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

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Research

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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 chronicle 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 Xiaochaihu Decoction by Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, <https://tcmspw.com/tcmssp.php>) [18]. Then screening the requested ingredients according to conditions that oral bioavailability (OB) $\geq 30\%$, 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 $\geq$ 30%, OL $\geq$ 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	<i>Scutellariae Radix</i>
MOL000096	(-)-catechin	49.68	0.24	<i>Jujubae Fructus</i>
MOL000098	quercetin	46.43	0.28	<i>Radix Bupleuri</i> <i>licorice</i> <i>Jujubae Fructus</i>
MOL000173	wogonin	30.68	0.23	<i>Scutellariae Radix</i>
MOL000211	Mairin	55.38	0.78	<i>licorice</i> <i>Jujubae Fructus</i>
MOL000228	(2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one	55.23	0.2	<i>Scutellariae Radix</i>
MOL000239	Jaranol	50.83	0.29	<i>licorice</i>
MOL000354	isorhamnetin	49.6	0.31	<i>Radix Bupleuri</i> <i>licorice</i>
MOL000358	beta-sitosterol	36.91	0.75	<i>Arum Ternatum Thunb</i> <i>Panax ginseng C. A. Mey.</i> <i>Scutellariae Radix</i> <i>Zingiber officinale</i> <i>Roscoe</i> <i>Jujubae Fructus</i>
MOL000359	sitosterol	36.91	0.75	<i>Scutellariae Radix</i> <i>licorice</i>
MOL000392	formononetin	69.67	0.21	<i>licorice</i>
MOL000417	Calycosin	47.75	0.24	<i>licorice</i>
MOL000422	kaempferol	41.88	0.24	<i>Radix Bupleuri</i> <i>Panax ginseng C. A. Mey.</i> <i>licorice</i>
MOL000449	Stigmasterol	43.83	0.76	<i>Arum Ternatum Thunb</i> <i>Panax ginseng C. A. Mey.</i> <i>Scutellariae Radix</i> <i>Zingiber officinale</i> <i>Roscoe</i> <i>Jujubae Fructus</i> <i>Radix Bupleuri</i>
MOL000490	petunidin	30.05	0.31	<i>Radix Bupleuri</i>
MOL000492	(+)-catechin	54.83	0.24	<i>Jujubae Fructus</i>
MOL000497	licochalcone a	40.79	0.29	<i>licorice</i>
MOL000500	licochalcone a	40.79	0.29	<i>licorice</i>
MOL000500	Vestitol	74.66	0.21	<i>licorice</i>
MOL000519	coniferin	31.11	0.32	<i>Arum Ternatum Thunb</i>
MOL000525	Norwogonin	39.4	0.21	<i>Scutellariae Radix</i>

MOL000552	5,2'-Dihydroxy-6,7,8-trimethoxyflavone	31.71	0.35	<i>Scutellariae Radix</i>
MOL000627	Stepholidine	33.11	0.54	<i>Jujubae Fructus</i>
MOL000783	Protoporphyrin	30.86	0.56	<i>Jujubae Fructus</i>
MOL000787	Fumarine	59.26	0.83	<i>Panax ginseng C. A. Mey.</i> <i>Jujubae Fructus</i>
MOL001454	berberine	36.86	0.78	<i>Jujubae Fructus</i>
MOL001458	coptisine	30.67	0.86	<i>Scutellariae Radix</i>
MOL001484	Inermine	75.18	0.54	<i>licorice</i>
MOL001490	bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate	43.59	0.35	<i>Scutellariae Radix</i>
MOL001506	Supraene	33.55	0.42	<i>Scutellariae Radix</i>
MOL001522	(S)-Coclaurine	42.35	0.24	<i>Jujubae Fructus</i>
MOL001645	Linoleyl acetate	42.1	0.2	<i>Radix Bupleuri</i>
MOL001689	acacetin	34.97	0.24	<i>Scutellariae Radix</i>
MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76	<i>Arum Ternatum Thunb</i>
MOL001771	poriferast-5-en-3beta-ol	36.91	0.75	<i>Zingiber officinale Roscoe</i>
MOL001792	DFV	32.76	0.18	<i>licorice</i>
MOL002311	Glycyrol	90.78	0.67	<i>licorice</i>
MOL002565	Medicarpin	49.22	0.34	<i>licorice</i>
MOL002670	Cavidine	35.64	0.81	<i>Arum Ternatum Thunb</i>
MOL002714	baicalein	33.52	0.21	<i>Arum Ternatum Thunb</i> <i>Scutellariae Radix</i>
MOL002773	beta-carotene	37.18	0.58	<i>Jujubae Fructus</i>
MOL002776	Baicalin	40.12	0.75	<i>Arum Ternatum Thunb</i> <i>Radix Bupleuri</i>
MOL002844	Pinocembrin	64.72	0.18	<i>licorice</i>
MOL002879	Diop	43.59	0.39	<i>Panax ginseng C. A. Mey.</i> <i>Scutellariae Radix</i>
MOL002897	epiberberine	43.09	0.78	<i>Scutellariae Radix</i>
MOL002908	5,8,2'-Trihydroxy-7-methoxyflavone	37.01	0.27	<i>Scutellariae Radix</i>
MOL002909	5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone	33.82	0.45	<i>Scutellariae Radix</i>

MOL002910	Carthamidin	41.15	0.24	<i>Scutellariae Radix</i>
MOL002911	2,6,2',4'-tetrahydroxy-6'-methoxychaleone	69.04	0.22	<i>Scutellariae Radix</i>
MOL002913	Dihydrobaicalin_qt	40.04	0.21	<i>Scutellariae Radix</i>
MOL002914	Eriodyctiol (flavanone)	41.35	0.24	<i>Scutellariae Radix</i>
MOL002915	Salvigenin	49.07	0.33	<i>Scutellariae Radix</i>
MOL002917	5,2',6'-Trihydroxy-7,8-dimethoxyflavone	45.05	0.33	<i>Scutellariae Radix</i>
MOL002925	5,7,2',6'-Tetrahydroxyflavone	37.01	0.24	<i>Scutellariae Radix</i>
MOL002926	dihydrooroxylin A	38.72	0.23	<i>Scutellariae Radix</i>
MOL002927	Skullcapflavone II	69.51	0.44	<i>Scutellariae Radix</i>
MOL002928	oroxylin a	41.37	0.23	<i>Scutellariae Radix</i>
MOL002932	Panicolin	76.26	0.29	<i>Scutellariae Radix</i>
MOL002933	5,7,4'-Trihydroxy-8-methoxyflavone	36.56	0.27	<i>Scutellariae Radix</i>
MOL002934	NEOBAICALEIN	104.34	0.44	<i>Scutellariae Radix</i>
MOL002937	DIHYDROOROXYLIN	66.06	0.23	<i>Scutellariae Radix</i>
MOL003410	Ziziphin_qt	66.95	0.62	<i>Jujubae Fructus</i>
MOL003578	Cycloartenol	38.69	0.78	<i>Arum Ternatum Thunb</i>
MOL003648	Inermin	65.83	0.54	<i>Panax ginseng C. A. Mey.</i>
MOL003656	Lupiwighteone	51.64	0.37	<i>licorice</i>
MOL003896	7-Methoxy-2-methyl isoflavone	42.56	0.2	<i>licorice</i>
MOL004328	naringenin	59.29	0.21	<i>licorice</i>
MOL004350	Ruvoside_qt	36.12	0.76	<i>Jujubae Fructus</i>
MOL004492	Chrysanthemaxanthin	38.72	0.58	<i>Panax ginseng C. A. Mey.</i>
MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone	31.97	0.59	<i>Radix Bupleuri</i>
MOL004609	Areapillin	48.96	0.41	<i>Radix Bupleuri</i>
MOL004624	Longikaurin A	47.72	0.53	<i>Radix Bupleuri</i>
MOL004628	Octalupine	47.82	0.28	<i>Radix Bupleuri</i>
MOL004644	Sainfuran	79.91	0.23	<i>Radix Bupleuri</i>

MOL004648	Troxeutin	31.6	0.28	<i>Radix Bupleuri</i>
MOL004653	(+)-Anomalin	46.06	0.66	<i>Radix Bupleuri</i>
MOL004702	saikosaponin c_qt	30.5	0.63	<i>Radix Bupleuri</i>
MOL004718	α -spinasterol	42.98	0.76	<i>Radix Bupleuri</i>
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	<i>licorice</i>
MOL004806	euchrenone	30.29	0.57	<i>licorice</i>
MOL004808	glyasperin B	65.22	0.44	<i>licorice</i>
MOL004810	glyasperin F	75.84	0.54	<i>licorice</i>
MOL004811	Glyasperin C	45.56	0.4	<i>licorice</i>
MOL004814	Isotrifoliol	31.94	0.42	<i>licorice</i>
MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one	39.62	0.35	<i>licorice</i>
MOL004820	kanzonols W	50.48	0.52	<i>licorice</i>
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	<i>licorice</i>
MOL004827	Semilicoisoflavone B	48.78	0.55	<i>licorice</i>
MOL004828	Glepidotin A	44.72	0.35	<i>licorice</i>
MOL004829	Glepidotin B	64.46	0.34	<i>licorice</i>
MOL004833	Phaseolinisoflavan	32.01	0.45	<i>licorice</i>
MOL004835	Glypallichalcone	61.6	0.19	<i>licorice</i>
MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	58.44	0.38	<i>licorice</i>
MOL004841	Licochalcone B	76.76	0.19	<i>licorice</i>
MOL004848	licochalcone G	49.25	0.32	<i>licorice</i>
MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	59.62	0.43	<i>licorice</i>
MOL004855	Licoricone	63.58	0.47	<i>licorice</i>
MOL004856	Gancaonin A	51.08	0.4	<i>licorice</i>
MOL004857	Gancaonin B	48.79	0.45	<i>licorice</i>
MOL004860	licorice glycoside E	32.89	0.27	<i>licorice</i>

MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone	66.37	0.41	<i>licorice</i>
MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	30.49	0.41	<i>licorice</i>
MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone	44.15	0.41	<i>licorice</i>
MOL004879	Glycyrin	52.61	0.47	<i>licorice</i>
MOL004882	Licocoumarone	33.21	0.36	<i>licorice</i>
MOL004883	Licoisoflavone	41.61	0.42	<i>licorice</i>
MOL004884	Licoisoflavone B	38.93	0.55	<i>licorice</i>
MOL004885	licoisoflavanone	52.47	0.54	<i>licorice</i>
MOL004891	shinpterocarpin	80.3	0.73	<i>licorice</i>
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	<i>licorice</i>
MOL004903	liquiritin	65.69	0.74	<i>licorice</i>
MOL004904	licopyranocoumarin	80.36	0.65	<i>licorice</i>
MOL004905	3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid	34.32	0.55	<i>licorice</i>
MOL004907	Glyzaglabrin	61.07	0.35	<i>licorice</i>
MOL004908	Glabridin	53.25	0.47	<i>licorice</i>
MOL004910	Glabranin	52.9	0.31	<i>licorice</i>
MOL004911	Glabrene	46.27	0.44	<i>licorice</i>
MOL004912	Glabrone	52.51	0.5	<i>licorice</i>
MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone	48.14	0.43	<i>licorice</i>
MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	62.9	0.53	<i>licorice</i>
MOL004915	Eurycarpin A	43.28	0.37	<i>licorice</i>
MOL004917	glycyroside	37.25	0.79	<i>licorice</i>
MOL004924	(-)-Medicocarpin	40.99	0.95	<i>licorice</i>
MOL004935	Sigmoidin-B	34.88	0.41	<i>licorice</i>
MOL004941	(2R)-7-hydroxy-2-(4-	71.12	0.18	<i>licorice</i>

	hydroxyphenyl)chroman-4-one			
MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	36.57	0.32	<i>licorice</i>
MOL004948	Isoglycyrol	44.7	0.84	<i>licorice</i>
MOL004949	Isolicoflavanol	45.17	0.42	<i>licorice</i>
MOL004957	HMO	38.37	0.21	<i>licorice</i>
MOL004959	1-Methoxyphaseollidin	69.98	0.64	<i>licorice</i>
MOL004961	Quercetin der.	46.45	0.33	<i>licorice</i>
MOL004966	3'-Hydroxy-4'-O-Methylglabridin	43.71	0.57	<i>licorice</i>
MOL004974	3'-Methoxyglabridin	46.16	0.57	<i>licorice</i>
MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol	36.21	0.52	<i>licorice</i>
MOL004980	Inflacoumarin A	39.71	0.33	<i>licorice</i>
MOL004985	icos-5-enoic acid	30.7	0.2	<i>licorice</i>
MOL004988	Kanzonol F	32.47	0.89	<i>licorice</i>
MOL004989	6-prenylated eriodictyol	39.22	0.41	<i>licorice</i>
MOL004990	7,2',4'-trihydroxy-5-methoxy-3-aryl coumarin	83.71	0.27	<i>licorice</i>
MOL004991	7-Acetoxy-2-methylisoflavone	38.92	0.26	<i>licorice</i>
MOL004993	8-prenylated eriodictyol	53.79	0.4	<i>licorice</i>
MOL004996	gadelaidic acid	30.7	0.2	<i>licorice</i>
MOL005000	Gancaonin G	60.44	0.39	<i>licorice</i>
MOL005001	Gancaonin H	50.1	0.78	<i>licorice</i>
MOL005003	Licoagrocarpin	58.81	0.58	<i>licorice</i>
MOL005007	Glyasperins M	72.67	0.59	<i>licorice</i>
MOL005008	Glycyrrhiza flavonol A	41.28	0.6	<i>licorice</i>
MOL005012	Licoagroisoflavone	57.28	0.49	<i>licorice</i>
MOL005013	18 α -hydroxyglycyrrhetic acid	41.16	0.71	<i>licorice</i>
MOL005016	Odoratin	49.95	0.3	<i>licorice</i>
MOL005017	Phaseol	78.77	0.58	<i>licorice</i>

MOL005018	Xambioona	54.85	0.87	<i>licorice</i>
MOL005020	dehydroglyasperins C	53.82	0.37	<i>licorice</i>
MOL005030	gondoic acid	30.7	0.2	<i>Arum Ternatum Thunb</i>
MOL005308	Aposiopamine	66.65	0.22	<i>Panax ginseng C. A. Mey.</i>
MOL005314	Celabenzine	101.88	0.49	<i>Panax ginseng C. A. Mey.</i>
MOL005317	Deoxyharringtonine	39.27	0.81	<i>Panax ginseng C. A. Mey.</i>
MOL005318	Dianthramine	40.45	0.2	<i>Panax ginseng C. A. Mey.</i>
MOL005320	arachidonate	45.57	0.2	<i>Panax ginseng C. A. Mey.</i>
MOL005321	Frutinone A	65.9	0.34	<i>Panax ginseng C. A. Mey.</i>
MOL005344	ginsenoside rh2	36.32	0.56	<i>Panax ginseng C. A. Mey.</i>
MOL005348	Ginsenoside-Rh4_qt	31.11	0.78	<i>Panax ginseng C. A. Mey.</i>
MOL005356	Girinimbin	61.22	0.31	<i>Panax ginseng C. A. Mey.</i>
MOL005357	Gomisin B	31.99	0.83	<i>Panax ginseng C. A. Mey.</i>
MOL005360	malkangunin	57.71	0.63	<i>Panax ginseng C. A. Mey.</i>
MOL005360	malkangunin	57.71	0.63	<i>Jujubae Fructus</i>
MOL005376	Panaxadiol	33.09	0.79	<i>Panax ginseng C. A. Mey.</i>
MOL005384	suchilactone	57.52	0.56	<i>Panax ginseng C. A. Mey.</i>
MOL005399	alexandrin_qt	36.91	0.75	<i>Panax ginseng C. A. Mey.</i>
MOL005401	ginsenoside Rg5_qt	39.56	0.79	<i>Panax ginseng C. A. Mey.</i>
MOL006129	6-methylgingediacetate2	48.73	0.32	<i>Zingiber officinale Roscoe</i>
MOL006936	10,13-eicosadienoic	39.99	0.2	<i>Arum Ternatum Thunb</i>
MOL006937	12,13-epoxy-9-hydroxynonadeca-7,10-	42.15	0.24	<i>Arum Ternatum Thunb</i>

	dienoic acid			
MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone	46.89	0.27	<i>Arum Ternatum Thunb</i>
MOL006967	beta-D-Ribofuranoside, xanthine-9	44.72	0.21	<i>Arum Ternatum Thunb</i>
MOL007213	Nuciferin	34.43	0.4	<i>Jujubae Fructus</i>
MOL008034	21302-79-4	73.52	0.77	<i>Jujubae Fructus</i>
MOL008206	Moslosooflavone	44.09	0.25	<i>Scutellariae Radix</i>
MOL008647	Moupinamide	86.71	0.26	<i>Jujubae Fructus</i>
MOL008698	Dihydrocapsaicin	47.07	0.19	<i>Zingiber officinale Roscoe</i>
MOL010415	11,13-Eicosadienoic acid, methyl ester	39.28	0.23	<i>Scutellariae Radix</i>
MOL012245	5,7,4'-trihydroxy-6-methoxyflavanone	36.63	0.27	<i>Scutellariae Radix</i>
MOL012246	5,7,4'-trihydroxy-8-methoxyflavanone	74.24	0.26	<i>Scutellariae Radix</i>
MOL012266	rivularin	37.94	0.37	<i>Scutellariae Radix</i>
MOL012921	stepharine	31.55	0.33	<i>Jujubae Fructus</i>
MOL012940	Spiradine A	113.52	0.61	<i>Jujubae Fructus</i>
MOL012946	zizyphus saponin I_qt	32.69	0.62	<i>Jujubae Fructus</i>
MOL012961	jujuboside A_qt	36.67	0.62	<i>Jujubae Fructus</i>
MOL012976	coumestrol	32.49	0.34	<i>Jujubae Fructus</i>
MOL012980	Daechuine S6	46.48	0.79	<i>Jujubae Fructus</i>
MOL012981	Daechuine S7	44.82	0.83	<i>Jujubae Fructus</i>
MOL012986	Jujubasaponin V_qt	36.99	0.63	<i>Jujubae Fructus</i>
MOL012989	Jujuboside C_qt	40.26	0.62	<i>Jujubae Fructus</i>
MOL012992	Mauritine D	89.13	0.45	<i>Jujubae Fructus</i>
MOL013187	Cubebin	57.13	0.64	<i>Radix Bupleuri</i>
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	<i>Jujubae Fructus</i>

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 Xiaochaihu 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- α , IL-1 β [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-1 β 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 secretion 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.

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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

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Not applicable.

Conflict of interest

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

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Figures

Figure 1

Venn map of common targets on Xiaochaihu Decoction and Pancreatitis. The orange circle indicated the targets of Xiaochaihu Decoction and the gray circle indicated the targets of pancreatitis. The part of two intersecting circles were the common targets.

Figure 2

Herb-Compound-Target-Disease network. The red square indicated the herb name, the green circle indicated the compounds, the orange circle indicated the target and the pink circle indicated the disease name.

Figure 3

Protein - protein interaction network (PPI interaction network). Orange, yellow, green circles indicated the proteins. The lines represented the nodes associated through protein-protein interactions.

Figure 4

Gene Ontology (Go) enrichment analysis of the top 20 pathways. (A) Biological Process (BP). (B) Cell Component (CC). (C) Molecular Function (MF).

Figure 5

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment. The color of circles was represented the Qvalue and the size of circles was represented the Count.

Figure 6

The protein-ligand of the docking simulation. (A) Quercetin and IL-6 (2D). (B) Quercetin and MAPK3 (2D). (C) Quercetin and TP53 (2D). (D) Quercetin and IL-6 (3D). (E) Quercetin and MAPK3 (3D). (F) Quercetin and TP53 (3D).