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EFFECTIVE CHEMICAL CONSTITUENT'S IDENTIFICATION OF EXTRACTING SOLUTION FROM HERBS – A REVIEW

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Abstract

Background and Objective: The aim of this article, was the definition, and targets of possible mechanisms of Yin lai Decoction by retrieving the herbals in the decoction and integrating information from multi-databases, which can be guidance for the followed experimental study.

Matherials and Methods: The information from multi-databases was integrated.

Results: In the study, we discovered 92 possible gene targets of Yin lai Decoction, 87% of which appeared in the targets of *Flos Lonicerae*, *Fructus Forsythiae* and *Scutellaria baicalensis Georgi*. The function of these targets focuses on the anti-infection and regulating immune system, and metabolism of the body.

Conclusion: Yin lai Decoction may affect the process of metabolism, immune response and infection by impact on the 92 possible gene targets, then it can mitigate the damage caused by infection and promote the body to health. But the definite mechanisms must be explored by further experimental study.

Keywords: Yin lai Decoction, Metabolism, Immune response, Infection, Gene targets.

Introduction

Yin lai Decoction, which was effective on the clinical practice used by Professor Xiaohong Gu to treat syndrome of lung-stomach heat retention, includes *Flos Lonicerae*, *Fructus Forsythiae*, *Scutellaria baicalensis* Georgi, *Semen Raphani*, *Radix Peucedan*, *Fructus Trichosanthis* and *Herba Houttuyniae*. This proved to be a significant formula in curing pediatric diseases, especially on children with cold, pneumonia or recurrent respiratory infection (Gu and Yu, 2008).

Yin lai Decoction makes *Flos lonicerae* and *Semen raphani* as king herb to disperse the superficial heat and purging fire in stomach as well as stimulate digestion and reverse the upward motion of qi, which is in connection with the pathogenesis of lung-stomach heat retention; *Herba houttuyniae*, *Radix peucedani*, *Scutellaria baicalensis* Georgi and *Fructus forsythiae* are playing a role as minister herb to clear the lungs and purge fire as well as reverse the upward motion of qi and cease coughing; *Fructus trichosanthis* can clear the heat in lungs and stomach and lubricate the large intestine as assistant herb and guide herb. All of herbs are compatible to clear lungs and disperse superficial evils as well as clear stomach and promote digestion (Khan et al., 2013; Rana et al., 2013).

Currently, the targets that have been proven by experiments that related with the mechanism of Yin lai Decoction include TNF-α (Tumor Necrosis Factor-α), IL-2 (Interleukin-2), IL-6 (Interleukin-6), IL-10 (Interleukin-10), and IFN-γ (Interferon-γ) (Zhang et al., 2013; Waqas et al., 2013; Wang, 2011).

We found the following problems during the study: (1) the experimental study as time-consuming and laborious because of great workload; (2) the experimental study has blindness for we cannot define the correlation between indicators and research purpose before we start to do the experiment; (3) the experimental study cannot provide comprehensive and multi-angle interpretation owing to finite experimental indicators in the study; (4) the experimental indicators are confined to protein level yet gene level since the restriction of the experiment.

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On account of limitations above, we seek to explore the new way to expound the mechanisms of Yin lai Decoction.

Along with the rapid improvement of modern information technology, the influence of public information databases based on the network spreads increasingly, the area of which has been overlapping. Then interdisciplinary research on base of cross-reference of database information becomes possible. That integrating information from multiple databases can not only lock the indicators before the experiment which can improve the targeting of the study, and also take full advantages of existing resources and reduce duplication of experiment, as well as intensify the experimental study to gene level and improve the comprehensiveness of the indicators. In this article, we use the data mining technology called integrating information of multi-databases to retrieve the herbs of Yin lai Decoction in order to probe the comprehensive and thorough its mechanism, meanwhile it can verify the previous experimental result and direct the design of following study.

Methods

The HIT, PubChem, and DAVID Databases were used to collect data and integrate information.

HIT Database

HIT Database (Herbal Ingredients' Targets Database) is a database for researchers to know the targets and ingredients of Chinese herbs. Derived from more than 3250 literatures, it currently contains 5208 entries about 1301 known protein targets (221 of which are described as direct targets) affected by 586 herbal compounds from more than 1300 reputable Chinese herbs. The information about targets supplied by HIT include: whether they are directly \ indirectly activator or inhibitor, whether it is the role of an enzyme substrate or product and IC50, Kd \ Ki of the enzyme (Ye et al., 2011; Liu et al., 2013; Asad et al., 2013).

PubChem Database

PubChem (http://pubchem.ncbi.nlm.nih.gov) is a public repository for biological activity data of small molecules and RNAi reagents. The mission of PubChem is to deliver free and easy access to all deposited data, and to provide intuitive data analysis tools. The PubChem BioAssay database currently contains 500 000 descriptions of assay protocols, covering 5000 protein targets, 30000 gene targets and providing over 130 million bioactivity outcomes. The PubChem information platform allows users to search, review and download bioassay description and data. The PubChem platform also enables researchers to collect, compare and analyze biological test results through web-based and programmatic tools (Wang et al., 2012).

DAVID Database

All tools in the DAVID Bioinformatics Resources aim to provide functional interpretation of large lists of genes derived from genomic studies. Researchers can interpret the biological function and mechanisms of genes from multi-angles through various analysis tools provided by DAVID. The biological information coverage in the DAVID Knowledgebase has been expanded dramatically by comprehensively integrating more than 20 types of major gene/protein identifiers and more than 40 well-known functional annotation categories from dozens of public databases (Huang et al., 2007).

Retrieval Methods

Login HIT database Home page (http://lifecenter.sgst.cn/hit/) and query the main chemical ingredients of herbs in Yin lai Decoction in the “HERB”. For example, input “Radix Paeoniae Rubra”, and then we can get eight ingredients of it: Paeonol, paeoniflorin, acetic acid, catechin, (+)-catechin, (-)-catechin, gallocatechin and epigallocatechin. Next we will take Paeonol as an example to illustrate the definite retrieval process

Log on Pubchem database Home page (http://www.ncbi.nlm.nih.gov/pccompound) and input “Paeonol” into query frame, and then we can get the

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CID of Paeonol: 11092. Next we backtrack to the homepage and click on the “Chemical Structure Search” under “Pubchem Tool”, then click on “CID, SMILES, INCHI” under “identity similarity” and input 11092, select “more than or equal to 90%” in “option menu” and “default” in other “qualification”. As shown in Figure 1, click on “search” to the next step (Liu et al., 2012).

We get 3129 outcomes as shown in Figure 2. Then we can see “BioActivity Experiments” under “Refine your results” on the right of the page and click it, it will show us that “Bioassays Active (226)”, which means that there is 226 active components, and click it. At last, click “Bioactivity Analysis” under “Action on your results” on the right of the page to retrieve the targets of 226 ingredients, and the results are shown in Figure 3, in which “Target” is the upshot we need. Download the figure and seek out “Sequence GI used in assays” of the targets corresponding with “Active compound 0-35”, then list this GI systematically to prepare for the next step.

Retrieve all the herbs in Yin lai Decoction as upon and find out all the GIs of targets related with ingredients of the decoction, then arrange them for the next step.

Login DAVID Database Home (http://david.abcc.ncifcrf.gov/summary.jsp) and click on “upload” under “Start Analysis”, then input all GIs of targets into “Step1” box and select “protein GI Accession” in “Step2” and “Gene List” in “Step3”, at last, click on “submit List” and start the retrieval process. The results are shown in Figure 4.Then click “GENETIC ASSOCIATION DB DISEASE CLASS” under the option of “Disease” and it will appear the page in Figure 5. Next, outcrop “NEUROLOGICAL” and “CARDIOVASCULAR” in the “Term” and click the “Gene” following them, then we can get all targets of Yin lai Decoction and click on “Download File” to complete the retrieval process.

Results

We can get 16 ingredients and 92 gene targets of 7 herbs in Yin lai Decoction through the retrieval method upon and the function of these targets focuses on three main field, which cover the regulation of immune system, anti-infection and metabolism. Among the herbs, the function of the targets, including *Flos lonicerae*, *Semen raphani*, *Fructus forsythiae*, *Scutellaria baicalensis* Georgi, *Fructus trichosanthis*, and *Herba houttuyniae* are related to immune, metabolism and anti-infection at the same time, but the target of *Radix peucedani* only focuses on the metabolism. The definite results are shown in following tables.

In Table 1, we can see that there is 30 gene targets related to anti-infection, 56 to immune function and 67 to metabolism among the 92 gene targets of Yin lai Decoction and the function of these gene targets are interweaving into a net, which display as the phenomenon:17 targets affect immune system, metabolism and anti-infection, 3 targets affect immune system and anti-infection, 18 targets affect immune system and metabolism, 6 targets affect metabolism and anti-infection, 18 targets only affect immune system, 4 targets only affect anti-infection and 26 targets only affect metabolism.

Many herbs in Yin lai Decoction have impact on the same targets as the statistics show that cytochrome P450 family 1 subfamily A polypeptide 2 and glucosidase alpha associate with 5 herbs, 6 targets with 4 herbs, 14 targets with 3 herbs, 30 targets with 2 herbs and 40 targets only with 1 herb.

As shown in Table 2, the 5 ingredients of *Flos Lonicerae*, which have been in research, associate with 76 gene targets, in which 25 gene targets have anti-infective function, 54 has impact on metabolism and 44 regulate immune system. Luteolin is concerned in these ingredients as the associated gene targets have 63, whose functions involve regulation of immune system and metabolism as well as anti-infection.

Table 3 shows that the ingredient of *Semen Raphani* studied has been in relationship with 3 gene target, in which 2 gene targets can play a role in anti-infection, 3 in affecting metabolism and 1 in regulation of immune function.

As shown in Table 4, 4 ingredients of *Fructus Forsythiae* that have been researched are related to 40 gene targets, in which 7 gene targets are anti-infective, 26 metabolic and 22 can regulate immune system.

Table 5 also shows that the 2 ingredients of *Scutellaria baicalensis* Georgi which have been in research concern 65 gene targets, 22 of which has anti-infective function, 40 has impact on metabolism and 46 immune function.

As shown in Table 6, the ingredient of *Fructus trichosanthis* that has been studied concerns 14 gene targets, 4 of them can play anti-infection, 9 metabolic regulation and 9 immune moderation.

As shown in Table 7, the 2 ingredients of *Herba houttuyniae* which have been researched are related to 16 gene targets, 4 of them has

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anti-infective function, 11 metabolic impaction and 8 immunoregulation.

As shown in Table 8, the ingredient of *Radix peucedani* that has been in research associates with 1 gene targets, whose function refers to regulation of metabolism.

Table 1: All targets of Yin Lai Decoction

Gene Name	Function
CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1	Infection
Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	Infection
Chemokine (C-X-C motif) receptor 6	Infection
Signal transducer and activator of transcription 1, 91kDa	Infection
Aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)	Metabolic
Amylase, alpha 1A (salivary); amylase, alpha 1B (salivary); amylase, alpha 1C (salivary)	Metabolic
Arachidonate 12-lipoxygenase	Metabolic
Arachidonate 15-lipoxygenase	Metabolic
Aryl hydrocarbon receptor	Metabolic
Aalmodulin 3 (phosphorylase kinase, delta); calmodulin 2 (phosphorylase kinase, delta); calmodulin 1 (phosphorylase kinase, delta)	Metabolic
Dopamine receptor D2	Metabolic
Galactokinase 1	Metabolic
Glucagon-like peptide 1 receptor	Metabolic
Glucosidase, alpha; acid	Metabolic
Glucosidase, beta; acid (includes glucosylceramidase)	Metabolic
Glycogen synthase kinase 3 beta	Metabolic
Hydroxysteroid (11-beta) dehydrogenase 1	Metabolic
Monoamine oxidase A	Metabolic
Multiple endocrine neoplasia I	Metabolic
Nuclear receptor coactivator 3	Metabolic
Nuclear receptor subfamily 1, group H, member 3	Metabolic
Nuclear receptor subfamily 5, group A, member 1	Metabolic
Opioid receptor, mu 1	Metabolic
Phospholipase A2, group IIA (platelets, synovial fluid)	Metabolic
Phospholipase A2, group IID	Metabolic
Protein tyrosine phosphatase, non-receptor type 1	Metabolic
Sex hormone-binding globulin	Metabolic
Similar to Werner syndrome protein; Werner syndrome, RecQ helicase-like	Metabolic
Solute carrier family 22 (organic anion/urate transporter), member 12	Metabolic
V-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	Metabolic
B-cell CLL/lymphoma 2	Immune

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DNA (cytosine-5-)-methyltransferase 1	Immune
T-cell receptor alpha constant; T-cell receptor alpha locus; T-cell receptor alpha variable 20; T-cell receptor delta locus; T-cell receptor delta variable 2	Immune
Arachidonate 5-lipoxygenase	Immune
Ataxin 2	Immune
Cholinergic receptor, muscarinic 1	Immune
Formyl peptide receptor 1	Immune
Integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	Immune
Matrix metallopeptidase 14 (membrane-inserted)	Immune
Neuropeptide S receptor 1	Immune
Neutrophil cytosolic factor 1; neutrophil cytosolic factor 1C pseudogene	Immune
Prostaglandin E receptor 2 (subtype EP2), 53kDa	Immune
Protein kinase C, eta	Immune
Protein tyrosine phosphatase, non-receptor type 6	Immune
Retinoid X receptor, alpha	Immune
Signal transducer and activator of transcription 3 (acute-phase response factor)	Immune
Tumor necrosis factor receptor superfamily, member 10b	Immune
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	Immune
ATP-binding cassette, sub-family B (MDR/TAP), member 1	Infection, metabolic, immune
SMAD family member 3	Infection, metabolic
Acid phosphatase 1, soluble	Infection, metabolic, immune
Adrenergic, beta-2-, receptor, surface	Infection, metabolic, immune
Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)	Infection, metabolic, immune
Cytochrome P450, family 1, subfamily A, polypeptide 1	Infection, metabolic, immune
Cytochrome P450, family 2, subfamily C, polypeptide 19	Infection, metabolic, immune
Cytochrome P450, family 2, subfamily D, polypeptide 6	Infection, metabolic, immune
Cytochrome P450, family 3, subfamily A, polypeptide 4	Infection, metabolic, immune
Estrogen receptor 1	Infection, metabolic, immune
Glutathione S-transferase mu 1	Infection, metabolic, immune
Glyoxalase I	Infection, immune
Heat shock 70kDa protein 1A; heat shock 70kDa protein 1B	Infection, metabolic, immune
Macrophage migration inhibitory factor (glycosylation-inhibiting factor)	Infection, metabolic, immune
Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Infection, immune
Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	Infection, metabolic, immune
Tumor necrosis factor (TNF superfamily, member 2)	Infection, metabolic, immune
Tumor necrosis factor (ligand) superfamily, member 10	Infection, immune
Tumor protein p53	Infection, metabolic, immune
Vitamin D (1,25- dihydroxyvitamin D3) receptor	Infection, metabolic, immune
Hydroxysteroid (11-beta) dehydrogenase 2	Infection, metabolic, immune
Hydroxysteroid (17-beta) dehydrogenase 2	Infection, metabolic
Hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription	Infection, metabolic

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factor)	
Insulin-degrading enzyme	Infection, metabolic
Melanocortin 4 receptor	Infection, metabolic
Microphthalmia-associated transcription factor	Infection, metabolic
CD38 molecule Homo sapiens	Metabolic, immune
NAD(P)H dehydrogenase, quinone 1	Metabolic, immune
NLR family, pyrin domain containing 3	Metabolic, immune
Aldo-keto reductase family 1, member B1 (aldose reductase)	Metabolic, immune
Alkaline phosphatase, liver/bone/kidney	Metabolic, immune
Androgen receptor	Metabolic, immune
Cytochrome P450, family 1, subfamily A, polypeptide 2	Metabolic, immune
Cytochrome P450, family 1, subfamily B, polypeptide 1	Metabolic, immune
Cytochrome P450, family 19, subfamily A, polypeptide 1	Metabolic, immune
Cytochrome P450, family 2, subfamily C, polypeptide 9	Metabolic, immune
Estrogen receptor 2 (ER beta)	Metabolic, immune
Glucokinase (hexokinase 4)	Metabolic, immune
Hepatocyte nuclear factor 4, alpha	Metabolic, immune
Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Metabolic, immune
Peroxisome proliferator-activated receptor alpha	Metabolic, immune
Peroxisome proliferator-activated receptor gamma	Metabolic, immune
Phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)	Metabolic, immune
Thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian)	Metabolic, immune

Table 2: Ingredients and targets of *Flos Lonicerae*

Geraniol		
ID	Gene Name	Function
1832253	arachidonate 15-lipoxygenase	Metabolic
Luteolin		
ID	Gene Name	Function
10864009	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1	Infection
13399304	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	Infection
6274552	signal transducer and activator of transcription 1, 91kDa	Infection
24497585	aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)	Metabolic
1351933	amylase, alpha 1A (salivary); amylase, alpha 1B (salivary); amylase, alpha 1C (salivary)	Metabolic
154426292	arachidonate 12-lipoxygenase	Metabolic
1832253	arachidonate 15-lipoxygenase	Metabolic
49037474	calmodulin 3 (phosphorylase kinase, delta); calmodulin 2	Metabolic

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	(phosphorylase kinase, delta); calmodulin 1 (phosphorylase kinase, delta)	
4503385	dopamine receptor D2	Metabolic
4503895	galactokinase 1	Metabolic
1724069	glucagon-like peptide 1 receptor	Metabolic
119393891	glucosidase, alpha; acid	Metabolic
496369	glucosidase, beta; acid (includes glucosylceramidase)	Metabolic
18860839	multiple endocrine neoplasia I	Metabolic
20070193	nuclear receptor subfamily 5, group A, member 1	Metabolic
2851402	opioid receptor, mu 1	Metabolic
129483	phospholipase A2, group IIA (platelets, synovial fluid)	Metabolic
131467	protein tyrosine phosphatase, non-receptor type 1	Metabolic
3719421	similar to Werner syndrome protein; Werner syndrome, RecQ helicase-like	Metabolic
74732700	solute carrier family 22 (organic anion/urate transporter), member 12	Metabolic
4503351	DNA (cytosine-5-)-methyltransferase 1	Immune
2358024	T-cell receptor alpha constant; T-cell receptor alpha locus; T-cell receptor alpha variable 20; T-cell receptor delta locus; T-cell receptor delta variable 2	Immune
126407	arachidonate 5-lipoxygenase	Immune
171543895	ataxin 2	Immune
37622910	cholinergic receptor, muscarinic 1	Immune
4503779	formyl peptide receptor 1	Immune
67191027	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	Immune
4826834	matrix metallopeptidase 14 (membrane-inserted)	Immune
115298672	neutrophil cytosolic factor 1; neutrophil cytosolic factor 1C pseudogene	Immune
281185512	protein kinase C, eta	Immune
4506755	retinoid X receptor, alpha	Immune
13272532	signal transducer and activator of transcription 3 (acute-phase response factor)	Immune
18418623	SMAD family member 3	Infection, metabolic
1709543	acid phosphatase 1, soluble	Infection, metabolic, immune
4501969	adrenergic, beta-2-, receptor, surface	Infection, metabolic, immune
90421313	cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)	Infection, metabolic, immune

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117139	cytochrome P450, family 1, subfamily A, polypeptide 1	Infection, metabolic, immune
4503219	cytochrome P450, family 2, subfamily C, polypeptide 19	Infection, metabolic, immune
40805836	cytochrome P450, family 2, subfamily D, polypeptide 6	Infection, metabolic, immune
31933	glutathione S-transferase mu 1	Infection, metabolic, immune
134039205	glyoxalase I	Infection, immune
12803275	heat shock 70kDa protein 1A; heat shock 70kDa protein 1B	Infection, metabolic, immune
1170955	macrophage migration inhibitory factor (glycosylation-inhibiting factor)	Infection, metabolic, immune
34577122	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Infection, immune
3915797	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	Infection, metabolic, immune
4507593	tumor necrosis factor (ligand) superfamily, member 10	Infection, immune
63054845	vitamin D (1,25- dihydroxyvitamin D3) receptor	Infection, metabolic, immune
544152	hydroxysteroid (17-beta) dehydrogenase 2	Infection, metabolic
32879895	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	Infection, metabolic
155969707	insulin-degrading enzyme	Infection, metabolic
40807040	microphthalmia-associated transcription factor	Infection, metabolic
118607	NAD(P)H dehydrogenase, quinone 1	Metabolic, immune
219518789	NLR family, pyrin domain containing 3	Metabolic, immune
113596	aldo-keto reductase family 1, member B1 (aldose reductase)	Metabolic, immune

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116734717	alkaline phosphatase, liver/bone/kidney	Metabolic, immune
113830	androgen receptor	Metabolic, immune
73915100	cytochrome P450, family 1, subfamily A, polypeptide 2	Metabolic, immune
48429256	cytochrome P450, family 1, subfamily B, polypeptide 1	Metabolic, immune
6686268	cytochrome P450, family 2, subfamily C, polypeptide 9	Metabolic, immune
10835013	estrogen receptor 2 (ER beta)	Metabolic, immune
4503951	glucokinase (hexokinase 4)	Metabolic, immune
31077205	hepatocyte nuclear factor 4, alpha	Metabolic, immune
3041727	peroxisome proliferator-activated receptor alpha	Metabolic, immune
Eugenol		
ID	Gene Name	Function
32307126	nuclear receptor coactivator 3	Metabolic
4826834	matrix metallopeptidase 14 (membrane-inserted)	Immune
11950843	melanocortin 4 receptor	Infection, metabolic
Isoeugenol		
ID	Gene Name	Function
5730106	chemokine (C-X-C motif) receptor 6	Infection
32307126	nuclear receptor coactivator 3	Metabolic
4826834	matrix metallopeptidase 14 (membrane-inserted)	Immune
11950843	melanocortin 4 receptor	Infection, metabolic
113596	aldo-keto reductase family 1, member B1 (aldose reductase)	Metabolic, immune
4503951	glucokinase (hexokinase 4)	Metabolic, immune
Chlorogenic Acid		
ID	Gene Name	Function
119393891	glucosidase, alpha; acid	Metabolic
281185512	protein kinase C, eta	Immune
219518789	NLR family, pyrin domain containing 3	Metabolic, immune

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Table 3: Ingredients and targets of *Semen Raphani*

Biotin		
ID	Gene Name	Function
18860839	multiple endocrine neoplasia I	Metabolic
42741659	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Infection, metabolic, immune
155969707	insulin-degrading enzyme	Infection, metabolic

Table 4: Ingredients and targets of *Fructus Forsythiae*

Ursolic Acid		
ID	Gene Name	Function
10864009	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1	Infection
24497585	aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)	Metabolic
20455502	glycogen synthase kinase 3 beta	Metabolic
118569	hydroxysteroid (11-beta) dehydrogenase 1	Metabolic
20139286	phospholipase A2, group IID	Metabolic
131467	protein tyrosine phosphatase, non-receptor type 1	Metabolic
231632	B-cell CLL/lymphoma 2	immune
46395496	neuropeptide S receptor 1	immune
115298672	neutrophil cytosolic factor 1; neutrophil cytosolic factor 1C pseudogene	immune
30316367	hydroxysteroid (11-beta) dehydrogenase 2	Infection, metabolic, immune
270133071	phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)	Metabolic, immune
189491771	thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian)	Metabolic, immune
Beta-ursolic Acid		
ID	Gene Name	Function
10864009	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1	Infection
24497585	aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)	Metabolic
20455502	glycogen synthase kinase 3 beta	Metabolic
118569	hydroxysteroid (11-beta) dehydrogenase 1	Metabolic
20139286	phospholipase A2, group IID	Metabolic
131467	protein tyrosine phosphatase, non-receptor type 1	Metabolic
231632	B-cell CLL/lymphoma 2	immune

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2358024	T-cell receptor alpha constant; T-cell receptor alpha locus; T-cell receptor alpha variable 20; T-cell receptor delta locus; T-cell receptor delta variable 2	immune
46395496	neuropeptide S receptor 1	immune
115298672	neutrophil cytosolic factor 1; neutrophil cytosolic factor 1C pseudogene	immune
30316367	hydroxysteroid (11-beta) dehydrogenase 2	Infection, metabolic, immune
13432234	peroxisome proliferator-activated receptor gamma	Metabolic, immune
270133071	phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)	Metabolic, immune
(-)-pinoresinol		
ID	Gene Name	Function
134907	sex hormone-binding globulin	Metabolic
4826834	matrix metallopeptidase 14 (membrane-inserted)	immune
116241312	cytochrome P450, family 3, subfamily A, polypeptide 4	Infection, metabolic, immune
117293	cytochrome P450, family 19, subfamily A, polypeptide 1	Metabolic, immune
Rutin		
ID	Gene Name	Function
13399304	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	Infection
1351933	amylase, alpha 1A (salivary); amylase, alpha 1B (salivary); amylase, alpha 1C (salivary)	Metabolic
119393891	glucosidase, alpha; acid	Metabolic
18860839	multiple endocrine neoplasia I	Metabolic
2851402	opioid receptor, mu 1	Metabolic
2358024	T-cell receptor alpha constant; T-cell receptor alpha locus; T-cell receptor alpha variable 20; T-cell receptor delta locus; T-cell receptor delta variable 2	immune
126407	arachidonate 5-lipoxygenase	immune
171543895	ataxin 2	immune
117139	cytochrome P450, family 1, subfamily A, polypeptide 1	Infection, metabolic, immune
219518789	NLR family, pyrin domain containing 3	Metabolic, immune
121069	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Metabolic, immune

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Table 5: Ingredients and targets of *Scutellaria baicalensis* Georgi

Oroxylin a		
ID	Gene Name	Function
10864009	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1	Infection
24497585	aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)	Metabolic
1832253	arachidonate 15-lipoxygenase	Metabolic
4503385	dopamine receptor D2	Metabolic
1724069	glucagon-like peptide 1 receptor	Metabolic
119393891	glucosidase, alpha; acid	Metabolic
496369	glucosidase, beta; acid (includes glucosylceramidase)	Metabolic
126407	arachidonate 5-lipoxygenase	immune
171543895	ataxin 2	immune
37622910	cholinergic receptor, muscarinic 1	immune
67191027	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	immune
4826834	matrix metallopeptidase 14 (membrane-inserted)	immune
281185512	protein kinase C, eta	immune
4506755	retinoid X receptor, alpha	immune
13272532	signal transducer and activator of transcription 3 (acute-phase response factor)	immune
117139	cytochrome P450, family 1, subfamily A, polypeptide 1	Infection, metabolic, immune
4503219	cytochrome P450, family 2, subfamily C, polypeptide 19	Infection, metabolic, immune
40805836	cytochrome P450, family 2, subfamily D, polypeptide 6	Infection, metabolic, immune
31933	glutathione S-transferase mu 1	Infection, metabolic, immune
134039205	glyoxalase I	Infection, immune
34577122	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Infection, immune
3915797	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	Infection, metabolic, immune
4507593	tumor necrosis factor (ligand) superfamily, member 10	Infection, immune
63054845	vitamin D (1,25- dihydroxyvitamin D3) receptor	Infection, metabolic, immune
219518789	NLR family, pyrin domain containing 3	Metabolic, immune
48429256	cytochrome P450, family 1, subfamily B, polypeptide 1	Metabolic, immune
10835013	estrogen receptor 2 (ER beta)	Metabolic, immune
4503951	glucokinase (hexokinase 4)	Metabolic, immune
31077205	hepatocyte nuclear factor 4, alpha	Metabolic, immune
121069	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Metabolic, immune
3041727	peroxisome proliferator-activated receptor alpha	Metabolic, immune
Baicalein		
ID	Gene Name	Function
10864009	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A)	Infection

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	small phosphatase 1	
13399304	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	Infection
24497585	aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)	Metabolic
154426292	arachidonate 12-lipoxygenase	Metabolic
1832253	arachidonate 15-lipoxygenase	Metabolic
49037474	calmodulin 3 (phosphorylase kinase, delta); calmodulin 2 (phosphorylase kinase, delta); calmodulin 1 (phosphorylase kinase, delta)	Metabolic
4503385	dopamine receptor D2	Metabolic
4503895	galactokinase 1	Metabolic
119393891	glucosidase, alpha; acid	Metabolic
496369	glucosidase, beta; acid (includes glucosylceramidase)	Metabolic
126407	arachidonate 5-lipoxygenase	immune
171543895	ataxin 2	immune
37622910	cholinergic receptor, muscarinic 1	immune
67191027	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	immune
4826834	matrix metallopeptidase 14 (membrane-inserted)	immune
281185512	protein kinase C, eta	immune
4506755	retinoid X receptor, alpha	immune
13272532	signal transducer and activator of transcription 3 (acute-phase response factor)	immune
117139	cytochrome P450, family 1, subfamily A, polypeptide 1	Infection, metabolic, immune
4503219	cytochrome P450, family 2, subfamily C, polypeptide 19	Infection, metabolic, immune
40805836	cytochrome P450, family 2, subfamily D, polypeptide 6	Infection, metabolic, immune
134039205	glyoxalase I	Infection, immune
34577122	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Infection, immune
3915797	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	Infection, metabolic, immune
4507593	tumor necrosis factor (ligand) superfamily, member 10	Infection, immune
63054845	vitamin D (1,25- dihydroxyvitamin D3) receptor	Infection, metabolic, immune
544152	hydroxysteroid (17-beta) dehydrogenase 2	Infection, metabolic
32879895	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	Infection, metabolic
219518789	NLR family, pyrin domain containing 3	Metabolic, immune
48429256	cytochrome P450, family 1, subfamily B, polypeptide 1	Metabolic, immune
10835013	estrogen receptor 2 (ER beta)	Metabolic, immune
4503951	glucokinase (hexokinase 4)	Metabolic, immune
121069	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Metabolic, immune
3041727	peroxisome proliferator-activated receptor alpha	Metabolic, immune

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Table 6: Ingredients and targets of *Fructus trichosanthis*

Pyrene		
ID	Gene Name	Function
3041653	aryl hydrocarbon receptor	Metabolic
4503385	dopamine receptor D2	Metabolic
113978	monoamine oxidase A	Metabolic
119533	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	Metabolic
231632	B-cell CLL/lymphoma 2	immune
171543895	ataxin 2	immune
281185512	protein kinase C, eta	immune
131469	protein tyrosine phosphatase, non-receptor type 6	immune
34577122	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Infection, immune
25952111	tumor necrosis factor (TNF superfamily, member 2)	Infection, metabolic, immune
269849759	tumor protein p53	Infection, metabolic, immune
32879895	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	Infection, metabolic
121069	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	Metabolic, immune
189491771	thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian)	Metabolic, immune

Table 7: Ingredients and targets of *Herba houttuyniae*

Brassicasterol		
ID	Gene Name	Function
20455502	glycogen synthase kinase 3 beta	Metabolic
23503089	nuclear receptor subfamily 1, group H, member 3	Metabolic
20070193	nuclear receptor subfamily 5, group A, member 1	Metabolic
31881630	prostaglandin E receptor 2 (subtype EP2), 53kDa	immune
62821794	estrogen receptor 1	Infection, metabolic, immune
63054845	vitamin D (1,25- dihydroxyvitamin D3) receptor	Infection, metabolic, immune
Quercitrin		
ID	Gene Name	Function
13399304	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	Infection
1351933	amylase, alpha 1A (salivary); amylase, alpha 1B (salivary); amylase, alpha 1C (salivary)	Metabolic
119393891	glucosidase, alpha; acid	Metabolic
18860839	multiple endocrine neoplasia I	Metabolic
2851402	opioid receptor, mu 1	Metabolic
2358024	T-cell receptor alpha constant; T-cell receptor alpha locus; T-cell receptor alpha variable 20; T-cell receptor delta locus; T-cell receptor delta variable 2	immune

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126407	arachidonate 5-lipoxygenase	immune
171543895	ataxin 2	immune
117139	cytochrome P450, family 1, subfamily A, polypeptide 1	Infection, metabolic, immune
219518789	NLR family, pyrin domain containing 3	Metabolic, immune

Table 8: Ingredient and target of *Radix peucedani*

Nodakenin		
ID	Gene Name	Function
119393891	glucosidase, alpha; acid	Metabolic

Discussion

Concerning the study about targets of Yin lai Decoction

Currently, the targets that have been proven by experiments that related with the mechanism of Yin lai Decoction include TNF-α, IL-2, IL-6, IL-10 and IFN-γ (Gu and Yu, 2008; Wang, 2011). In the study, we can see that Yin lai Decoction can reduce the expression of IL-6, TNF-α,but promote release of IL-2, IL-10 and IFN-γ, regulate the immune function of organisms and ease the damage caused by inflammation.

In this study, we totally find out 92 possible targets of Yin lai Decoction by data mining technology, which means that this study make the research about Yin lai Decoction penetrate deeply into genetic level and consummate the probable mechanisms of the Decoction, and also provides targeted guidance for the future experimental study.

Concerning the mechanisms of Yin lai Decoction

The results of this study illustrate that Yin lai Decoction can display a pharmacological effect through regulating the metabolism of the organisms in addition to immunoregulation and anti-infection that has been proven by previous experiments. Take the IDE (Insulin-degrading Enzyme) gene for an example, it's expression can be regulated by Yin lai Decoction, then the metabolism of the organisms will be impacted and the body will be promoted to healthy. But the concrete process of regulation should be verified by the further experiments.

Concerning the network of gene targets about Yin lai Decoction

The effects of possible gene targets about Yin lai Decoction become a net. More than 20% of these targets can adjust and control immunological mechanisms, metabolism and inflammatory response, which make HSP (heat shock 70kDa protein 1A， heat shock 70kDa protein 1B， hsp) as representative. And this phenomenon reflects the complexity of the biological modulation.

Concerning the targeted gene of one herb in Yin lai Decoction

Concerning the quantity of the targeted gene, we can know that *Flos lonicerae*, *Fructus forsythiae* and *Scutellaria baicalensis* Georgi play a major effect, whose gene targets overlap the 87% of all targets about Yin lai Decoction and function involve anti-infection, regulation of metabolism and immunological mechanisms. The function of *Flos lonicerae* and *Fructus forsythiae* mainly centralizes the metabolism, then immunological mechanisms, and last anti-infection which commonly thought to be the predominant. The function of *Scutellaria baicalensis* Georgi centralizes immunological mechanisms, then metabolism, and last anti-infection.

As clinical matched pair in Traditional Chinese Medicine, the effects of *Flos lonicerae* and *Fructus forsythiae* are clearing qi and cooling

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blood, clearing heat and removing toxin, detumescence, reducing stagnation and pain. *Scutellaria baicalensis* Georgi is bitter in taste and cold in property, the function of which is clearing heat and drying dampness, purging fire and removing toxin, cooling blood and hemostasis. These three herbs can clearing heat, cooling blood and removing toxin at the same time as well as the ingredients of them can monitor the expression of targeted gene-- cyp4501A1(cytochrome P450, family 1, subfamily A, polypeptide 1) to regulate metabolism, immune system and anti-infection.

The function of cyp450

Cyp450 is a gene superfamily made up of genes that have the similar structures and functions, the zymoproteins coded by which exist in liver microsomes and involve in the phase I biotransformation of many endogenous or exogenous compounds *in vivo*, which means that most metabolic substrates would lose their activities through the process of oxidation, reduction or hydrolysis. CYP4501A1 can activate the precarcinogen or translate the virulent substances into innoxious substances (Wu et al., 2007; Lei et al., 2010) as the major metabolic enzymes of polycyclic aromatic hydrocarbons, precarcinogen and some toxins. Then it can participate in the process of immune, metabolism and anti-infection of the organisms.

The molecular mechanism of the herbal ingredients regulating cyp4501a1

The ingredients targeted cyp4501a1 in Flos Lonicerae, Fructus Forsythiae and Scutellaria baicalensis Georgi are luteolin, rutin, oroxylin a and baicalein. Previous studies have been shown that luteolin and baicalein had a strong inhibitory effect on expression of CYP4501A1 (Ying et al., 2010; Liao and Chen, 2012; Li, 2010), make the bioactivity of CYP4501A1 decreased by reducing the production and inhibiting the activation, then the biological effects could be visualized. The decrease in bioactivity of CYP4501A1 would make the activity of translating the exogenous compounds into toxins weaken, which limits the toxicities of bacteria and viruses, or translate the toxins of bacteria and viruses into innoxious substances, then the anti-infection would be brought into play; at the same time, CYP4501A1 would regulate the immunological mechanisms by participating in the immune response of organisms to bacteria and viruses; also CYP4501A1 can promote the body to healthy by taking part in many metabolic processes. But all the genes mentioned above have no reliable experimental evidence to be confirmed.

Concerning the ingredients of Yin lai Decoction

The ingredients of Yin lai Decoction in this study only contain these have been published in literature and definite targeted gene, as a result, the ingredients of every herb are not exhaustive and we cannot preclude the possibility of the teeming of new targets in the future. This study retrieved only the possible gene targets of herbs in Yin lai Decoction, but the specific pharmacology effect and the regulatory mechanism should be studied more deeply.

Conclusion

All retrieve herbs in Yin lai Decoction by integrating information from multi-databases show that Yin lai Decoction can take part in the metabolism, inflammation and immune response by regulating the 92 possible gene targets, treat the damage caused by inflammation and promote the body to healthy, thus the effect could be visualized. But the definite regulatory mechanism should be explored and proven in the further experiments.

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