Uncovering the Pharmacological of Xiaochaihu Decoction in the Treatment of Pancreatitis Based on the Network Pharmacology

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Research

Keywords: Xiaochaihu Decoction (XD), pancreatitis, network pharmacology

DOI: https://doi.org/10.21203/rs.3.rs-90020/v1

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Abstract

Background

Xiaochaihu Decoction (XD) was a traditional prescription, has been demonstrated the pharmacodynamic on pancreatitis. But the underline mechanism remained to be explored. Therefore, this study was aimed to combined network pharmacology method and molecular docking technology to demonstrate the potential mechanism of XD treated with pancreatitis.

Methods

Firstly, compounds of seven herbs containing XD were collected from TCMSP Database and the putative targets of Pancreatitis were obtained from OMIM, TTD, Genecards Database. Then PPI network was constructed according to the matching results between XD potential targets and pancreatic neoplasms targets. Furthermore, enrichment analysis on GO and KEGG by DAVID utilized bioinformatics resources. Finally, Molecular Docking was performed to simulate the interaction between the active compound of XD and putative targets.

Results

A total of 196 active ingredients and 91 putative targets were selected out. The PPI interaction network analysis demonstrated that Quercetin was the candidate agents and MAPK3, IL-6 and TP53 were the potential targets for the XD treatment of pancreatitis. The KEGG analysis revealed that pathways in cancers, TNF signaling way, MAPK signaling way might play an important role in pancreatitis therapy. And Molecular Docking results showed that Quercetin combined well with MAPK3, IL-6 and TP53.

Conclusion

This study illustrated that Quercetin containing in XD might played an important role in pancreatitis therapy by acting the key genes of MPAK3, IL-6 and TP53. And it also provided a strategy to elucidate the mechanisms of Traditional Chinese Medicine (TCM) at the level of network pharmacology.

Background

Pancreatitis is highly variable disease characterized by acute inflammation and necrosis of the pancreatic parenchyma which associated with a high mortality of about 20%-30% [1-3]. And it bought on mainly some factors that were gallstones, chronic alcohol and obesity [4-6]. Pancreatitis could divide into local complications including ascites, acute fluid collections, as well as infected necrosis and systemic complications including single organ failure or multiple organ dysfunction syndrome (MODS) [7, 8]. At present, the major therapeutic measures for pancreatitis was symptomatic treatment such as easement of pain, the correction of fluid, electrolyte, and pH balances [9]. Currently, there is lack of effective therapeutic strategy for pancreatitis, so valid drug needed to be developed. Due to the widespread
application of Traditional Chinese Medicine (TCM), it had been testified that Chinese decoctions had significant curative effect on the treatment of Pancreatitis [10, 11].

Xiaochaihu Decoction (XD) was chronic in Shanghan Lun, a famous Chinese ancient book, which was composed of Chaihu (Radix Bupleuri), Banxia (Arum Ternatum Thunb), Renshen (Panax ginseng C. A. Mey.), Gancao (licorice), Huangqin (Scutellariae Radix), Shengjiang (Zingiber officinale Roscoe) and Dazao (Jujubae Fructus), and in recent years experiments showed that XD was beneficial to prevention and cure of Pancreatitis [12, 13]. Shugen Zhang et al indicated that XD could protect pancreas against chronic injury and improve pancreatic exocrine function in DBTC induced rat CP model [14]. This hinted that XD might be a potential alternative medicine for treatment of Pancreatitis, but its pharmacological mechanism is not well understood.

With the rapid development of Network pharmacology in systems biology, it frequently used in systematically investigate the interaction between Chinese medicine and the complicated human body [15]. Network pharmacology was combined with systems biology, pharmacology and computer technology to explore the complex mechanism by which Chinese formulations treat complex diseases [16]. Furthermore, Network pharmacology applied to the research of TCM could be analysis the rationality of pharmacodynamics mechanism [17].

In the study, we aimed to use a comprehensive network pharmacology-based approach to investigate the mechanisms of how XD exerts the therapeutic effects on Pancreatitis.

**Materials And Methods**

**Data collection of 7 herbs contained in XD**

We collected the chemical ingredients of 7 herbs contained in Xiaohaihu Decoction by Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, https://tcmspw.com/tcmsp.php) [18]. Then screening the requested ingredients according to conditions that oral bioavailability (OB) ≥ 30%, drug likeness (DL) ≥ 0.18. The putative targets of 7 herbs contained in Xiaochaihu Decoction were searched in Drugbank (https://www.drugbank.ca/unearth/advanced/bio_entities)

**The putative targets of Pancreatitis collection**

By “Pancreatitis” in order to search words, search out the putative targets in GeneCards database (https://auth.lifemapsc.com/) , OMIM database (https://www.omim.org/) and TTD database (http://db.idrblab.net/ttd/) with the with the species limited as “Homo sapiens”. Then removed the duplicate value to get the relative putative.

**Gene name correction and common targets screening**
Firstly, Gene name of Xiaochaihu Decoction and Pancreatitis were adjusted by Uniprot database (https://www.uniprot.org/) and then make the intersection map of component targets and disease targets by Venn map to obtain the intersection targets, and further to get the potential therapeutic targets of XD on the treatment of Pancreatitis.

**TCM-Compound-Target-Disease Network construction**

Intersection targets obtained from Venn map were reverse screening for corresponding chemical ingredients and herbs. And then TCM-Compound-Target-Disease Network could be constructed which was also visualized by Cytoscape 3.6.1.

**Protein protein interaction (PPI) network**

Targets obtained from Venn map was uploaded to STRING Database (http://string-db.org/) and the PPI network was generated with the species limited as “Homo sapiens” and medium confidence as “0.4”. And acquired PPI network was imported into Cytoscape 3.6.1 to visually analyze.

**Pathway enrichment performance**

The intersection targets were imported into DAVID Database (https://david.ncifcrf.gov/) and then obtained the gene function as well as the effects in the pathway. Gene ontology (GO) and pathway enrichment analyses were performed, setting list type to gene list and limiting species to Homo sapiens, and sorted the top 20 term to draw histogram by Graphpad Prism. Kyoto Encyclopedia of Genes and Genomes database (KEGG, http://www.genome.jp/kegg/) analysis was visualization by ggplot2 database.

**Molecular docking method**

Active compounds owed the most targets and targets closely related with Pancreatitis were imported into Discovery Studio 4 software, and then molecular docking was performed by using CDOCKER model.

**Results**

**Active ingredients of Xiaochaihu Decoction**

There were 196 active ingredients of 7 herbs containing in Xiaochaihu Decoction which were collected from TCMSP Database with the limited lists “OB≥30%, OL≥0.18”. As is shown in Table.1, the active composition included 17 in Chaihu, 13 in Banxia, 36 in Huangqin, 22 in Renshen, 29 in Daozao, 5 in shenjiang, 94 in Gancao.
Table 1: Active ingredients information of Xiaochaihu Decoction
| Mol ID     | Molecule Name                                      | OB (%) | DL  | Herb                                      |
|------------|---------------------------------------------------|--------|-----|-------------------------------------------|
| MOL000073  | ent-Epicatechin                                    | 48.96  | 0.24| *Scutellariae Radix*                      |
| MOL000096  | (-)-catechin                                       | 49.68  | 0.24| *Jujubae Fructus*                         |
| MOL000098  | quercetin                                          | 46.43  | 0.28| *Radix Bupleuri*licorice*Jujubae Fructus* |
| MOL00173   | wogonin                                           | 30.68  | 0.23| *Scutellariae Radix*                      |
| MOL00211   | Mairin                                             | 55.38  | 0.78| licoriceJujubae Fructus                  |
| MOL00228   | (2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one     | 55.23  | 0.2 | *Scutellariae Radix*                      |
| MOL00239   | Jaranol                                            | 50.83  | 0.29| licorice                                 |
| MOL00354   | isorhamnetin                                       | 49.6   | 0.31| *Radix Bupleuri*licorice                  |
| MOL00358   | beta-sitosterol                                    | 36.91  | 0.75| *Arum Ternatum Thunb*Panax ginseng C. A. Mey.licoriceScutellariae RadixZingiber officinaleRoscoellicoriceJujubae Fructus |
| MOL00359   | sitosterol                                         | 36.91  | 0.75| *Scutellariae Radix*licorice              |
| MOL00392   | formononetin                                       | 69.67  | 0.21| licorice                                 |
| MOL00417   | Calycosin                                          | 47.75  | 0.24| licorice                                 |
| MOL00422   | kaempferol                                         | 41.88  | 0.24| *Radix Bupleuri*Panax ginseng C. A. Mey.licorice |
| MOL00449   | Stigmasterol                                       | 43.83  | 0.76| *Arum Ternatum Thunb*Panax ginseng C. A. Mey.licoriceScutellariae RadixZingiber officinaleRoscoellicoriceJujubae FructusRadix Bupleuri |
| MOL00490   | petunidin                                          | 30.05  | 0.31| *Radix Bupleuri*                         |
| MOL00492   | (+)-catechin                                       | 54.83  | 0.24| *Jujubae Fructus*                        |
| MOL00497   | licochalcone a                                     | 40.79  | 0.29| licorice                                 |
| MOL00500   | licochalcone a                                     | 40.79  | 0.29| licorice                                 |
| MOL00500   | Vestitol                                           | 74.66  | 0.21| licorice                                 |
| MOL00519   | coniferin                                          | 31.11  | 0.32| *Arun Ternatum Thunb*                    |
| MOL00525   | Norwogonin                                         | 39.4   | 0.21| *Scutellariae Radix*                     |
| Code      | Compound                                      | Value 1 | Value 2 | Source                                    |
|-----------|-----------------------------------------------|---------|---------|-------------------------------------------|
| MOL000552 | 5,2'-Dihydroxy-6,7,8-trimethoxyflavone         | 31.71   | 0.35    | Scutellariae Radix                        |
| MOL000627 | Stepholidine                                  | 33.11   | 0.54    | Jujubae Fructus                           |
| MOL000783 | Protoporphyrin                                | 30.86   | 0.56    | Jujubae Fructus                           |
| MOL000787 | Fumarine                                      | 59.26   | 0.83    | Panax ginseng C. A. Mey. & Jujubae Fructus |
| MOL001454 | berberine                                     | 36.86   | 0.78    | Jujubae Fructus                           |
| MOL001458 | coptisine                                     | 30.67   | 0.86    | Scutellariae Radix                        |
| MOL001484 | Inermine                                      | 75.18   | 0.54    | licorice                                  |
| MOL001490 | bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate | 43.59  | 0.35    | Scutellariae Radix                        |
| MOL001506 | Supraene                                      | 33.55   | 0.42    | Scutellariae Radix                        |
| MOL001522 | (S)-Coclaurine                                | 42.35   | 0.24    | Jujubae Fructus                           |
| MOL001645 | Linoleyl acetate                              | 42.1    | 0.2     | Radix Bupleuri                            |
| MOL001698 | acacetin                                      | 34.97   | 0.24    | Scutellariae Radix                        |
| MOL001755 | 24-Ethylcholest-4-en-3-one                    | 36.08   | 0.76    | Arum Ternatum Thunb                       |
| MOL001771 | poriferast-5-en-3beta-ol                     | 36.91   | 0.75    | Zingiber officinale Roscoe                |
| MOL001792 | DFV                                           | 32.76   | 0.18    | licorice                                  |
| MOL002311 | Glycyrol                                      | 90.78   | 0.67    | licorice                                  |
| MOL002565 | Medicarpin                                    | 49.22   | 0.34    | licorice                                  |
| MOL002670 | Cavidine                                      | 35.64   | 0.81    | Arum Ternatum Thunb                       |
| MOL002714 | baikalein                                     | 33.52   | 0.21    | Arum Ternatum Thunb Scutellariae Radix    |
| MOL002773 | beta-carotene                                 | 37.18   | 0.58    | Jujubae Fructus                           |
| MOL002776 | Baicalin                                      | 40.12   | 0.75    | Arum Ternatum Thunb & Radix Bupleuri      |
| MOL002844 | Pinocembrin                                   | 64.72   | 0.18    | licorice                                  |
| MOL002879 | Diop                                          | 43.59   | 0.39    | Panax ginseng C. A. Mey. & Scutellariae Radix |
| MOL002897 | epiberberine                                  | 43.09   | 0.78    | Scutellariae Radix                        |
| MOL002908 | 5,8,2'-Trihydroxy-7-methoxyflavone            | 37.01   | 0.27    | Scutellariae Radix                        |
| MOL002909 | 5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone     | 33.82   | 0.45    | Scutellariae Radix                        |
| MOL002910 | Carthamidin                  | 41.15 | 0.24 | Scutellariae Radix |
|-----------|-----------------------------|-------|------|--------------------|
| MOL002911 | 2,6,2',4'-tetrahydroxy-6' -methoxychaleone | 69.04 | 0.22 | Scutellariae Radix |
| MOL002913 | Dihydrobaicalin_qt           | 40.04 | 0.21 | Scutellariae Radix |
| MOL002914 | Eriodyctiol (flavanone)      | 41.35 | 0.24 | Scutellariae Radix |
| MOL002915 | Salvigenin                   | 49.07 | 0.33 | Scutellariae Radix |
| MOL002917 | 5,2',6'-Trihydroxy-7,8-dimethoxyflavone | 45.05 | 0.33 | Scutellariae Radix |
| MOL002925 | 5,7,2',6'-Tetrahydroxyflavone | 37.01 | 0.24 | Scutellariae Radix |
| MOL002926 | dihydroorxylin A             | 38.72 | 0.23 | Scutellariae Radix |
| MOL002927 | Skullcapflavone II           | 69.51 | 0.44 | Scutellariae Radix |
| MOL002928 | oroxylin a                   | 41.37 | 0.23 | Scutellariae Radix |
| MOL002932 | Panicolin                    | 76.26 | 0.29 | Scutellariae Radix |
| MOL002933 | 5,7,4'-Trihydroxy-8-methoxyflavone | 36.56 | 0.27 | Scutellariae Radix |
| MOL002934 | NEOBAICALEIN                 | 104.34| 0.44 | Scutellariae Radix |
| MOL002937 | DIHYDROOROXYLIN              | 66.06 | 0.23 | Scutellariae Radix |
| MOL003410 | Ziziphin_qt                  | 66.95 | 0.62 | Jujubae Fructus    |
| MOL003578 | Cycloartenol                 | 38.69 | 0.78 | Arum Ternatum Thunb |
| MOL003648 | Inermin                      | 65.83 | 0.54 | Panax ginseng C. A. Mey. |
| MOL003656 | Lupiwighteone                | 51.64 | 0.37 | licorice           |
| MOL003896 | 7-Methoxy-2-methyl isoflavone| 42.56 | 0.2  | licorice           |
| MOL004328 | naringenin                   | 59.29 | 0.21 | licorice           |
| MOL004350 | Ruvoside_qt                  | 36.12 | 0.76 | Jujubae Fructus    |
| MOL004492 | Chrysanthemaxanthin          | 38.72 | 0.58 | Panax ginseng C. A. Mey. |
| MOL004598 | 3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone | 31.97 | 0.59 | Radix Bupleuri    |
| MOL004609 | Areapillin                   | 48.96 | 0.41 | Radix Bupleuri    |
| MOL004624 | Longikaurin A                | 47.72 | 0.53 | Radix Bupleuri    |
| MOL004628 | Octalupine                   | 47.82 | 0.28 | Radix Bupleuri    |
| MOL004644 | Sainfuran                    | 79.91 | 0.23 | Radix Bupleuri    |
| ID      | Compound                                      | Amount | p.p.m. | Plant            |
|---------|-----------------------------------------------|--------|--------|------------------|
| MOL004648 | Troxerutin                                    | 31.6   | 0.28   | Radix Bupleuri   |
| MOL004653 | (+)-Anomalin                                   | 46.06  | 0.66   | Radix Bupleuri   |
| MOL004702 | saikosaponin c_qt                             | 30.5   | 0.63   | Radix Bupleuri   |
| MOL004718 | α-spinasterol                                  | 42.98  | 0.76   | Radix Bupleuri   |
| MOL004805 | (2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one | 31.79  | 0.72   | licorice         |
| MOL004806 | euchrenone                                     | 30.29  | 0.57   | licorice         |
| MOL004808 | glyasperin B                                  | 65.22  | 0.44   | licorice         |
| MOL004810 | glyasperin F                                  | 75.84  | 0.54   | licorice         |
| MOL004811 | Glyasperin C                                  | 45.56  | 0.4    | licorice         |
| MOL004814 | Isotrifoliol                                  | 31.94  | 0.42   | licorice         |
| MOL004815 | (E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one | 39.62  | 0.35   | licorice         |
| MOL004820 | kanzonols W                                   | 50.48  | 0.52   | licorice         |
| MOL004824 | (2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one | 60.25  | 0.63   | licorice         |
| MOL004827 | Semilicoisoavone B                            | 48.78  | 0.55   | licorice         |
| MOL004828 | Glepidotin A                                  | 44.72  | 0.35   | licorice         |
| MOL004829 | Glepidotin B                                  | 64.46  | 0.34   | licorice         |
| MOL004833 | Phaseolinisoflavan                            | 32.01  | 0.45   | licorice         |
| MOL004835 | Glypallichalcone                              | 61.6   | 0.19   | licorice         |
| MOL004838 | 8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol | 58.44  | 0.38   | licorice         |
| MOL004841 | Licochalcone B                               | 76.76  | 0.19   | licorice         |
| MOL004848 | licochalcone G                                | 49.25  | 0.32   | licorice         |
| MOL004849 | 3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin | 59.62  | 0.43   | licorice         |
| MOL004855 | Licoricone                                    | 63.58  | 0.47   | licorice         |
| MOL004856 | Gancaonin A                                  | 51.08  | 0.4    | licorice         |
| MOL004857 | Gancaonin B                                  | 48.79  | 0.45   | licorice         |
| MOL004860 | licorice glycoside E                          | 32.89  | 0.27   | licorice         |
| MOL004863 | 3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone | 66.37 | 0.41 | licorice |
| MOL004864 | 5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone | 30.49 | 0.41 | licorice |
| MOL004866 | 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone | 44.15 | 0.41 | licorice |
| MOL004879 | Glycyrrhizin | 52.61 | 0.47 | licorice |
| MOL004882 | Licocoumarone | 33.21 | 0.36 | licorice |
| MOL004883 | Licoisoflavone | 41.61 | 0.42 | licorice |
| MOL004884 | Licoisoflavone B | 38.93 | 0.55 | licorice |
| MOL004885 | licoisoflavanone | 52.47 | 0.54 | licorice |
| MOL004891 | shinpterocarpin | 80.3 | 0.73 | licorice |
| MOL004898 | (E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one | 46.27 | 0.31 | licorice |
| MOL004903 | liquiritin | 65.69 | 0.74 | licorice |
| MOL004904 | licopyranocoumarin | 80.36 | 0.65 | licorice |
| MOL004905 | 3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid | 34.32 | 0.55 | licorice |
| MOL004907 | Glyzaglabrin | 61.07 | 0.35 | licorice |
| MOL004908 | Glabridin | 53.25 | 0.47 | licorice |
| MOL004910 | Glabranin | 52.9 | 0.31 | licorice |
| MOL004911 | Glabrene | 46.27 | 0.44 | licorice |
| MOL004912 | Glabrone | 52.51 | 0.5 | licorice |
| MOL004913 | 1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone | 48.14 | 0.43 | licorice |
| MOL004914 | 1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone | 62.9 | 0.53 | licorice |
| MOL004915 | Eurycarpin A | 43.28 | 0.37 | licorice |
| MOL004917 | glycyroside | 37.25 | 0.79 | licorice |
| MOL004924 | (-)-Medicocarpin | 40.99 | 0.95 | licorice |
| MOL004935 | Sigmoidin-B | 34.88 | 0.41 | licorice |
| MOL004941 | (2R)-7-hydroxy-2-(4- | 71.12 | 0.18 | licorice |
| MOL004945 | (2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one | 36.57 | 0.32 | licorice |
| MOL004948 | Isoglycyrol | 44.7 | 0.84 | licorice |
| MOL004949 | Isolicoaflavonol | 45.17 | 0.42 | licorice |
| MOL004957 | HMO | 38.37 | 0.21 | licorice |
| MOL004959 | 1-Methoxyphaseollidin | 69.98 | 0.64 | licorice |
| MOL004961 | Quercetin der. | 46.45 | 0.33 | licorice |
| MOL004966 | 3’- Hydroxy-4’-O-Methylglabridin | 43.71 | 0.57 | licorice |
| MOL004974 | 3’- Methoxyglabridin | 46.16 | 0.57 | licorice |
| MOL004978 | 2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol | 36.21 | 0.52 | licorice |
| MOL004980 | Inflacoumarin A | 39.71 | 0.33 | licorice |
| MOL004985 | Icos-5-enoic acid | 30.7 | 0.2 | licorice |
| MOL004988 | Kanzonol F | 32.47 | 0.89 | licorice |
| MOL004989 | 6-prenylated eriodictyol | 39.22 | 0.41 | licorice |
| MOL004990 | 7,2’,4’- trihydroxy[5-methoxy-3-arylcoumarin | 83.71 | 0.27 | licorice |
| MOL004991 | 7-Acetoxy-2-methylisoflavone | 38.92 | 0.26 | licorice |
| MOL004993 | 8-prenylated eriodictyol | 53.79 | 0.4 | licorice |
| MOL004996 | gadelaidic acid | 30.7 | 0.2 | licorice |
| MOL005000 | Gancaonin G | 60.44 | 0.39 | licorice |
| MOL005001 | Gancaonin H | 50.1 | 0.78 | licorice |
| MOL005003 | Licoagrocarpin | 58.81 | 0.58 | licorice |
| MOL005007 | Glyasperins M | 72.67 | 0.59 | licorice |
| MOL005008 | Glycyrhriza flavonol A | 41.28 | 0.6 | licorice |
| MOL005012 | Licoagroisoﬂavone | 57.28 | 0.49 | licorice |
| MOL005013 | 18α-hydroxyglycyrrhetic acid | 41.16 | 0.71 | licorice |
| MOL005016 | Odoratin | 49.95 | 0.3 | licorice |
| MOL005017 | Phaseol | 78.77 | 0.58 | licorice |
| MOL005018 | Xambioona | 54.85 | 0.87 | licorice |
| MOL005020 | dehydroglyasperins C | 53.82 | 0.37 | licorice |
| MOL005030 | gondoic acid | 30.7 | 0.2 | Arum Ternatum Thunb |
| MOL00508 | Aposiopolamine | 66.65 | 0.22 | Panax ginseng C. A. Mey. |
| MOL005314 | Celabenzine | 101.88 | 0.49 | Panax ginseng C. A. Mey. |
| MOL005317 | Deoxyharringtonine | 39.27 | 0.81 | Panax ginseng C. A. Mey. |
| MOL005318 | Dianthramine | 40.45 | 0.2 | Panax ginseng C. A. Mey. |
| MOL005320 | arachidonate | 45.57 | 0.2 | Panax ginseng C. A. Mey. |
| MOL005321 | Frutinone A | 65.9 | 0.34 | Panax ginseng C. A. Mey. |
| MOL005344 | ginsenoside rh2 | 36.32 | 0.56 | Panax ginseng C. A. Mey. |
| MOL005348 | Ginsenoside-Rh4_qt | 31.11 | 0.78 | Panax ginseng C. A. Mey. |
| MOL005356 | Girinimbin | 61.22 | 0.31 | Panax ginseng C. A. Mey. |
| MOL005357 | Gomisin B | 31.99 | 0.83 | Panax ginseng C. A. Mey. |
| MOL005360 | malkangunin | 57.71 | 0.63 | Panax ginseng C. A. Mey. |
| MOL005360 | malkangunin | 57.71 | 0.63 | Jujubae Fructus |
| MOL005376 | Panaxadiol | 33.09 | 0.79 | Panax ginseng C. A. Mey. |
| MOL005384 | suchilactone | 57.52 | 0.56 | Panax ginseng C. A. Mey. |
| MOL005399 | alexandrin_qt | 36.91 | 0.75 | Panax ginseng C. A. Mey. |
| MOL005401 | ginsenoside Rg5_qt | 39.56 | 0.79 | Panax ginseng C. A. Mey. |
| MOL006129 | 6-methylgingediacetate2 | 48.73 | 0.32 | Zingiber officinale Roscoe |
| MOL006936 | 10,13-eicosadienoic | 39.99 | 0.2 | Arum Ternatum Thunb |
| MOL006937 | 12,13-epoxy-9-hydroxynonadeca-7,10- | 42.15 | 0.24 | Arum Ternatum Thunb |
| Compound ID   | Chemical Name                                                                 | MW  | Purity |
|---------------|-------------------------------------------------------------------------------|------|--------|
| MOL006957     | dienoic acid (3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone     | 46.89| 0.27   |
| MOL006967     | beta-D-Ribofuranoside, xanthine-9                                             | 44.72| 0.21   |
| MOL007213     | Nuciferin                                                                     | 34.43| 0.4    |
| MOL008034     | 21302-79-4                                                                    | 73.52| 0.77   |
| MOL008206     | Moslosooflavone                                                               | 44.09| 0.25   |
| MOL008647     | Moupinamide                                                                   | 86.71| 0.26   |
| MOL008698     | Dihydrocapsaicin                                                              | 47.07| 0.19   |
| MOL010415     | 11,13-Eicosadienoic acid, methyl ester                                        | 39.28| 0.23   |
| MOL012245     | 5,7,4'-trihydroxy-6-methoxyflavanone                                         | 36.63| 0.27   |
| MOL012246     | 5,7,4'-trihydroxy-8-methoxyflavanone                                         | 74.24| 0.26   |
| MOL012266     | rivularin                                                                     | 37.94| 0.37   |
| MOL012921     | stepharine                                                                    | 31.55| 0.33   |
| MOL012940     | Spiradine A                                                                   | 113.52| 0.61 |
| MOL012946     | zizyphus saponin Iₗₜ                                                          | 32.69| 0.62   |
| MOL012961     | jujuboside Aₗₜ                                                                | 36.67| 0.62   |
| MOL012976     | coumestrol                                                                    | 32.49| 0.34   |
| MOL012980     | Daechuine S6                                                                  | 46.48| 0.79   |
| MOL012981     | Daechuine S7                                                                  | 44.82| 0.83   |
| MOL012986     | Jujubasaponin Vₗₜ                                                            | 36.99| 0.63   |
| MOL012989     | Jujuboside Cₗₜ                                                                | 40.26| 0.62   |
| MOL012992     | Mauritine D                                                                   | 89.13| 0.45   |
| MOL013187     | Cubebin                                                                       | 57.13| 0.64   |
| MOL013357     | (3S,6R,8S,9S,10R,13R,14S,17R)-17-[(1R,4R)-4-ethyl-1,5-dimethylhexyl]-10,13-dimethyl-2,3,6,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3,6-diol | 34.37| 0.78   |
Intersection targets of Xiaochaihu Decoction and Pancreatitis

Xiaochaihu Decoction had 169 targets obtained from Drugbank Database and Pancreatitis had 2344 targets collected from OMIM, GeneCards and TTD Databases. Then, Venn map showed that it had 91 intersection targets on Xiaochaihu Decoction and Pancreatitis (Fig.1).

Herb-Compound-Target-Disease Network analysis

To clarify the relationship between herb of Xiaochaihu Decoction, compound target and pancreatitis targets, the herb-compound-target-disease network was constructed by Cytoscape software. The network had 293 nodes consisted of 1 disease, 7 herbs, 194 compounds and 91 putative targets. In the terms of the relationship between compounds and targets, there were 12 compounds having targets greater than 30, and they were MOL000098 (Quercetin), MOL000422 (Kaempferol), MOL003896 (7-Methoxy-2-methyl isoflavone), MOL000787 (Fumarine), MOL000354 (Isorhamnetin), MOL000392 (formononetin), MOL002565 (Medicarpin), MOL000358 (Beta-sitosterol), MOL000449 (Stigmasterol), MOL004978(2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol), MOL000500 (Vestitol), MOL004891 (Shinpterocarpin) acting on 75, 44, 43, 38, 34, 34, 34, 32, 31, 31, 30, 30 targets respectively. And PTGS2, HSP90A, CAMKK2, ESR1, AR, PTGS1, NOS2, NCOA2, PRSS1, F10 and SCN5A were interact with 138, 100, 97, 90, 89, 86, 83, 74, 73 and 71 compounds (Fig.2).

PPI interaction network analysis

The common targets of compounds and pancreatitis were putted into STRING database to obtain the PPI interaction network in order to provide an intuitive understand of the mechanism of Xiaochaihu Decoction acting on pancreatitis. By the analysis of STRING, it was showed that the network was composed with 91 nodes as well as 1015 edges and the average node degree was 22.3. Furthermore, network topological analysis indicated that the top 3 degrees were Mitogen-activated protein kinase 3 (MAPK3, degree=58), Interleukin - 6 (IL-6, degree=57), Tumor Protein (TP53, degree=56) which involving with the cell growth, cell apoptosis as well as inflammatory response, had the greater node degree value than other targets (Fig.3).

Enrichment of functions analysis

To clarified the mechanism of Xiaochaihu Decoction on pancreatitis in detail, the Go enrichment analysis was performed by DAVID Bioinformatics Resources. Go enrichment analysis got 484 items including 363 items of Biological process (BP), 53 items of Cell Component (CC) and 68 items of Molecular Function (MF) \(P<0.05\) and the items which Gene count proportion greater than 10 were showed as Fig.4. Biological process was mainly related to positive regulation of transcription from RNA polymerase II promoter and Molecular Function was closely in connection with protein binding.
KEGG pathway analysis indicated that Xiaochaihu Decoction exerted its pharmacological effects on pancreatitis was closely associated with pathways in cancers (fold enrichment=5.4, \( P<0.001 \)), TNF signaling way (fold enrichment=12.2, \( P<0.001 \)), PI3K-Akt signaling pathway (fold enrichment=3.7, \( P<0.001 \)), Influenza A (fold enrichment=7.1, \( P<0.001 \)), Chagas disease (fold enrichment=11.0, \( P<0.001 \)) and MAPK signaling pathway (fold enrichment=4.5, \( P<0.001 \)) which were involving with MAPK3, TP53, TNF and so on (Fig.5).

**Molecular docking to determine the potential targets**

Three targets (IL-6, MAPK3, TP53) were selected according to the results of PPI network as the core targets of Xiaochaihu Decoction treated pancreatitis. And Herb-compound-Target-Disease network indicated Quercetin could not only interacted with 75 targets but also closely related with the three targets. Therefore, Molecular Docking technology was used to simulate the interaction between Quercetin and the three targets. The results showed that Quercetin interacted with the IL-6, MAPK3, TP53, forming Vander Waals, Carbon hydrogen bond, Pi-sulfur, Salt Bridge and so on. Moreover, TP53 had the most abundant bonds with Quercetin among the three targets (Fig.6).

**Discussion**

Xiaochaihu Decoction was an ancient herbal formula which had been as the therapeutic agents for the treatment of pancreatitis in clinical [19]. In this study, a network pharmacology approach was applied to construct the “Herb-Compound-Target-Disease Network” in order to explore the underlying mechanism of Xichaihu Decoction in pancreatitis. Results of the study described herein revealed that Xiaochaihu Decoction exerted on the pancreatitis by multiple pathways, target points.

According to the results of Network pharmacology analysis, Quercetin (OB=46.43%, DL=0.28), Kaempferol (OB=41.88%, DL=0.24) and so on became the potential bioactive compounds. Quercetin is a flavonoid found which could attenuated pancreatic and ileal pathological damages through reduced the production of IL-6, TNF-\( \alpha \), IL-1\( \beta \) [20]. Besides, In vitro active experiment shows that, Quercetin had a significant anti-pancreatitis activity through reducing the intracellular ROS production and enhancing apoptotic cell death[21]. Kaempferol, a kind of polyphenol, ameliorated acute inflammatory and nociceptive symptoms in pancreatitis [22]. Yun Jung Lee et al had been demonstrated that kaempferol could protect pancreatic cells from dRib-induced associated oxidative damage by inhibiting the intracellular ROS and apoptosis [23].

KEGG analysis revealed that pathways in cancers, TNF signaling way, PI3K-Akt signaling pathway and MAPK signaling pathway had linkage with Xiaochaihu Decoction treatment for pancreatitis. As we all known, TNF was mainly generated by activated mononuclear macrophages and involved in inducing the production of Inflammatory cytokines such as IL-6 causing the necrosis of pancreatic tissue [24]. Thus, TNF signaling way might be the important proinflammatory cytokine for the occurrence and development of pancreatitis.
PPI network analysis showed that the degree of MAPK3 (degree=58), IL-6 (degree=57), TP53 (degree=56) were higher than others. MAPK was an important transmitter of signals from the cell surface to the inside of the nucleus and MAPK 3 acted as an essential component of the MAPK signal transduction pathway [25]. The MAPK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements [26]. It had been reported that pancreatitis could be alleviated via reducing the production of TNF-α, IL-6, IL-1β which was associated with regulating the MAPK signaling way [27]. Xiang-Peng Zeng et al found that inhibiting the MAPK cascade including MAPK3 might be a potential anti-inflammatory strategy for pancreatitis [28]. IL-6 was one of the most biologically active cytokines, had many biological functions and was considered as the reliable marker for severity in acute pancreatitis [29]. IL-6 promoted the neutrophil function p-regulation, cytokine section and inflammatory mediator production leading the development of pancreatitis [30]. Besides, IL-6 triggered the strong STAT3 phosphorylation in the pancreas and high circulating levels of neutrophil attractant CXCL1 which resulting in the severity of pancreatitis [31]. TP53, the regulatory factor of apoptosis, could interact with Bcl2 family proteins in the cytoplasm that causing mitochondrial outer membrane permeability increased and cell apoptosis [32]. In clinical, pancreatic tissues from patients with pancreatitis exhibited apoptotic nuclei, and increased p53 expression [33]. Consistently, Lei Zhou et al found that TP53 suppressed on mouse pancreatitis model obviously inhibited pancreatic acinar cell apoptosis and the inflammation [34]. Given that inflammation and apoptosis were closely related with pancreatitis, they were likely to be the molecules regulated by Xiaochaihu Decoction in the treatment of pancreatitis.

Molecular docking was the widely use technology for calculating protein-ligand interactions [35]. And the results also showed that Quercetin could docked well with MAPK3, IL-6 and TP53. Besides, Quercetin formed Vander Waals with THRA150, CYSA229, THRA230, LEUA145, TRPA146, PHEA109, VALA157 of TP53, Carbon Hydrogen with PROA223 of TP53, Pi-Sigma with VALA147 of TP53 and so on. In other words, Xiaochaihu Decoction exerted pharmacodynamic actions on pancreatitis via the interaction between active ingredients and key proteins.

**Conclusion**

In general, this study combined network pharmacology method and molecular docking technology to demonstrate the potential mechanism of Xiaochaihu Decoction treated with pancreatitis that Quercetin might played an important role in pancreatitis therapy by acting the key genes of MPAK3, IL-6 and TP53. Although our findings were needed further experiment to support, it still revealed the potential mechanism of Xiaochaihu Decoction in the treatment of Pancreatitis.

**Abbreviations**

XD = Xiaochaihu Decoction

TCM = Traditional Chinese Medicine
TCMSP = Traditional Chinese Medicine Systems Pharmacology
BP = Biological process
CC = Cell Component
MF = Molecular Function
GO = Gene ontology
KEGG = Kyoto Encyclopedia of Genes and Genomes

**Declarations**

**Acknowledgments**
Not applicable.

**Author’s contribution**
Lianghui Zhan and Chunlian Ji conceived and designed the experiments. Lianghui Zhan and Jinbao Pu contributed significantly to analysis and manuscript preparation. Yijuan Hu, Pan Xu and Weiqing Liang helped perform the analysis with constructive discussions.

**Funding**
No

**Availability of data and materials**
All data generated or analyzed during this study are included in this published article. Please contact the author for the code of the software and the documentation.

**Ethics approval and consent to participate**

**Consent for publication**
Not applicable.
Conflict of interest

The authors declare no conflicts of interest in association with this manuscript.

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