Heliyon 10 (2024) e27365

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Study on the mechanism of Shugan Lidan Xiaoshi granule in preventing acute pancreatitis based on network pharmacology and molecular docking

Jiaxing Wang [a,b,1], Yang Wang [a,b,1], Zitong Chen [a,b], Bin Liu [a,b], Wujie Wang [a,b,**], Yuliang Li [a,b,*]

[a] Department of Interventional Medicine and Microinvasive Oncology, The Second Hospital, Cheello College of Medicine, Shandong University, Jinan, China

[b] Institute of Interventional Oncology, Shandong University, Jinan, China

ARTICLE INFO

Keywords:
Acute pancreatitis
Shugan Lidan Xiaoshi granules
Molecular docking
Network pharmacology
Traditional Chinese medicine

ABSTRACT

Background: Shugan Lidan Xiaoshi granules (SLXG) is a herbal granule formulation developed by extensively modifying multiple traditional Chinese medicine compound prescriptions known for their ability to dissolve stones. It is primarily used for the prevention and treatment of cholelithiasis and possesses significant therapeutic potential in both preventing and treating acute pancreatitis. However, the preventive effects of SLXG on cholelithiasis-related complications, such as acute pancreatitis (AP), have been inadequately researched.

Methods: TCMSP database was searched to identify the active components and targets of SLXG's action. The disease gene databases (GeneCards, OMMI, PharmGKB, DrugBank) were used to retrieve the targets associated with AP. A TCM ingredient target network was then constructed by using the intersection of these two datasets. The overlapping targets underwent network analyses, including Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG)and Protein-Protein Interaction (PPI) analyses. Molecular docking was performed to examine the interaction patterns between the active ingredients and central targets.

Results: A "Traditional Chinese Medicine-Component-Target" complex network consisting of 10 traditional Chinese medicines, 114 compounds, and 164 targets was constructed. GO and KEGG analysis showed that SLXG has the potential to regulate the response of oxygen-containing compounds, apoptosis, and inflammatory factors. Nine central genes were identified by the PPI network and subnetwork. IL6 was chosen as the most significant gene for molecular docking. The three active compounds of SLXG: quercetin, luteolin, and paeoniflorin, along with the active site of IL6 have a good binding ability and thus play a preventive role in AP.

Conclusion: This study provides evidence of the effective preventive role of SLXG against AP, as indicated by bioinformatics analysis. The preventive effect of SLXG is attributed to its multi-component, multi-target, and multi-pathway mechanisms. This finding provides a solid foundation for future research on the clinical application and mechanism of action of drugs.

* Corresponding author. Department of Interventional Medicine and Microinvasive Oncology, The Second Hospital, Cheello College of Medicine, Shandong University, Jinan, 250000, China.

** Corresponding author. Department of Interventional Medicine and Microinvasive Oncology, The Second Hospital, Cheello College of Medicine, Shandong University, Jinan, 250000, China.

E-mail addresses: dr.wangwujie@sdu.edu.cn (W. Wang), lyl.pro@sdu.edu.cn (Y. Li).

[1] Authors contributed equally.

https://doi.org/10.1016/j.heliyon.2024.e27365
Received 19 October 2023; Received in revised form 21 February 2024; Accepted 28 February 2024
Available online 6 March 2024

1. Introduction

Acute pancreatitis (AP) is a prevalent cause of acute abdominal pain, with a fatality rate ranging from 1% to 5% [1]. Common causes of AP include gallstones (40%–70%), alcohol (25%–35%), hypertriglyceridemia (1%–14%), and endoscopic retrograde cholangiopancreatography (ERCP) (3%–5%) [2]. A prolonged follow-up study revealed that individuals with gallstones carry a 7% risk of developing biliary pancreatitis [3]. There are several hypotheses about the mechanism of gallstone-induced pancreatitis. Biliary pancreatitis can occur due to ampullary obstruction or local inflammation caused by stones, as well as temporary bile reflux into the pancreatic duct. Additionally, the risk of gallstone pancreatitis is higher when there are fewer gallstones [4,5]. Currently, the primary minimally invasive treatments for cholelithiasis are percutaneous transhepatic biliary drainage (PTPBD) and ERCP-related techniques. However, the incidence of acute pancreatitis after ERCP ranges from 1% to 9.8% and can reach up to 14% in high-risk patients [6,7]. Recent studies have indicated a potentially lower incidence of pancreatitis after PTPBD compared to ERCP [8,9]. Nonetheless, regardless of the method used (PTPBD or ERCP), the possibility of acute postoperative pancreatitis still exists. As a result, finding strategies to reduce the incidence of cholelithiasis-related or postoperative acute pancreatitis has become an urgent clinical challenge that requires attention.

Currently, the etiology and optimal treatment duration for acute pancreatitis (AP) remain poorly understood, and there is currently no specific medication that can alter the outcome of this condition [10]. The primary treatment for AP consists mainly of fluid resuscitation, pain management, and enteral nutrition support. Chinese herbal medicine has emerged as a significant non-surgical treatment modality for AP in recent years [11]. Multiple studies focusing on traditional Chinese medicine, including compound preparations such as Xiao Chaihu decoction, Dachengqi decoction, Shenmai injection, and Salvia miltiorrhiza, have demonstrated the efficacy of traditional Chinese medicine in ameliorating AP [12–15]. However, considering the limited availability of effective pharmacotherapy options for acute pancreatitis, it is imperative to further explore potential drugs for the treatment of this condition.

Traditional Chinese medicine decoctions based on the Shugan Lidan recipe are commonly used in the clinical treatment of cholelithiasis and have been shown to have a specific preventive effect on acute pancreatitis [16–18], although their mechanism remains unclear. SLXG is a comprehensive improved formulation of traditional Chinese medicines such as ShuganLidan decoction (SLD), Chaihu Shugan San (CSS), etc., which have the functions of soothing the liver, promoting bile excretion, and dissolving stones. The prescription consists of 11 traditional Chinese medicines: Bupleuri Radix (chaihu,CH), Chuanxiong Rhizoma (chuanxiong,CX), Aurantii Fructus (zhike,ZK), Glycyrrhizae Radix et Rhizoma (gancao,GC), Lysimachiae Herba (jinqiancao,JQC), Galli Gigerii Endothelium Coreneum (jineijin,JNJ), Curcumae Radix (yujin,YJ), Lygodii Spora (haijinsha,HJS), Artemisiae Scopariae Herba (yinchen, YC) , Lonicerae Japonicae Flos (erhua,EH) , Paeoniae Radix Alba (baishao,BS). Previous clinical experience has shown that combining ERCP with SLD in the management of choledocholithiasis significantly reduces the incidence of postoperative AP [18]. Additionally, studies have demonstrated the notable clinical efficacy of CSS therapy in the management of acute pancreatitis [19,20]. However, the mechanisms of these SLXG-related traditional Chinese medicine formulas in preventing and treating acute pancreatitis remain unclear. Accordingly, this study utilizes network pharmacology and molecular docking to explore the potential efficacy of SLXG in preventing acute pancreatitis. Furthermore, it provides an analysis of its potential mechanism, aiming to contribute to the development of effective prevention strategies and novel drug therapies for acute pancreatitis.

2. Materials and methods

2.1. Collection of components and targets of SLXG

Through the utilization of the traditional Chinese medicine system pharmacology database and analysis platform (TCMSP) [21], the active components of SLXG were identified. The database provided information on the chemical structure, half-life (HL), drug-like (DL), oral bioavailability (OB), drug targets, and other information of herbal components. In order to select compounds for further analysis, we performed a screening of candidate compounds according to the following parameters: OB $\geq$ 30%, HL and DL $\geq$ 0.18. The active components of JNJ were not included in TCMSP, it was screened by the BATMAN-TCM database [22]. In TCMSP, relevant drug targets for each active compound were obtained. All the targets found in the above search were standardized into gene names and UniProtIDs by searching "*Homo sapiens*" in the UniProt database [23]. Additionally, the content of various Chinese medicinal herbs in SLXG was provided in Table S1.

2.2. Collection of therapeutic targets related to AP

The keyword "acute pancreatitis" was used to search Genecards [24], OMIM database [25], PharmGKB database [26], and DrugBank database [27] to screen the target genes of AP. GeneCards identified multiple target genes associated with AP, which were subsequently screened using a relevance score cutoff of >5. The target genes associated with AP were determined by consolidating the findings from the four databases.

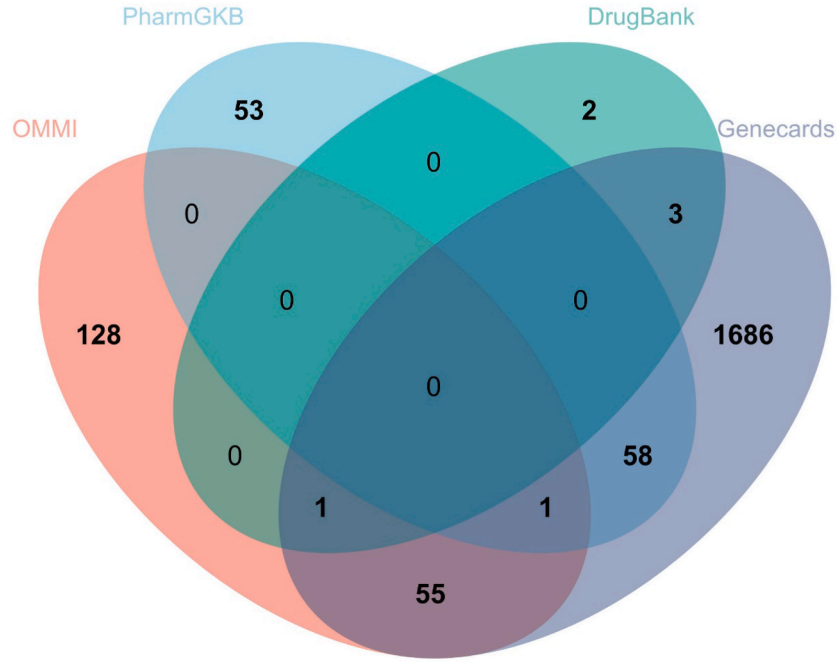
2.3. Network construction and enrichment analysis of "traditional Chinese medicine-component-target"

We utilized Cytoscape 3.9.1 [28] to construct the intricate target interaction network of SLXG. The network splitter module of the Cytoscape software was utilized for conducting the topological analysis. Utilizing the sangerbox platform [29], we conducted analyses

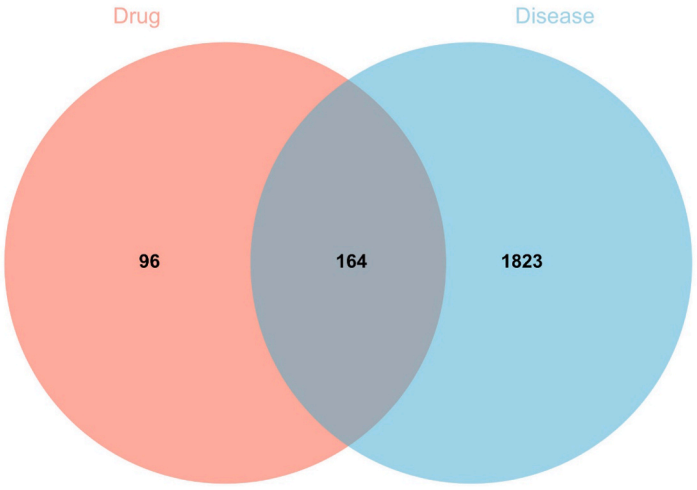
on the GO and KEGG pathways to identify potential mechanisms involving cell components (CC), biological processes (BP), molecular functions (MF), and key signaling pathways.

2.4. Construction and topology analysis of PPI network

The STRING database [30] was used to ul the PPI network with SLXG targets and AP-related gene sets. The parameter was set to a confidence level >0.900. Subsequently, the PPI network of STRING was integrated into Cytoscape to build key subnetworks. Xia et al.'s method was consulted for the selection of core subnetworks, and two methods to screen core subnetworks were applied [31]. The PPI network was first analyzed in Cytoscape using the CytoNCA plug-in. In the primary score file generated by CytoNCA, each scoring metric including Betweenness, Closeness, Degree, Eigenvector, LAC, and Network, exceeded the median threshold. These parameters



(A)Identify AP-related genes from online databases



(B) Common targets of drugs and disease

Fig. 1. The Wayne diagram of disease targets and drug targets.

are also important indicators of new drug discovery and target prediction. The identified genes were then utilized to create a subnetwork, and the filtering procedure was repeated to obtain the ultimate key subnetwork. Another way for screening key subnetworks is to utilize the CytoHubba plug-in within Cytoscape to discover the top 17 most important genes within the PPI network.

2.5. Detection of the binding ability of effective active components to key targets by molecular docking

Searching on the Pubchem website (https://pubchem.ncbi.nlm.nih.gov) yielded the 3D SDF structure file of the compound, which was then converted into a PDB file using the OpenBabel 2.4.1. The RSCB PDB database (https://www.rcsb.org/) was searched to obtain the receptor protein IL6 (PDB:1ALU), and PYMOL2.6.0 software was used to dehydrate and remove original ligand from the receptor protein [32]. The receptor protein was modified by hydrogenation and charge calculation using AutoDockTools1.5.7 software. The receptor protein was docked with small ligand molecules by AutoDockVina1.1.2 [33]. The grid boxes covering the entire protein were constructed to facilitate blind docking, and the binding energies were subsequently scored. A strong affinity between the active components and the action targets is represented by the binding energy < -5 kcal/mol [34,35].

3. Result

3.1. Effective components and target screening of SLXG

According to the criteria mentioned above, 117 active compounds and 260 drug targets were screened from the ten traditional Chinese medicines of SLXG using the TCMSP database. Octalupine was excluded in the above process because its drug targets could not be retrieved. The JNJ screened from the BATMAN-TCM database was excluded in the above method because of the low correlation between its active components and target genes with acute pancreatitis.

3.2. Acquisition of AP-related targets and intersection targets

The databases Genecards, OMIM, PharmGKB, and DrugBank provided information on 1804, 185, 112, and 6 genes associated with AP. After merging search results and eliminating duplicates, 1987 AP-related genes were obtained (Fig. 1A). Additionally, 164 intersection target genes were identified by intersecting disease-related genes with compound target genes (Fig. 1B).

3.3. Construction of herb-compound-target interaction pharmacology network

The data regarding intersection targets, active components, and traditional Chinese medicine was imported into Cytoscape 3.9.1 software for visual analysis, resulting in the generation of a compound target interaction network comprising 387 nodes and 2095

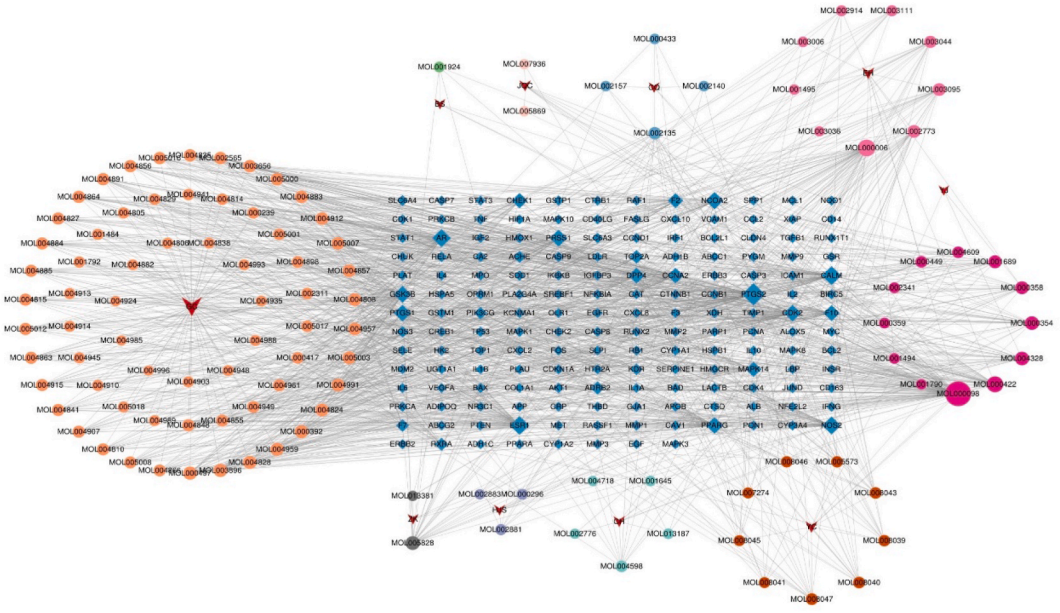


Fig. 2. The Herb-compound-target interaction pharmacology network. compounds in SLXG are represented by circles. The ingredients of Traditional Chinese medicine are represented by an arrow. The AP-related target genes are represented by a diamond, and the interaction between compounds and the target genes is represented by the edges. According to topology analysis results, the size of the node is proportional to the value of the degree centrality.

edges (Fig. 2). It was observed that multiple active compounds can target a single gene, whereas a single compound may target multiple genes, highlighting the multi-component, multi-target, and multi-pathway nature of SLXG, which contributes to the prevention and treatment of AP. Notably, among the 164 genes analyzed, PTGS2 stood out as the gene featuring the highest number of targeted components within the SLXG framework.

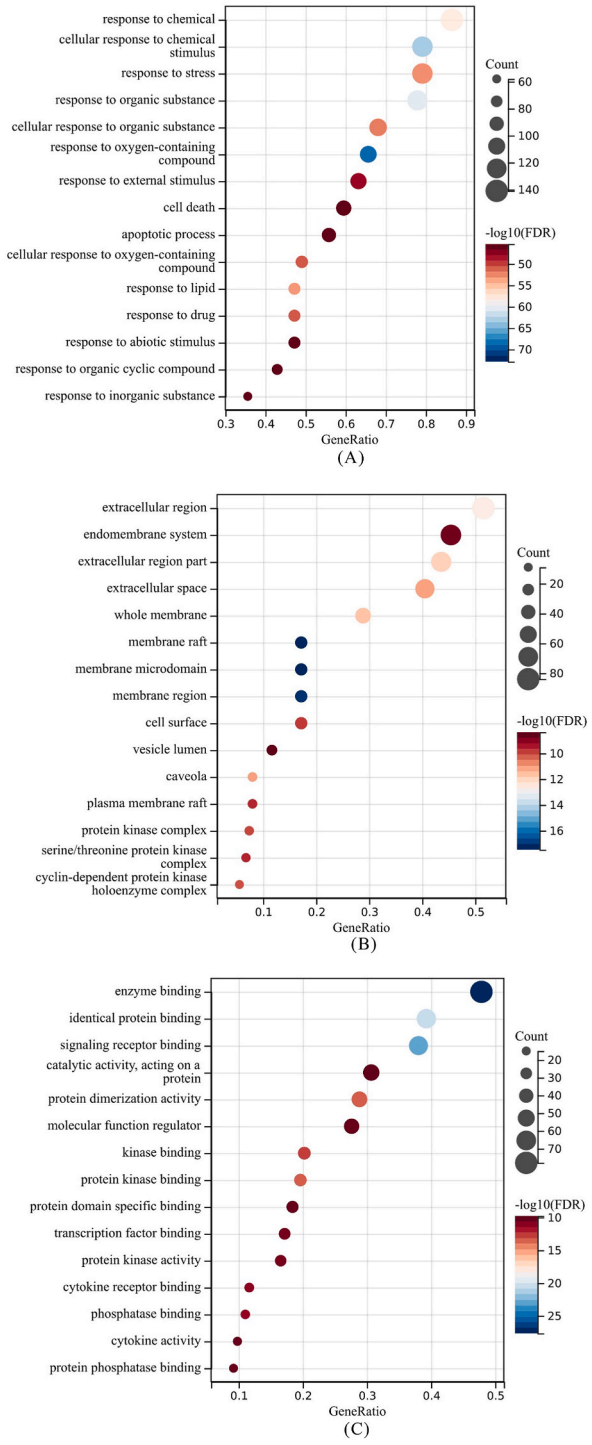


Fig. 3. GO enrichment analysis of the target genes. (A): BP (B): CC (C): MF. Gene counts are the total number of enriched genes, whereas gene ratio is the ratio of enriched genes to all target genes.

3.4. GO enrichment analysis

The potential CC, BP, and MF of 164 target genes were identified by means of GO enrichment analysis. By setting the filter to $P < 0.05$ and FDR <0.1, 3807 significantly enriched GO terms were obtained, including 3401 BPs, 164 MFs, and 242 CCs. The top 15 terms are shown in Fig. 3A–C. GO terminology indicates that BPs are mainly involved in cellular response to oxygen-containing compounds, abiotic stimuli, cellular response to organic substance, chemical stimuli, apoptosis, etc.

3.5. KEGG enrichment analysis

The enrichment analysis using KEGG identified pathways enriched for 164 target genes. The filter condition was set with adjusted $P < 0.05$ and FDR <0.1. There are 168 KEGG pathways that are significantly enriched, which suggests that these target genes have an impact on signal pathways related to viral infection, inflammatory factors, and the onset and progression of cancer. The bubble diagram depicting the 15 most significant KEGG pathways is presented in Fig. 4.

3.6. PPI network and critical subnetwork

The 164 target genes were imported into the STRING database, with the species *Homo sapiens* and the minimum confidence level set at 0.9. Simultaneously, the free points were hidden, and the information on target-protein interaction was transferred to cytoscope 3.9.1 software to visually analyze the PPI network diagram (Fig. 5A–B). The network diagram contains 149 nodes and 797 edges. Finally, by employing CytoNCA and CytoHubba, respectively, two significant subnetworks consisting of 17 target genes were discovered (Fig. 5C–F).

3.7. Molecular docking of active compounds with proteins encoded by IL6

According to the Maximal Clique Centrality (MCC) values, which was regarded as the most effective method to find hub nodes [28]; two key subnetworks (Fig. 6A) and nine genes and their importance were examined (Table 1). Severe acute pancreatitis is associated with elevated levels of cytokines. IL6 is one of the best distinguishing markers for mild and severe acute pancreatitis, and blood IL6 levels are related to the mortality rate of organ failure [36]. IL6 was chosen as the most crucial gene for molecular docking. Afterward, three compounds that targeted the IL6 protein were isolated from the compound-target interaction network. The three compounds are quercetin, luteolin, and paeoniflorin. These compounds may all readily enter and bind to the active pocket of the IL6 protein, as demonstrated by the molecular docking (Fig. 6B–D). The docking score is recorded in Table 2.

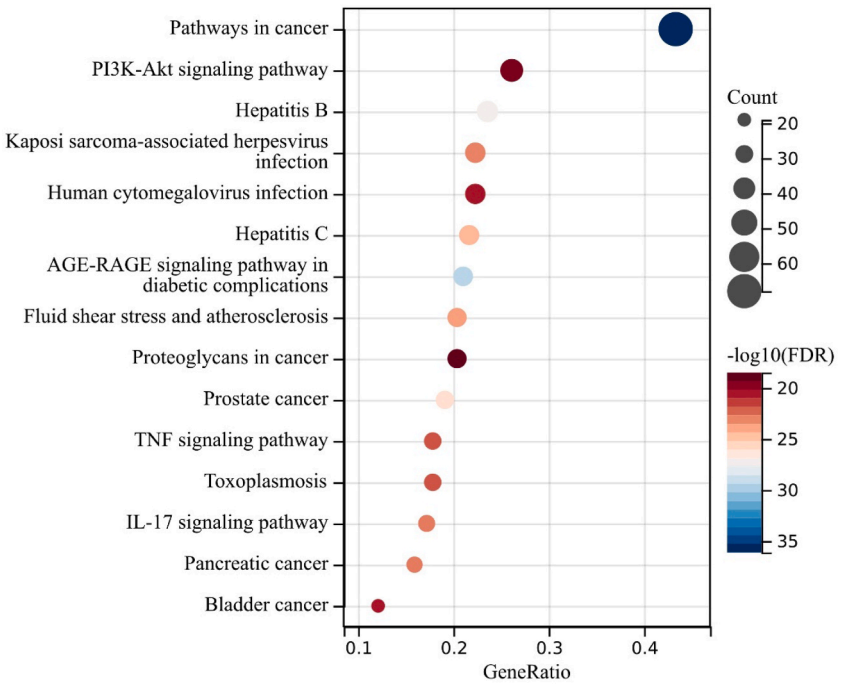
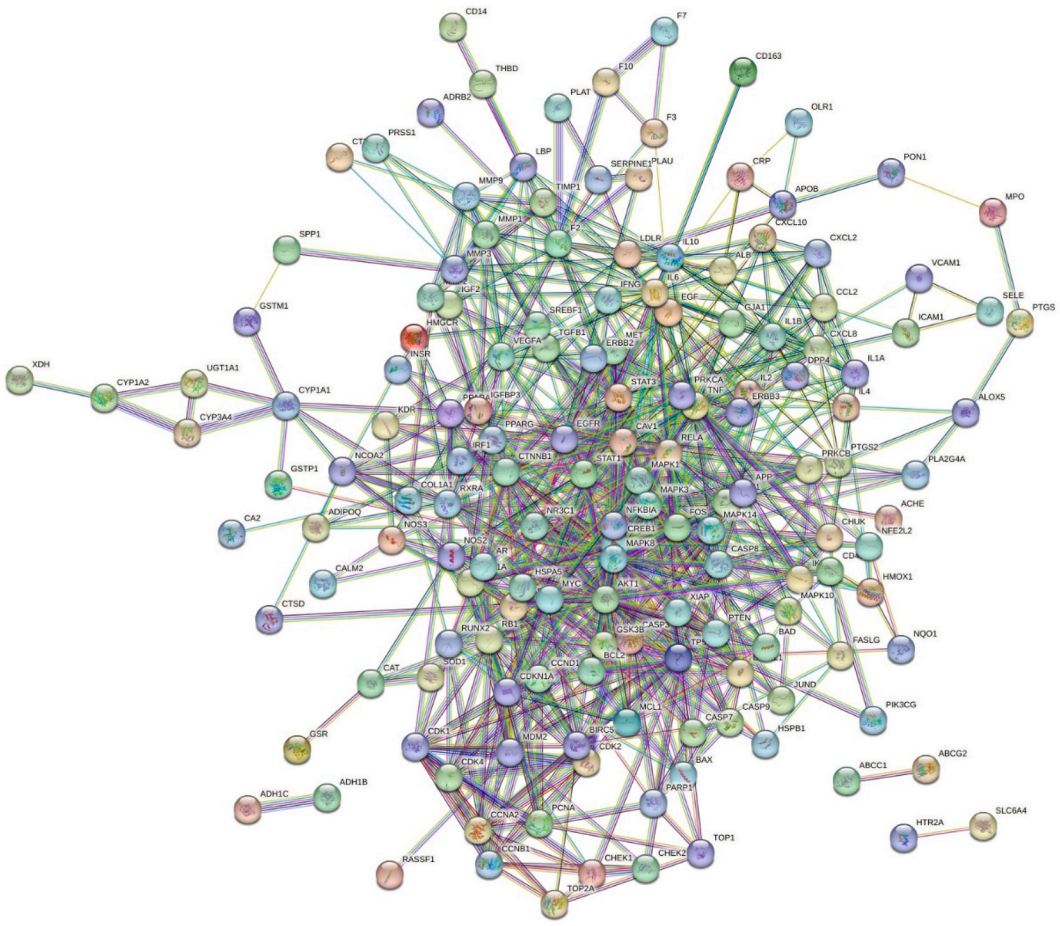


Fig. 4. KEGG enrichment analysis of the target genes.



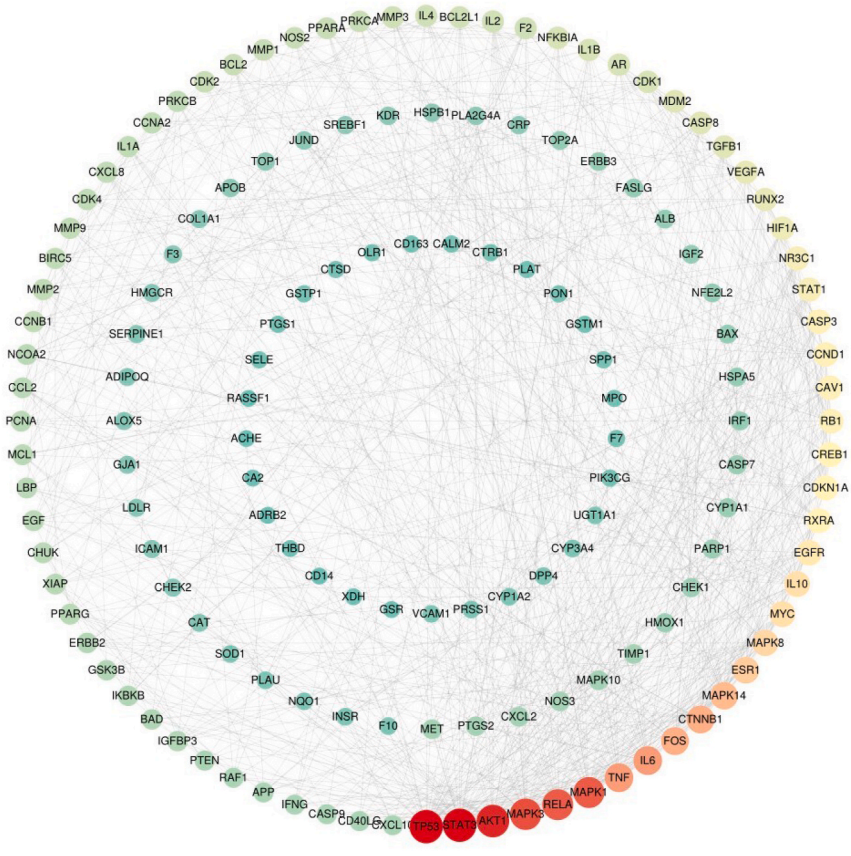
(A)

Fig. 5. Identification of key subnetwork using Cytoscape. (A) Analysis diagram illustrating the network of target-protein interactions (B) According to topology analysis results, the size and color of the node are proportional to the degree centrality value. (C) Performing the first filtering in the PPI network through Cyto-NCA, the screened yellow nodes with scores surpassing the median. (D) The subnetwork was built through a secondary filtration process using CytoNCA. Orange nodes were selected based on scores exceeding the median value. (E) Final key subnetwork identified after undergoing two rounds of filtration with CytoNCA. (F) Key subnetwork of top 17 nodes analyzed by CytoHubba.

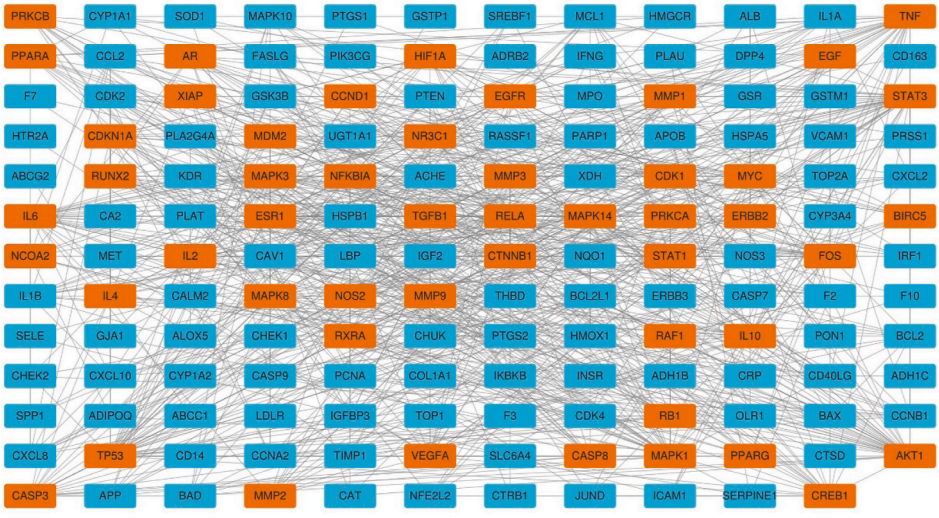
4. Discussion

Cholelithiasis is the primary cause of acute pancreatitis globally, responsible for approximately 20–70% of all cases in Western countries [37,38]. Epidemiological studies have demonstrated an increasing prevalence of cholelithiasis with age. This suggests a correlation between the incidence of acute pancreatitis and demographic changes [39]. The obstruction of the Oddi sphincter by a stone is the initial reported cause of acute necrotizing pancreatitis. Experimental acute pancreatitis can be induced through pancreatic duct obstruction and/or bile acid infusion [10]. Women constitute approximately two-thirds of individuals with acute biliary pancreatitis, as they have a higher likelihood of developing gallstones compared to men [38]. Within this medical context, there is a growing research focus on the prevention and management of acute pancreatitis and its associated complications stemming from cholelithiasis.

Traditional Chinese medicine has the advantages of having many targets and few side effects, Consequently, it is increasingly being considered for clinical use. Traditional Chinese medicine can prevent and treat both cholelithiasis and pancreatitis. SLXG is composed of modified prescriptions based on the famous prescription of Shugan Lidan, which plays a key role in preventing and treating cholelithiasis in clinical settings. The previous studies on traditional Chinese medicine compound prescription of cholelithiasis primarily focus on the treatment and prevention of the disease itself. However, there are few reports that explain whether the treatment and prevention can influence the complications of the disease. Therefore, it was considered whether SLXG has the potential to prevent

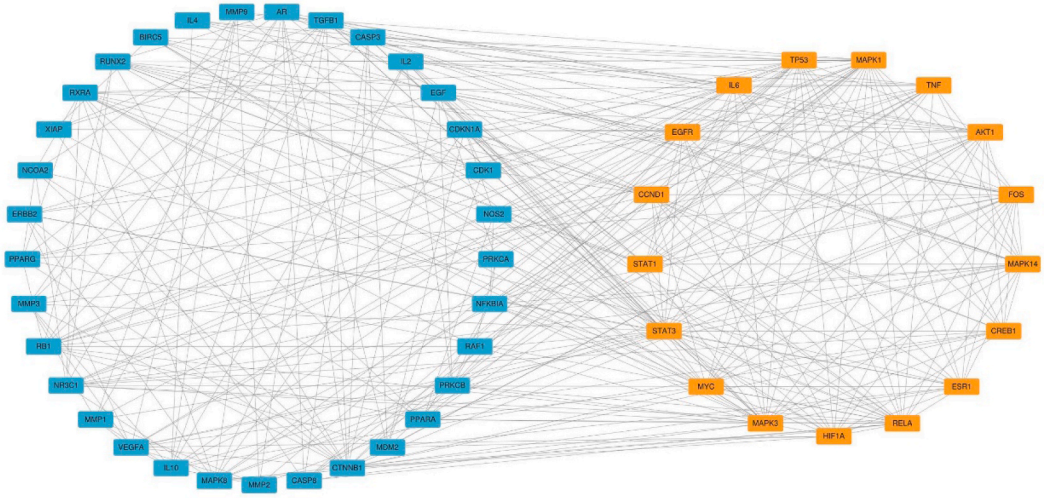


(B)

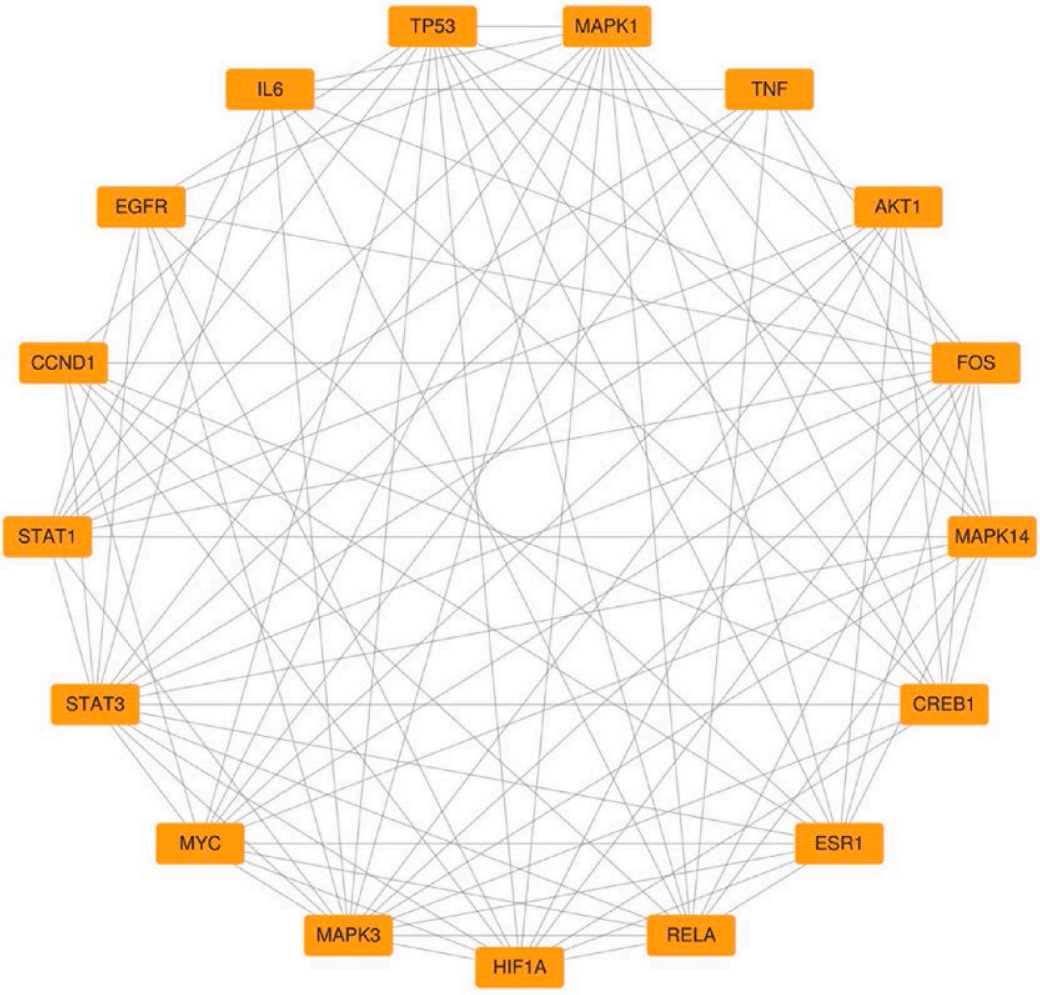


(C)

Fig. 5. (*continued*).

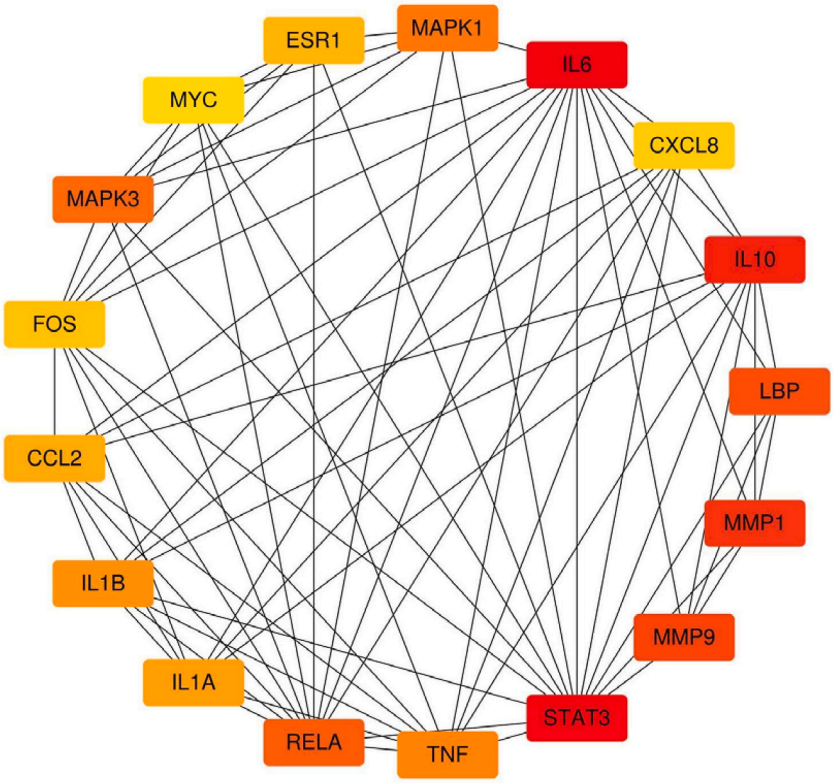


(D)



(E)

Fig. 5. (*continued*).



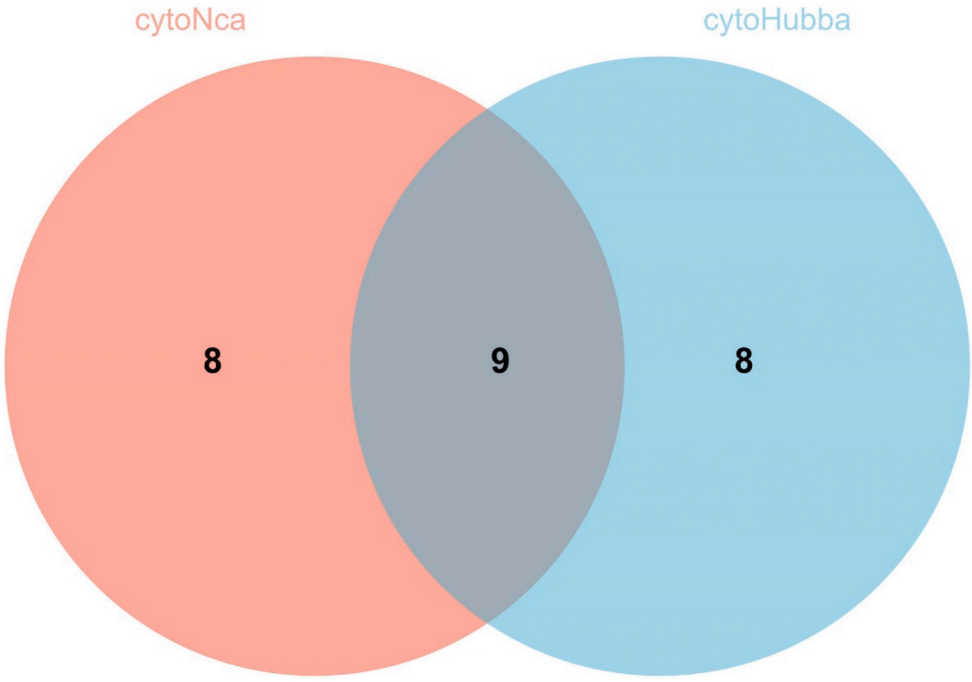
(F)

Fig. 5. (*continued*).

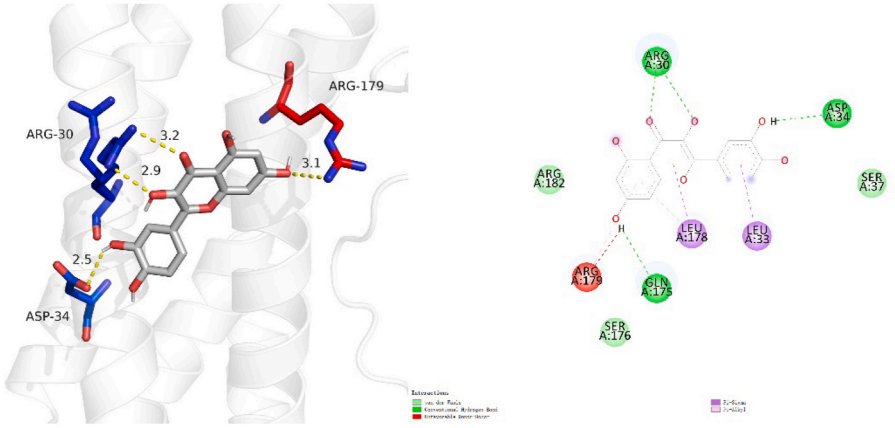
or treat AP. In recent years, studying and exploring the mechanism of action of traditional Chinese medicine compound prescriptions has been greatly aided by the analytical methods of network pharmacology and molecular docking. Therefore, we used the same strategy in this study.

A related gene set of SLXG targeting AP, consisting of 164 target genes, was constructed in this research through the analysis of the active components of 10 SLXG components. The association between active substances, targets, and traditional Chinese medicine is described by a complex target network. In the current study, 114 effective compounds and 164 candidate targets of SLXG for the treatment of acute pancreatitis (AP) were identified. Additionally, 87.80% of the 164 possible therapeutic targets for SLXG can overlap with at least two active compounds, suggesting that the effective compounds in SLXG may work together against AP by multi-target coordination. In addition, 92.98% of the 114 active compounds (106 out of 114) act on at least two candidate therapeutic targets. In addition, quercetin is found in five herbs (CH, YC, JQC, EH,GC). Luteolin is found in EH, and six herbs (CH, BS, GC, EH, JQC and HJS) contain kaempferol. They act on 108, 50, and 40 candidate AP therapeutic targets, respectively, indicating that SLXG effectively addresses acute pancreatitis (AP) by utilizing a synergistic blend of various herbal ingredients, compounds, and targeted therapeutic mechanisms.

It was speculated that quercetin would be crucial in the treatment of AP because it targets the most predictive targets. Quercetin, luteolin, kaempferol and paeoniflorin are part of the natural flavonoid compound family. Flavonoids have been shown to possess antioxidant properties by scavenging reactive oxygen species, bolstering endogenous antioxidants, downregulating the expression and synthesis of inflammatory cytokines such as IL-1β, IL-6, TNF-α, NF-κB, inhibiting inflammatory enzymes, and promoting the production of anti-inflammatory cytokines like IL-10 [40]. Previous research has demonstrated that quercetin is effective in treating acute pancreatitis by inhibiting the production of inflammatory and apoptotic factors (IL-6, TNF- α, and IL-1 β, as well as MAPK3 and TP53) [13,41]. Quercetin has been demonstrated in another study to provide protection against acute pancreatitis by up-regulating miR-216b and inhibiting both TNF-α and the p38/MAPK signaling pathway, consequently suppressing the release of inflammatory factors such as IL6 [42].Several studies have confirmed that luteolin can inhibit the expression of inflammatory factors such as TNF-α, IL-6, and IL-1β [43–45]. According to another study, luteolin reduces the severity of AP in mice by activating heme oxygenase (HO-1), which exerts anti-inflammatory and antioxidant effects [46]. This activity is linked to the suppression of NF-KB signaling pathway activation. Studies by Kim et al. have shown that kaempferol not only has free radical scavenging and anti-inflammatory activities in vitro but also can effectively inhibit the inflammatory symptoms in vivo [47]. A variety of inflammatory signaling components, such as Src, Syk, and IRAK4, which are essential for the activation of NF-kB and AP-1, can be inhibited by kaempferol, in particular. Kaempferol inhibits matrix metalloproteinase-1 (MMP-1) and down-regulates MMP-1 expression by inhibiting the activation of transcription factor-1



(A) Common targets of the two key subnetworks

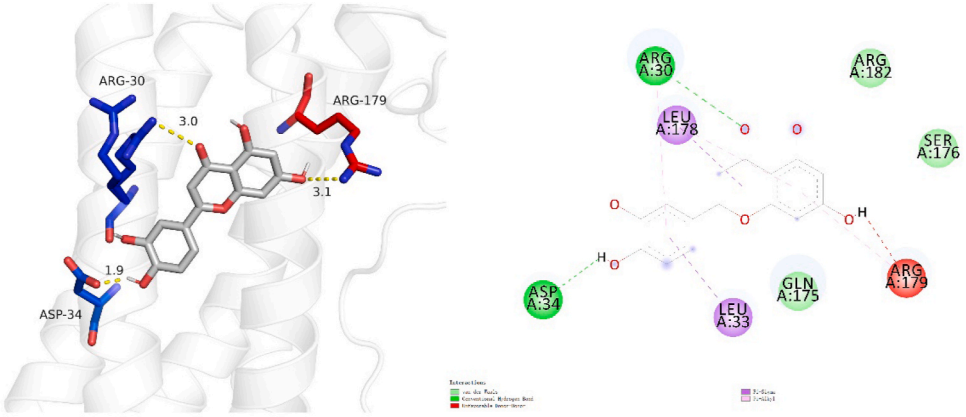


(B) IL6-quercetin

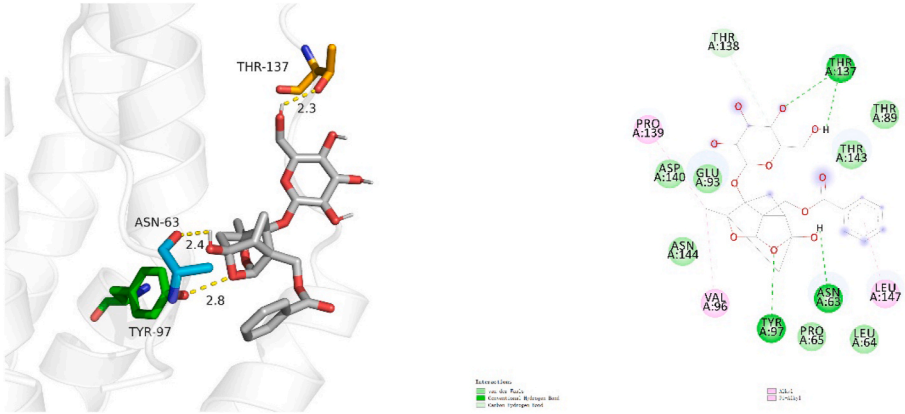
Fig. 6. The selection of key genes within the subnetwork and molecular docking diagram of chemical composition to target. (A) The identification of key genes by the intersection of the two crucial subnetworks. (B) IL6-quercetin. (C) IL6-luteolin. (D) IL6-paeoniflorin.

(AP-1) [48]. These studies suggest that there are a variety of active components in SLXG that can improve the symptoms of pancreatitis through different mechanisms. The effectiveness of SLXG in preventing AP can be predicted from numerous studies on the action mechanisms of these components, including the anti-inflammatory, antioxidant, and anti-apoptotic effects.

The GO enrichment analysis of this study showed that SLXG could participate in the process of cellular response to chemical stimulus,cellular response to organic substance,abiotic stimulation, response to oxygen containing compound, cell apoptosis, etc. KEGG pathway analysis shows that the target genes are mainly related to the PI3K-Akt signaling pathway, AGE-RAGE signaling pathway, etc., and play a role in prostate cancer, pancreatic cancer, bladder cancer, and other cancer pathways; Human cytomegalovirus infection, Kaposi sarcoma-associated herpesvirus infection and other virus-related pathways were also involved; and TNF



(C) IL6-luteolin



(D) IL6- paeoniflorin

Fig. 6. (*continued*).

Table 1
The most critical nine genes and MMC values.

RANK	1	2	3	4	5	6	7	8	9
Gene	IL6	STAT3	RELA	MAPK3	MAPK1	TNF	ERS1	FOS	MYC
MCC	53368	51273	28258	24356	23234	22862	20556	20320	15422

Table 2
Molecular docking scores.

NO	Mol ID	Compound name	Docking score (kcal/mol)
1	MOL000098	quercetin	−7.1
2	MOL000006	luteolin	−7.2
3	MOL001924	paeoniflorin	−6.6

signaling pathway and IL17 signaling pathway are related. PI3K/AKT is a crucial signal transduction pathway that regulates several signal transduction pathways, including stress, apoptosis, and proliferation. The expression of p-Akt and the activity of NF-kB in pancreatic tissue were significantly elevated in the AP model induced by pancreatic duct ligation [49]. Research showed that by inhibiting the PI3K pathway of SAP rats, the activity of NF-kB was decreased, the expression of the apoptosis inhibitory gene and the

release of inflammatory factors were reduced, and the condition of rats was alleviated [50]. According to research by Sun et al. [12], AP can be improved by regulating the PI3K/AKT signal pathway, promoting apoptosis, and inhibiting the inflammatory response and pathological damage. TNF signaling pathway and IL-17 signaling pathway are classic inflammatory signal pathways crucial in the occurrence and development of pancreatitis [51]. Many of the key components, main targets, and pathways of SLXG are related to cancer, suggesting that SLXG might help to treat and prevent cancer. From the above enrichment analysis results, it can be seen that SLXG may improve the symptoms of pancreatitis through multiple signal pathways.

The PPI network and key network modules were constructed by 164 target genes. The topological analysis found the nine most critical central targets in the PPI network. This study centered on the crucial gene IL6, and molecular docking was carried out to confirm the interaction between the active compounds in SLXG and IL6. The findings of molecular docking showed that quercetin, luteolin, and paeoniflorin could bind well with IL6. In addition, the inhibitory effects of quercetin, luteolin, paeoniflorin, and other active ingredients in acute pancreatitis have been reported. Only a few studies have proved that paeoniflorin can improve acute pancreatitis and acute kidney injury and lung injury caused by acute pancreatitis in rats [52,53]. The findings of molecular docking showed that paeoniflorin might be crucial in treating acute pancreatitis; However, the specific mechanism of paeoniflorin in acute pancreatitis is still unclear, which needs further research and exploration.

5. Conclusion

In conclusion, this study conducted molecular docking validation and network pharmacological analysis to anticipate the action targets and main signal pathway of SLXG in treating AP. The key targets include IL6, STAT3, RELA, MAPK3, MAPK1, TNF, ESR1, FOS, MYC, etc. The key pathways mainly involve the PI3K-Akt signal pathway, IL17 signal pathway, TNF signal pathway, etc. Some potential active ingredients of SLXG may have a certain intervention effect on the clinical symptoms of AP. The therapeutic effect of SLXG may be achieved by affecting multiple targets and related pathways simultaneously, which also provides some references for further exploring its mechanism of action. In summary, the findings of this study demonstrate the perspective of bioinformatics on the efficacy of SLXG in the treatment of AP, offer a new prospect for SLXG application, and may also facilitate the basic research and design of targeted drugs for acute pancreatitis. It also provides a fresh concept for the development of a traditional Chinese medicine compound, that is, whether the traditional Chinese medicine compound can prevent and cure the related complications while treating the disease itself. The limitations of this study include that it only explores the theoretical level of the possibility; further animal tests and clinical trials are needed to verify the results of this research.

Ethics approval and consent to participate

As this study does not involve animal and patient experiments, the ethical approval and consent to participate are not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All the data can be obtained from the open source platform provided in the article.

Founding

This study was supported by the Jinan New Support Projects for Universities (Talent Development Special Fund,Grant No:20228118) and Program for Integrated Traditional Chinese and Western Medicine in Shandong Province of China (Grant No: YXH2019ZXY007).

Data availability statement

Data included in article/supplementary material/referenced in article.

CRediT authorship contribution statement

Jiaxing Wang: Writing – original draft, Investigation. **Yang Wang:** Writing – original draft, Formal analysis. **Zitong Chen:** Software, Methodology. **Bin Liu:** Validation, Data curation. **Wujie Wang:** Writing – review & editing, Supervision, Data curation. **Yuliang Li:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank everyone who contributed to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27365.

References

[1] M.S. Petrov, D. Yadav, Global epidemiology and holistic prevention of pancreatitis, Nat. Rev. Gastroenterol. Hepatol. 16 (3) (2019) 175–184.
[2] K.S. Chan, V.G. Shelat, Diagnosis, severity stratification and management of adult acute pancreatitis-current evidence and controversies, World J. Gastrointest. Surg. 14 (11) (2022) 1179–1197.
[3] J.A. Moreau, A.R. Zinsmeister, L.J. Melton, E.P. DiMagno, Gallstone pancreatitis and the effect of cholecystectomy: a population-based cohort study, Mayo Clin. Proc. 63 (5) (1988) 466–473.
[4] N.G. Venneman, W. Renooij, J.F. Rehfeld, G.P. VanBerge-Henegouwen, P.M.N.Y.H. Go, I.A.M.J. Broeders, K.J. van Erpecum, Small gallstones, preserved gallbladder motility, and fast crystallization are associated with pancreatitis, Hepatology 41 (4) (2005) 738–746.
[5] M.M. Lerch, A.K. Saluja, M. Rünzi, R. Dawra, M. Saluja, M.L. Steer, Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum, Gastroenterology 104 (3) (1993) 853–861.
[6] K. Kato, M. Shiba, Y. Kakiya, H. Maruyama, M. Ominami, S. Fukunaga, S. Sugimori, Y. Nagami, T. Watanabe, K. Tominaga, Y. Fujiwara, Celecoxib oral administration for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized prospective trial, Pancreas 46 (7) (2017) 880–886.
[7] B. Kochar, V.S. Akshintala, E. Afghani, B.J. Elmunzer, K.J. Kim, A.M. Lennon, M.A. Khashab, A.N. Kalloo, V.K. Singh, Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials, Gastrointest. Endosc. 81 (1) (2015).
[8] B. Liu, J. Ma, S. Li, C. Li, H. Qi, D. Nian, C. Yin, J. Zhu, C. Wang, Y. Jia, T. Jiang, J. Lu, L. Wang, D. Shen, X. Hou, D. Li, Z. Zhang, F. Du, H. Wu, T. Yu, Y. Li, Percutaneous transhepatic papillary balloon dilation versus endoscopic retrograde cholangiopancreatography for Common bile duct stones: a multicenter prospective study, Radiology 300 (2) (2021) 470–478.
[9] Y.R. Seo, J.H. Moon, H.J. Choi, D.C. Kim, T.H. Lee, S.-W. Cha, Y.D. Cho, S.-H. Park, S.-J. Kim, Papillary balloon dilation is not itself a cause of post-endoscopic retrograde cholangiopancreatography pancreatitis; results of anterograde and retrograde papillary balloon dilation, J. Gastroenterol. Hepatol. 28 (8) (2013) 1416–1421.
[10] P. Szatmary, T. Grammatikopoulos, W. Cai, W. Huang, R. Mukherjee, C. Halloran, G. Beyer, R. Sutton, Acute pancreatitis: diagnosis and treatment, Drugs 82 (12) (2022) 1251–1276.
[11] H. Xiang, Q. Zhang, B. Qi, X. Tao, S. Xia, H. Song, J. Qu, D. Shang, Chinese herbal medicines attenuate acute pancreatitis: pharmacological activities and mechanisms, Front. Pharmacol. 8 (2017) 216.
[12] W. Sun, Y. Chen, H. Li, H. Liu, J. Li, J. Chen, D. Feng, Material basis and molecular mechanisms of Dachengqi decoction in the treatment of acute pancreatitis based on network pharmacology, Biomed. Pharmacother. 121 (2020) 109656.
[13] L. Zhan, J. Pu, Y. Hu, P. Xu, W. Liang, C. Ji, Uncovering the pharmacology of xiaochaihu decoction in the treatment of acute pancreatitis based on the network pharmacology, BioMed Res. Int. 2021 (2021) 6621682.
[14] K. Zhu, M. Zhang, J. Long, S. Zhang, H. Luo, Elucidating the mechanism of action of Salvia miltiorrhiza for the treatment of acute pancreatitis based on network pharmacology and molecular docking Technology, Comput. Math. Methods Med. 2021 (2021) 8323661.
[15] Y. He, C. Hu, S. Liu, M. Xu, G. Liang, D. Du, T. Liu, F. Cai, Z. Chen, Q. Tan, L. Deng, Q. Xia, Anti-inflammatory effects and molecular mechanisms of Shenmai injection in treating acute pancreatitis: network pharmacology analysis and experimental verification, Drug Des. Dev. Ther. 16 (2022) 2479–2495.
[16] Y. Ma, H. Jiang, Y. Wang, The protective effect of Shuganlidan Particles on acute pancreatitis in rats, Pharmacology and Clinics of Chinese Materia Medica 28 (3) (2012) 3.
[17] Z. Su, X. Li, H. Lin, Prevention of recurrence of acute biliary pancreatitis by soothing the liver and promoting gallbladder: a report of 64 cases, Chinese J. Integrated Tradit. Western Med. Digest. 21 (12) (2013) 659.
[18] E. Wang, Clinical observation of Shugan Lidan decoction combined with ERCP in the treatment of biliary pancreatitis, Res. Integrated Tradit. Chinese Western Med. 11 (3) (2019) 138–139 [In Chinese].
[19] W. Jin, J. Zhang, Clinical effect of modified Chaihu Shugan powder in the adjuvant treatment of biliary acute pancreatitis, Chinese J. Primary Medicine Pharmacy 26 (4) (2019) 428–431 [In Chinese].
[20] X. Shi, H. Zeng, Study on the clinical effect of Chaihu Shugan Powder enema in the treatment of acute pancreatitis, J. Notrh Sichuan Medical College 34 (5) (2019) 619–621 [In Chinese].
[21] J. Ru, P. Li, J. Wang, W. Zhou, B. Li, C. Huang, P. Li, Z. Guo, W. Tao, Y. Yang, X. Xu, Y. Li, Y. Wang, L. Yang, TCMSP: a database of systems pharmacology for drug discovery from herbal medicines, J. Cheminf. 6 (2014) 13.
[22] Z. Liu, F. Guo, Y. Wang, C. Li, X. Zhang, H. Li, L. Diao, J. Gu, W. Wang, D. Li, F. He, BATMAN-TCM: a bioinformatics analysis tool for molecular mechANism of traditional Chinese medicine, Sci. Rep. 6 (2016) 21146.
[23] UniProt: a hub for protein information, Nucleic Acids Res. 43 (Database issue) (2015) D204–D212.
[24] M. Rebhan, V. Chalifa-Caspi, J. Prilusky, D. Lancet, GeneCards: integrating information about genes, proteins and diseases, Trends Genet. 13 (4) (1997) 163.
[25] J.S. Amberger, C.A. Bocchini, F. Schiettecatte, A.F. Scott, A. Hamosh, OMIM.org: online Mendelian Inheritance in Man (OMIM®), an online catalog of human genes and genetic disorders, Nucleic Acids Res. 43 (Database issue) (2015) D789–D798.
[26] J.M. Barbarino, M. Whirl-Carrillo, R.B. Altman, T.E. Klein, PharmGKB: a worldwide resource for pharmacogenomic information, Wiley Interdiscip Rev Syst Biol Med 10 (4) (2018) e1417.
[27] D.S. Wishart, Y.D. Feunang, A.C. Guo, E.J. Lo, A. Marcu, J.R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, D. Le, A. Pon, C. Knox, M. Wilson, DrugBank 5.0: a major update to the DrugBank database for 2018, Nucleic Acids Res. 46 (D1) (2018) D1074–D1082.
[28] P. Shannon, A. Markiel, O. Ozier, N.S. Baliga, J.T. Wang, D. Ramage, N. Amin, B. Schwikowski, T. Ideker, Cytoscape: a software environment for integrated models of biomolecular interaction networks, Genome Res. 13 (11) (2003) 2498–2504.
[29] W. Shen, Z. Song, X. Zhong, M. Huang, D. Shen, P. Gao, X. Qian, M. Wang, X. He, T. Wang, S. Li, X. Song, Sangerbox: a comprehensive, interaction-friendly clinical bioinformatics analysis platform, iMeta 1 (3) (2022) e36.
[30] D. Szklarczyk, A.L. Gable, D. Lyon, A. Junge, S. Wyder, J. Huerta-Cepas, M. Simonovic, N.T. Doncheva, J.H. Morris, P. Bork, L.J. Jensen, Mering Cv, STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, Nucleic Acids Res. 47 (D1) (2019) D607–D613.

[31] Q.-D. Xia, Y. Xun, J.-L. Lu, Y.-C. Lu, Y.-Y. Yang, P. Zhou, J. Hu, C. Li, S.-G. Wang, Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19, Cell Prolif. 53 (12) (2020) e12949.
[32] S. Yuan, H.S. Chan, Z. Hu, Using PyMOL as a platform for computational drug design, Wiley Interdiscip. Rev. Comput. Mol. Sci. 7 (2) (2017) e1298.
[33] O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem. 31 (2) (2010) 455–461.
[34] K. Gong, W. Guo, K. Du, F. Wang, M. Li, J. Guo, Mechanism of huoluo xiaoling dan in the treatment of psoriasis based on network pharmacology and molecular docking, Evid Based Complement Alternat Med 2022 (2022) 7053613.
[35] N.T. Nguyen, T.H. Nguyen, T.N.H. Pham, N.T. Huy, M.V. Bay, M.Q. Pham, P.C. Nam, V.V. Vu, S.T. Ngo, Autodock vina adopts more accurate binding poses but Autodock4 forms better binding affinity, J. Chem. Inf. Model. 60 (1) (2020) 204–211.
[36] P.K. Garg, V.P. Singh, Organ failure due to systemic injury in acute pancreatitis, Gastroenterology 156 (7) (2019) 2008–2023.
[37] B. Matta, A. Gougol, X. Gao, N. Reddy, R. Talukdar, R. Kochhar, M.K. Goenka, A. Gulla, J.A. Gonzalez, V.K. Singh, M. Ferreira, T. Stevens, S.T. Barbu, H. Nawaz, S.C. Gutierrez, N.O. Zarnescu, G. Capurso, J. Easler, K. Triantafyllou, M. Pelaez-Luna, S. Thakkar, C. Ocampo, E. de-Madaria, G.A. Cote, B.U. Wu, P. Paragomi, I. Pothoulakis, G. Tang, G.I. Papachristou, Worldwide variations in demographics, management, and outcomes of acute pancreatitis, Clin. Gastroenterol. Hepatol. 18 (7) (2020).
[38] P.G. Lankisch, C. Assmus, D. Lehnick, P. Maisonneuve, A.B. Lowenfels, Acute pancreatitis: does gender matter? Dig. Dis. Sci. 46 (11) (2001) 2470–2474.
[39] F. Lammert, K. Gurusamy, C.W. Ko, J.-F. Miquel, N. Méndez-Sánchez, P. Portincasa, K.J. van Erpecum, C.J. van Laarhoven, D.Q.H. Wang, Gallstones, Nat. Rev. Dis. Prim. 2 (2016) 16024.
[40] N.R. Chanu, P. Gogoi, P.A. Barbhuiya, P.P. Dutta, M.P. Pathak, S. Sen, Natural flavonoids as potential therapeutics in the management of diabetic wound: a review, Curr. Top. Med. Chem. 23 (8) (2023) 690–710.
[41] K.M.M.B. Carvalho, T.C. Morais, T.S. de Melo, G.A. de Castro Brito, G.M. de Andrade, V.S. Rao, F.A. Santos, The natural flavonoid quercetin ameliorates cerulein-induced acute pancreatitis in mice, Biol. Pharm. Bull. 33 (9) (2010) 1534–1539.
[42] B. Sheng, L. Zhao, X. Zang, J. Zhen, Y. Liu, W. Bian, W. Chen, Quercetin inhibits caerulein-induced acute pancreatitis through regulating miR-216b by targeting MAP2K6 and NEAT1, Inflammopharmacology 29 (2) (2021) 549–559.
[43] J. Fei, B. Liang, C. Jiang, H. Ni, L. Wang, Luteolin inhibits IL-1β-induced inflammation in rat chondrocytes and attenuates osteoarthritis progression in a rat model, Biomed. Pharmacother. 109 (2019) 1586–1592.
[44] S. Jang, K.W. Kelley, R.W. Johnson, Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1, Proc. Natl. Acad. Sci. U.S.A. 105 (21) (2008) 7534–7539.
[45] Z. Jia, P. Nallasamy, D. Liu, H. Shah, J.Z. Li, R. Chitrakar, H. Si, J. McCormick, H. Zhu, W. Zhen, Y. Li, Luteolin protects against vascular inflammation in mice and TNF-alpha-induced monocyte adhesion to endothelial cells via suppressing IKBα/NF-κB signaling pathway, J. Nutr. Biochem. 26 (3) (2015) 293–302.
[46] J. Xiong, K. Wang, C. Yuan, R. Xing, J. Ni, G. Hu, F. Chen, X. Wang, Luteolin protects mice from severe acute pancreatitis by exerting HO-1-mediated anti-inflammatory and antioxidant effects, Int. J. Mol. Med. 39 (1) (2017) 113–125.
[47] S.H. Kim, J.G. Park, G.-H. Sung, S. Yang, W.S. Yang, E. Kim, J.H. Kim, V.T. Ha, H.G. Kim, Y.-S. Yi, J.H. Kim, K.-S. Baek, N.Y. Sung, M-n Lee, J.-H. Kim, J.Y. Cho, Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain, Mol. Nutr. Food Res. 59 (7) (2015) 1400–1405.
[48] H. Lim, H.P. Kim, Inhibition of mammalian collagenase, matrix metalloproteinase-1, by naturally-occurring flavonoids, Planta Med. 73 (12) (2007) 1267–1274.
[49] I. Samuel, M.A. Yorek, A. Zaheer, R.A. Fisher, Bile-pancreatic juice exclusion promotes Akt/NF-kappaB activation and chemokine production in ligation-induced acute pancreatitis, J. Gastrointest. Surg. 10 (7) (2006) 950–959.
[50] G. Wang, B. Han, H. Zhou, L. Wu, Y. Wang, G. Jia, J. Lv, Z. Cheng, S. Pan, J. Liu, Y. Zhou, B. Sun, Inhibition of hydrogen sulfide synthesis provides protection for severe acute pancreatitis rats via apoptosis pathway, Apoptosis 18 (1) (2013) 28–42.
[51] G. Li, H. Chen, L. Liu, P. Xiao, Y. Xie, X. Geng, T. Zhang, Y. Zhang, T. Lu, H. Tan, L. Li, B. Sun, Role of interleukin-17 in acute pancreatitis, Front. Immunol. 12 (2021) 674803.
[52] Y. Hu, W. Yang, Paeoniflorin can improve acute lung injury caused by severe acute pancreatitis through Nrf2/ARE pathway, Comput. Math. Methods Med. 2022 (2022) 5712219.
[53] P. Wang, W. Wang, Q. Shi, L. Zhao, F. Mei, C. Li, T. Zuo, X. He, Paeoniflorin ameliorates acute necrotizing pancreatitis and pancreatitis-induced acute renal injury, Mol. Med. Rep. 14 (2) (2016) 1123–1131.