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Mechanism of Action of Baohe Pills in Improving Functional Dyspepsia

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Abstract: The aim of this study was to predict the mechanism of action of Baohe Pill in the treatment of functional dyspepsia using network pharmacology. Predict the main active ingredients and action targets of Baohe Pill by TCMSP platform database of Traditional Chinese Medicine Systematic Pharmacological Analysis Platform, and convert the collected drug targets into gene names using Uniprot database; obtain FD genes by GeneGards, TTD, OMIM database, and use Cytoscape 3. 9.0 to visualize the "drug-ingredient -target" network visualization; and protein-protein interaction (PPI) network by using String platform; GO and KEGG analysis of common targets by using Metascape database; molecular docking by using AutoDock software to verify the binding activity of active ingredients to target proteins. After database display analysis, 107 active ingredients, 511 potential action targets and 2560 FD disease targets of Bohol Pill were screened. By KEGG analysis, GO analysis yielded 6382 biological process entries, 1101 molecular function entries, 586 cellular component entries, and 291 pathways.

1. Introduction

Functional dyspepsia, as one of the clinical common gastrointestinal diseases, is a group of clinical symptoms caused by gastrointestinal dysfunction, excluding organic lesions, which mainly manifests as abdominal pain, bloating, lack of appetite, nausea, vomiting and other symptoms, and some patients also have headache, impatience, depression, insomnia, lack of concentration and other uncomfortable symptoms. In recent years, due to the increasing social pressure, irregular diet and life, the incidence of FD is increasing and has become one of the high incidences affecting the modern life. The pathogenesis of FD has not been fully understood, and it is generally associated with abnormal secretion of gastric acid and digestive enzymes, and there is no clinical cure. Chinese medicine treatment emphasizes holistic concept and evidence-based treatment, and multi-level, multi-path and multi-target treatment of FD through the combination of drugs, which has achieved better efficacy in the treatment of FD and is widely used clinically and can effectively relieve patients' symptoms such as epigastric pain, abdominal burning sensation, early satiety and postprandial fullness. Baohe Pill originated from the Danxixin Method written by Zhu Danxi in the

Yuan Dynasty. It is composed of Chenpi, Lianqiao, Shanzha, Laifuzi, Shenqv, Fuling and Banxia. It can eliminate food stagnation, move Qi and harmonize the stomach, and is widely used in clinical practice to relieve FD symptoms. This study utilized network pharmacology to further explore the mechanism of action of Baohe Pill in the treatment of FD, and verified the binding of each component of Bohe pill to FD targets by molecular docking, which provides a reference for further research on the pharmacological effects of Bohe pill on FD.

2. Materials and Methods

2.1 Target Screening of Bohe Pills

The database of the TCM Systematic Pharmacology Technology Platform was searched for the active ingredients of seven Chinese herbal medicines, namely, Banxia, Chenpi, Fuling, Lianqiao, Laifuzi, Shanzha and Shenqu, active ingredients were initially screened according to oral bioavailability (OB)≥20% , drug sample (DL)≥0.10[1]. For those that were not recorded in the database, the corresponding compounds were obtained from BATMAN and the Chinese General Knowledge Resources Database by searching the relevant literature, and then screened by the SwissADME database, and those with high Gi Absorption and in accordance with Lipinski's five The components with high Gi Absorption and Lipinski's five-fold rule were selected as the final active ingredients[2]. And the constituent targets were collected using Swiss Target Prediction database, and those with Probability ≥ 0.2 were used as the final drug targets of the drug. After screening, species condition is set to “Human” and the collected targets were normalized to their gene names using the UniProt database.

2.2 FD Target Gene Screening

The search terms “Functional Dyspepsia” was used in GeneCards, OMIM and TTD databases, and the FD targets in the three databases were combined and de-duplicated to obtain the final FD gene targets.

2.3 To Construct the Network Diagram of “TCM - Ingredient - Target” between Bohe Pills and FD

The targets of Baohe pill and FD were imported into Venny 2.1.0 separately to obtain their common targets and draw Venn diagrams. Using CytoScape 3.9.0 software, the “herbal-component-target” network diagrams of Baohe Pill and FD were constructed.

2.4 PPI Network and Screening of Key Genes

The PPI network diagram of the common target was obtained with String11.0 platform. Download TSV format and import Cytoscape 3.9.0 software to screen core targets and perform topological analysis via Network Analyzer.

2.5 Go and KEGG Analysis

Will get common target import metscape platform, species condition is set to “Homosapiens,” GO and KEGG analysis, select before 20 $P < 0.01$ data mapping, analysis of the biological significance of FD treatment and the possible mechanism [3].

2.6 Molecular Docking

The top 6 drug components with strong association in Baohe pill selection and correlation in the PPI strong before six common protein targets for molecular docking. The 3D structures of drug components and target protein download structure respectively from PubChem and PDB database. AutoDock software was used to hydrogenate and root small molecules and hydrogenate and dehydrogenate large molecules[4].Then the molecular docking was verified and the results were plotted by Pymol software.

3. Results

3.1 The Active Ingredients and Corresponding Targets of Baohe Pill

The components and corresponding targets of five Chinese herbal medicines were retrieved from the TCMSP, and the active ingredients and targets of Shanzha were supplemented with BATMAN, and the active ingredients of Shen Qu were supplemented by searching relevant literature, and the corresponding Canonical SMILES were retrieved from the PubChem [5]. The corresponding Canonical SMILES were downloaded from the PubChem, and the ingredients with high GI Absorption and in accordance with Lipinski's five-fold rule were used as the final active ingredients through the SwissADME database to obtain 107 active ingredients of Baohe Pill, including 9 Chenpi, 8 Fuling, 10 Laifuzi, 21Banxia, 26 Lianqiao, 5 Shenqu, and 28 Shanzha. After deleting the duplicate targets, the targets were transformed into corresponding gene names using Uniprot database, and finally 511 drug target genes were obtained.

3.2 Target Genes of FD

The keyword “Functional Dyspepsia” was used to search FD-related targets, among which 2535 genes were retrieved from GeneCards, 30 from OMIM and 1 from TTD, and 2560 FD disease genes were finally after remove duplicate genes.

3.3 The “Herbal-Component-Target” Network Diagram of Baohe Pill and FD

Venn diagram was drawn, and 253 common targets of active component and FD were obtained, as shown in Figure 1. Abbreviate traditional Chinese medicine according to the initial letter of pinyin, such as hawthorn (shan zha, SZ), and code the six ingredients in Baohe Wan as A, B, C, D, E and F respectively, as Table 1. Hawthorn and divine comedy components were completed through the BATMAN database and literature review, as shown in Table 2. The network diagram of “TCM - component - target” was drawn, as Figure 2. Network Analysis was used to calculate and analyze 347 nodes (87 active components associated with FD, 253 common targets, 7 drug names) and 864 edges, indicating that 87 active components acted on FD in Bohe Pills, and the lines represented the relationship between the components of Bohe Pills and FD targets.

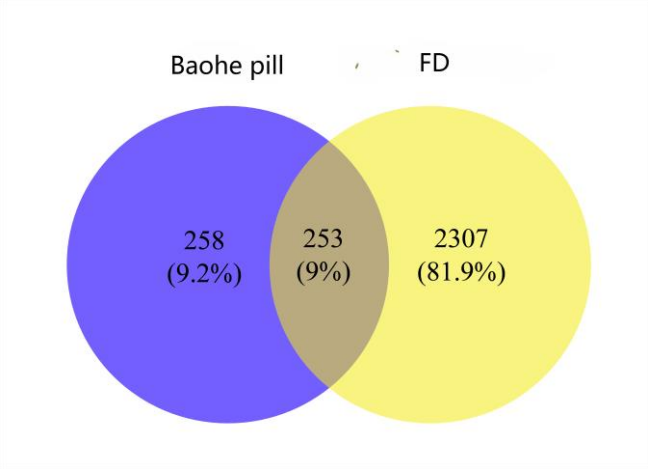


Figure 1: Bohe Pill Withvenn Diagram of Functional Dyspepsia Target

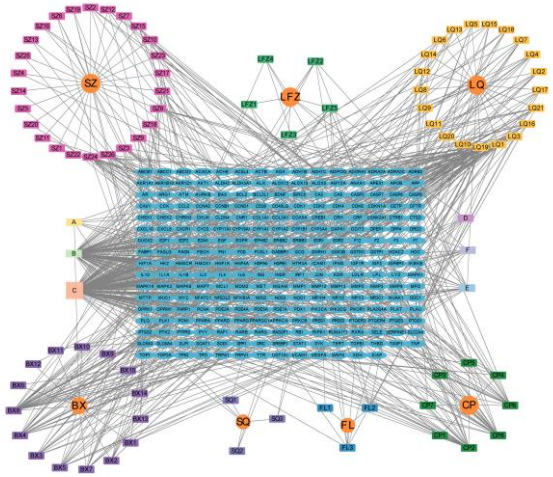


Figure 2: Visualization Network of "Bohe Marine-Component-Target"

Table 1: Basic information of active ingredients in Baohe pills

Chinese Medicine	Number	Mol ID	Ingredients	OB	DL
CP	CP1	MOL003538	()-Ledene	51.84	0.1
CP	CP2	MOL004328	Naringenin	47.74	0.27
CP	CP3	MOL005100	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one	49.63	0.13
CP	CP4	MOL000057	DIBP	23.91	0.58
CP	CP5	MOL005811	Hepta-3	21.38	0.43
CP	CP6	MOL005814	Tangeretin	86.9	0.51
CP	CP7	MOL005815	Citromitin	61.67	0.52
CP	CP8	MOL005828	Nobiletin	47.74	0.27
FL	FL1	MOL000284	L-uridine	23.4	0.11
FL	FL2	MOL000295	alexandrin	20.63	0.63
FL	FL3	MOL000296	Hederagenin	36.91	0.75
LFZ	LFZ1	MOL001398	Methyllinolenate	46.15	0.17
LFZ	LFZ2	MOL001631	Erucic acid	28.56	0.26
LFZ	LFZ3	MOL001641	METHYL LINOLEATE	41.93	0.17

LFZ	LFZ4	MOL002203	Exceparl M-OL	31.9	0.16
LFZ	LFZ5	MOL000676	DBP	64.54	0.13
BX	BX1	MOL001818	Methyl palmitelaidate	34.61	0.12
BX	BX2	MOL002495	6-shogaol	31	0.14
BX	BX3	MOL002670	Cavidine	35.64	0.81
BX	BX4	MOL002714	Baicalein	33.52	0.21
BX	BX5	MOL000449	Stigmasterol	43.83	0.76
BX	BX6	MOL005030	gondoic acid	30.7	0.2
BX	BX7	MOL000519	Coniferin	31.11	0.32
BX	BX8	MOL000675	oleic acid	33.13	0.14
BX	BX9	MOL006936	10,13-eicosadienoic	39.99	0.2
BX	BX10	MOL006944	8-Octadecenoic acid	33.13	0.14
BX	BX11	MOL006951	pedatisectine a	64.09	0.16
BX	BX12	MOL006956	cyclo-(leu-tyr)	111.16	0.15
BX	BX13	MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl) piperazine-2,5-quinone	46.89	0.27
BX	BX14	MOL006958	cyclo-(val-tyr)	122.79	0.14
BX	BX15	MOL006967	beta-D-Ribofuranoside, xanthine-9	44.72	0.21
LQ	LQ1	MOL000173	Wogonin	30.68	0.23
LQ	LQ2	MOL000263	oleanolic acid	29.02	0.76
LQ	LQ3	MOL003283	(2R,3R,4S)-4-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-2,3-dimethylol-tetralin-6-ol	66.51	0.39
LQ	LQ4	MOL003290	(3R,4R)-3,4-bis[(3,4-dimethoxyphenyl) methyl]oxolan-2-one	52.3	0.48
LQ	LQ5	MOL003295	(+)-pinoresinol monomethyl ether	53.08	0.57
LQ	LQ6	MOL003300	forsythide_qt	46.6	0.1
LQ	LQ7	MOL003302	forsythidmethylester_qt	121.84	0.12
LQ	LQ8	MOL003306	ACon1_001697	85.12	0.57
LQ	LQ9	MOL003308	(+)-pinoresinol monomethyl ether-4-D-beta-glucoside_qt	61.2	0.57
LQ	LQ10	MOL003315	3beta-Acetyl-20,25-epoxydammarane-24alpha-ol	33.07	0.79
LQ	LQ11	MOL003322	FORSYTHINOL	81.25	0.57
LQ	LQ12	MOL003330	(-)-Phillygenin	95.04	0.57
LQ	LQ13	MOL003347	Hyperforin	44.03	0.6
LQ	LQ14	MOL003354	(2R,3R,4R)-2-(3,4-dihydroxyphenyl) chroman-3,4,5,7-tetrol	20.73	0.27
LQ	LQ15	MOL003358	Euxanthone	92.98	0.16
LQ	LQ16	MOL003360	Norlapachol	46.99	0.11
LQ	LQ17	MOL003370	Onjixanthone I	79.16	0.3
LQ	LQ18	MOL000522	Arctiin	34.45	0.84
LQ	LQ19	MOL000006	Luteolin	36.16	0.25
LQ	LQ20	MOL000702	Guajavarin	29.65	0.7
LQ	LQ21	MOL000791	bicuculline	69.67	0.88
LQ,BX	A	MOL000357	Sitogluside	20.63	0.62
LQ,SQ	B	MOL000422	Kaempferol	41.88	0.24
LQ,SQ	C	MOL000098	Quercetin	46.43	0.28
BX,LFZ	D	MOL000131	EIC	41.9	0.14
BX,LQ	E	MOL000358	beta-sitosterol	36.91	0.75
BX,LFZ	F	MOL000432	linolenic acid	45.01	0.15

Table 2: Basic information of effective ingredients of Shan Zha and Shen Qu

Chinese Medicine	Number	Ingredients
SZ	SZ1	1,2,3-Trimethylbenzene
SZ	SZ2	1,2-Dimethylbenzene
SZ	SZ3	12-Oxoarundoin
SZ	SZ4	1-Ethyl-2-Methylbenzene
SZ	SZ5	20-Hexadecanoylingenol
SZ	SZ6	2-Methyl-1,2-Cyclopentanediol
SZ	SZ7	3,4,4-Trimethyl-2-Hexene
SZ	SZ8	3,5-Dimethylbutylbenzene
SZ	SZ9	3,7,11-Trimethyldodeca-1,7,10-Trien-3-Ol-9-One
SZ	SZ10	3-Methylhexane
SZ	SZ11	3-Methylhistidin
SZ	SZ12	4-(1,5-Dimethyl-1,4-Hexadienyl)-1-Methyl-Cyclohexene
SZ	SZ13	4-Methylcyclohexanone
SZ	SZ14	Acetylcholine(acetylcholine)
SZ	SZ15	Caffeic Acid Dimethyl Ether
SZ	SZ16	Citronellal
SZ	SZ17	Dimethyl Camphorate
SZ	SZ18	Epicatechin
SZ	SZ19	Eriodictyol-7,3-Diglucoside
SZ	SZ20	Gamma-Decanolactone
SZ	SZ21	Linoleyl Acetate
SZ	SZ22	Methylbenzene
SZ	SZ23	Methylcyclohexane
SZ	SZ24	Methylheptenone
SZ	SZ25	Stearin
SZ	SZ26	Ursolicacid
SQ	SQ1	Artemisinin
SQ	SQ2	ferulic acid
SQ	SQ3	vanillic acid

3.4 PPI Network Map and Key Targets

Using the String database, the PPI interactions of common targets were exported with scores ≥ 0.4 and “Human sapiens”, and import TSV format of results into Cytoscape 3.9.0 to create a visual PPI, see Figure 3.

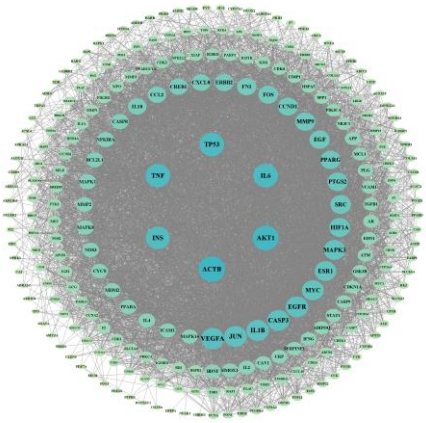


Figure 3: Gene PPI Network of Bohe Pill and Functional Dyspepsia

3.5 GO and KEGG Enrichment Analysis

Will receive 253 common target import metscape database for GO analysis, set up P < 0.01, and select 20 data online before drawing. Enrichment analysis of BP yielded 6382 data, biological process was mainly related to related to responses to inorganic substances, hormones and xenobiotic, see Figure 4-A. Cellular component was associated with membrane raft and vesicle lumen, see Figure 4-B. Molecular function was mainly connected with protein kinase activity, DNA-binging transcription factor binding, and signaling receptor activity, as 4-C.KEGG analysis showed that a total of 291 pathways, as Figure 4-D. The results of KEGG enrichment showed that it was related to pathways in cancer and lipid pathway, with the most significant enrichment in the cancer pathway, it suggests that it may very important to treat FD.

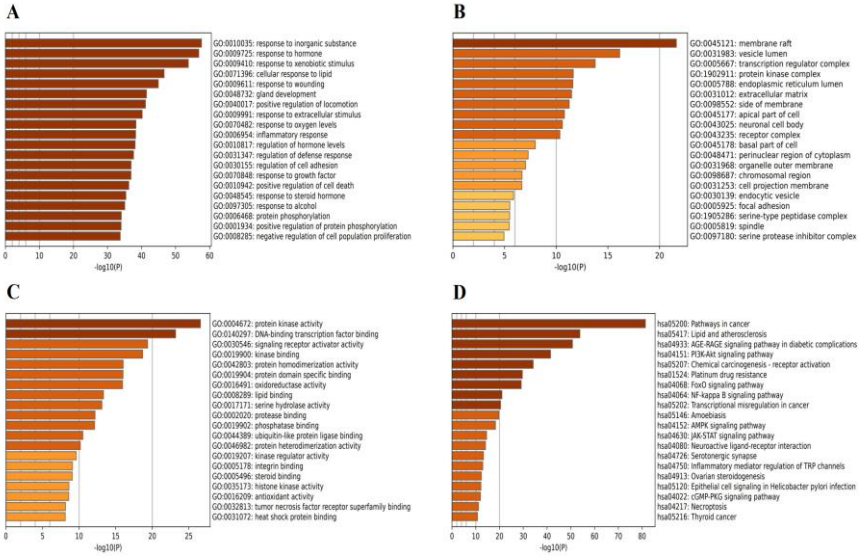
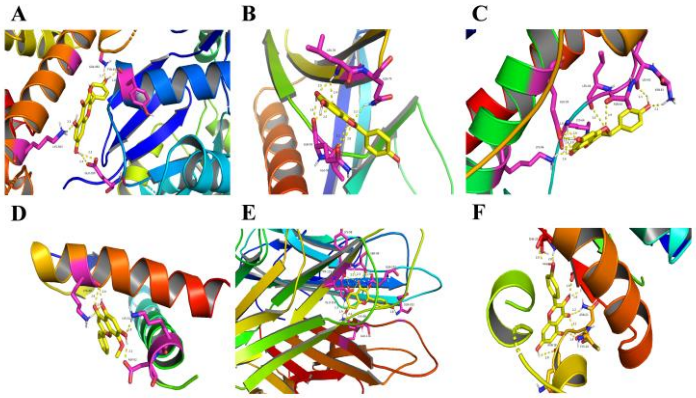


Figure 4: GO Functional Analysis BP (a), CC (B), MF (C) and KEGG Pathway Analysis (d)

3.6 Molecular Docking



A: ACTB and kaempferol; B: AKT1 and kaempferol; C: IL6 and naringein; D: TP53 and wogonin; E: TNF and kaempferol; F: INS and kaempferol

Figure 5: Diagram of Docking Bohe Pills with Target Protein Molecules

The highest value of six kinds of effective ingredients, quercetin, kaempferol, luteolin, oleic acid, wogonin and naringenin, were selected by Cytoscape 3.9.0 and docked with the top 6 FD genes in

the PPI. The docking results with the lowest binding energy were selected and plotted by pymol software, as Figure 5.

4. Discussion

In this formula, Shan Zha, Laifuzi and Shen Qu work together to eliminate food and stagnation. The three herbs together can eliminate all kinds of food and stagnation, while Ban Xia and Chen Pi work together to move Qi and eliminate stagnation. Fu Ling strengthens the spleen and dispels dampness, and Lian Qiao disperses heat and eliminates stagnation. The combination of the seven herbs works together to strengthen the spleen and stomach, eliminate food and stagnation. Through the visualization network of "drug-component-target" between Baohe pill and FD, a total of 87 drug components were found to be related to Baohe pill for the treatment of FD, among which quercetin, kaempferol, luteolin, all have anti-inflammatory, antioxidant, anti-tumor and immunoregulatory functions.They are the core compounds of Bohol Pill, mainly plant polyphenols, which can regulate inflammatory factors through RAGE/NF-κB/MAPK pathways to regulate the expression of tumor necrosis genes and inflammatory mediators. By PPI network analysis, ACTB is the main target genes of Bohol pill for FD treatment. It was found that ACTB is associated with the development of cancer, and the dysregulation of ACTB expression is associated with the occurrence of many cancers such as esophageal cancer, pancreatic cancer and gastric cancer. Using Autodock, we found that all six drug components docked with six target proteins at low binding energies, further justifying the application of Bohol pills for the treatment of FD.

In summary, the active ingredients in Baohe pill, such as quercetin, kaempferol, luteolin, oleic acid, wogonin and naringenin can alleviate inflammatory response, reduce visceral hypersensitivity, improve psychological factors such as anxiety and depression, promote gastrointestinal. This study demonstrated the mechanism of action of Baohe Pills in the treatment of FD, further proved the natural advantages of TCM in the treatment of diseases, and provided certain theoretical guidance for the subsequent experimental research.

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