, and suggested that IL-17 is a predictor of AP and relate to the severity of organ failure [35]. Besides, IL-17 has been reported as a prognostic factor for length of hospitalization, organ dysfunction and mortality in AP patients [36]. TNF, as inflammatory cytokines including TNF-α and TNF-β mainly produced by macrophages and T lymphocytes, has a wide range of biological activities. It has been reported that TNF-α plays an important role in the development and evolution of AP [37]. In addition, TNF-α has long been considered as one of the initial triggers of inflammatory cascade since it stimulated synthesis and release of various cytokines in AP patients [38, 39].

The molecular docking results showed that the main effective components quercetin, luteolin had strong binding activity to the core potential therapeutic targets AKT1, IL6, AKT1 and TNF. Quercetin, as a kind of flavonoid, is widely distributed in fruits, vegetables and nuts, exhibits various biological functions. Among them, quercetin's anti-inflammatory ability deserved special attention. Studies showed that quercetin could protect pancreatic cell by inhibiting p38 MAPK signaling pathway via up-regulating miR-216b and down-regulating TNF-α expression. Quercetin also exerts a protective effects against pancreatic cell injury by inhibiting p38 MAPK signaling pathway via up-regulation of miR-216b and reducting of TNF-α expression. Besides, NEAT1, a long non-coding RNA, is involved in regulating mitogen-activated protein kinase kinase 6 (MAP2K6) via miR-216, which could be inhibited by quercetin. In addition, quercetin reduces the level of inflammatory mediators TNF-α and IL-6 by inhibiting TNF receptor-associated factor 2 (TRAF2) and MAP3K5 [40]. Luteolin, as a natural flavonoid, was first isolated from the annual herb
Reseda odorata L. At present, it has been found in many herbs and vegetables and wildly used for the treatment of inflammation-related diseases. Studies showed that luteolin increased HO-1-mediated anti-inflammatory and decreased the activation of NF-κB pathway in the pancreas of mouse. Luteolin also can greatly ameliorate pathological changes of pancreatic tissue and decrease the levels of TNF-α and IL-6 [41, 42].

5. Conclusions

This research revealed that the potential therapeutic targets and molecular mechanisms of XBJ in the treatment of AP through network pharmacology, molecular docking, bioinformatics and other methods, and confirmed that quercetin and luteolin, as the main effective components, may replace XBJ for the treatment of AP patients. These results may provide evidence for the clinical application of XBJ in the treatment of AP.

Declarations

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Author Contributions

Zhongjian Liu and Wenxue Wang provided the conception. Li Li, ChenChen Huang and Jianmei Gao collected and analyzed the data. Wen Zhang, Jinli Wang, Xisha Li and Lilan Wan contributed to find references. Chunman Li are the guarantors of this work. Zhongjian Liu wrote the manuscript. All authors read and approved the final manuscript.

Data availability

Data is contained within the article and Supplementary Materials.

Conflicts of interest

The authors declare that they have no know competing financial interests tin this paper.

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Figures
Figure 1

The network of the relationship between the effective components and the potential targets of XBJ.
Figure 2

DEGs of AP in GEO datasets (GSE194331). (A) Volcano map. (B) Heat map.
Figure 3

Screen potential therapeutic targets associated with AP. (A) The Venn diagram for screening AP therapeutic targets. (B) The Venn diagram for screening the potential therapeutic targets of XBJ in the treatment of AP.
Figure 4

GO and KEGG enrichment analysis of the potential therapeutic targets of XBJ for AP treatment. (A) GO enrichment analysis including BP, CC and MF (top 10). (B) KEGG enrichment analysis (top 30).
Figure 5

PPI network of XBJ potential therapeutic targets for the treatment of AP. (A) PPI network. (B) The core targets.
Figure 6

Molecular docking results of AP's potential targets and XBJ's core components. AKT1 and kaempferol (binding energy -6.4 kcal/mol), AKT1 and luteolin (binding energy -6.07 kcal/mol), AKT1 and quercetin (binding energy -5.94 kcal/mol), TNF and luteolin (binding energy -6.02 kcal/mol), TNF and kaempferol (binding energy -5.32 kcal/mol), TNF and baicalein (binding energy -5.22 kcal/mol), IL6 and luteolin (binding energy -5.02 kcal/mol), IL6 and quercetin (binding energy -5.11 kcal/mol).
Figure 7

PPI network, GO and KEGG enrichment analysis of quercetin's potential therapeutic targets for AP treatment. (A) the number of potential therapeutic targets of the main components in XBJ. (B) The Venn diagram between the potential therapeutic targets of quercetin and XBJ for AP treatment. (C) PPI network of quercetin's potential therapeutic targets for AP treatment. (D) GO enrichment analysis of quercetin's
potential therapeutic targets for AP treatment including BP, CC and MF (top 10). (E) KEGG enrichment analysis of quercetin's potential therapeutic targets for AP treatment (top 30).

Figure 8

PPI network, GO and KEGG enrichment analysis of luteolin's potential therapeutic targets for AP treatment. (A) The Venn diagram between the potential therapeutic targets of luteolin and XBJ for AP treatment. (B) PPI network of luteolin's potential therapeutic targets for AP treatment. (C) GO enrichment analysis of luteolin's potential therapeutic targets for AP treatment including BP, CC and MF (top 10). (D) KEGG enrichment analysis of luteolin's potential therapeutic targets for AP treatment (top 30).
Figure 9

The potential therapeutic targets of XBJ's main effective components for AP treatment in IL-17 signaling pathway (https://www.kegg.jp/pathway/hsa04657). The red rectangle represents the potential therapeutic targets of quercetin in XBJ for AP treatment; the blue rectangle represents the potential therapeutic targets of luteolin in XBJ for AP treatment.
Figure 10

The potential therapeutic targets of XBJ’s main effective components for AP treatment in TNF signaling pathway (https://www.kegg.jp/pathway/hsa04668). The red rectangle represents the potential therapeutic targets of quercetin in XBJ for AP treatment; the blue rectangle represents the potential therapeutic targets of luteolin in XBJ for AP treatment.

Supplementary Files

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