

EFFECTIVE CHEMICAL CONSTITUENT'S CONFIRMATION OF EXTRACTING SOLUTION FROM HERBS AND THEIR GENE TARGETS

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Ixeris sonchifolia Hance, a normal perennial herb, has effects on appendicitis, headache, menstruation, blood circulation, blood stasis, pain, fibrinolytic enzymes, thrombus formation, coronary artery, myocardial infarct size, PGI₂, ET, TXA₂, TNF- α , IL-6 and IL-8, etc. However, there was no full coverage about the molecular basis and gene targets of *Ixeris sonchifolia* injection. PubChem Database and DAVID Database had been used conjunctively to detect the gene IDs, gene targets and their functions. There were 3008 genes found in the final results, 16 kinds of definite functions had been detected, 9 of which had been proved and the effects were focused on the psychological, immune, neurological, metabolic, cardiovascular and cancer functions. *Ixeris sonchifolia* had a wide effects on various symptoms, which had been reported by previous experiments and verified by this research; however its influences on aging, chemdependency, developmental, normalvariation, reproduction, pharmacogenomic and psychologic functions should be confirmed in the future experiments.

Key words: database, gene targets, functions, information integration, *Ixeris sonchifolia* Hance

INTRODUCTION

Ixeris sonchifolia Hance, a member of the Compositae Family, is widely distributed in the northeastern place of China, is a small and bitter perennial herb (YAOCHUN *et al.*, 2009). In China, as a kind of well-known folk medicine, *Ixeris sonchifolia* has also been used for many

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years to cure appendicitis, reduce headache, normalize menstruation, invigorate blood circulation and eliminate blood stasis in order to relieve pain (HE *et al.*, 2006; FENG *et al.*, 2001). More recently, raw extract of *Ixeris sonchifolia* has been made into an injectable formulation, according to the reports, which has biological activities in several aspects such as inhibition of platelet aggregation, relaxation of vascular smooth muscle, enhancement of cerebral blood flow, improvement of the activities of fibrinolytic enzymes and inhibition of thrombus formation (MAO and JING, 2012). A clinical observation and an animal study have confirmed that the injection is able to expand coronary artery, increase flow of blood, reduce cardiac load and decrease myocardial infarct size (ZHAOAN and SHOUYUAN, 2005; WANG *et al.*, 2006). The formulation has also been found in a study to exhibit therapeutic efficiency in restoring stroke patients' neural functions and recovery of daily vasomotor activities (YI *et al.*, 2005).

Presently, targets related to the mechanism of *Ixeris sonchifolia* injection, which has been proven by several researches, include prostaglandin I₂ (PGI₂), endothelin (ET), thromboxane A₂ (TXA₂), tumor necrosis Factor- α (TNF- α), interleukin-6 (IL-6), interleukin-8 (IL-8), and protein Bcl-2/Bax (ZHAO-LIANG *et al.*, 2013; LIFANG and MEIJIAN, 2013; WANG *et al.*, 2013).

However, based on the review of above experiments, there was no full coverage about the molecular basis and gene targets of *Ixeris sonchifolia* injection. Therefore, particularly it is important to conduct research of *Ixeris sonchifolia* injection's pharmaceutical effect mechanism, material basis on molecular level and gene targets.

Currently, with the development of Public Databases and Networked Pharmacology Method, according to the information integration among various databases, the interdisciplinary research has become possible, which is able to basically identify the indexes before the experiments, enhance the accuracy and reduce the repeated frequency, and at the same time, the research can be finished on the level of molecular and gene targets (DI *et al.*, 2013).

So the author had conducted the gene targets of *Ixeris sonchifolia* Injection based on the method of information integration among various databases in this research, not only to verify the previous experiments but also to give advice to the following designs.

MATERIALS AND METHODS

Data sources

The data sources used were PubChem Database and DAVID Database.

PubChem Database

PubChem (<http://pubchem.ncbi.nlm.nih.gov>), whose mission is to provide intuitive data analysis tools, and to deliver free and easy access to all deposited data, is a public repository for biological activity data of small molecules and RNAi reagents. 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. Bioassay description and data can be searched, reviewed and downloaded on the PubChem information platform by users. And it also enables researchers to collect, compare and analyze biological test results through web-based and programmatic tools (WANG *et al.*, 2009).

DAVID Database

All tools in the DAVID Bioinformatics Resources (<http://david.niaid.nih.gov>) aim to provide functional interpretation of large lists of genes derived from genomic studies. DAVID Knowledgebase and five integrated, web-based functional annotation tool suites are consisted in

the newly updated DAVID Bioinformatics Resources. The expanded DAVID Knowledgebase now integrates almost all major and well-known public bioinformatics resources centralized by the DAVID Gene Concept, a single-linkage method to agglomerate tens of millions of diverse gene/protein identifiers and annotation terms from a variety of public bioinformatics databases. For any uploaded gene list, the DAVID Resources now provides not only the typical gene-term enrichment analysis, but also new tools and functions that allow users to condense large gene lists into gene functional groups, convert between gene/protein identifiers, visualize many-genes-to-many-terms relationships, cluster redundant and heterogeneous terms into groups, search for interesting and related genes or terms, dynamically view genes from their lists on bio-pathways and more. With DAVID, investigators gain more power to interpret the biological mechanisms associated with large gene lists. (SHERMAN *et al.*, 2007).

Effective Constituents of *Ixeris sonchifolia* Injection

According to previous experiments, the effective constituents of *Ixeris sonchifolia* injection basically include chicoric acid; uridine; guanosine; adenosine; 1-caffeoylquinic acid; 3,4-dihydroxy-caftaric acid; 3-caffeoylquinic acid; caffeic anhydride; 11, 13-dihydro-13-prolyl-ixerin Z; 3-p-coumaroylquinic acid; 5-caffeoylquinic acid; 3-feruloylquinic acid; 4-caffeoylquinic acid; caffeic acid; 5-p-coumaroylquinic acid; 1, 3-dicaffeoylquinic acid; 4-feruloylquinic acid; luteolin-7-O- β -D-gentiobioside; sonchifolactone D; luteolin-7-O- β -D-glucuronide; luteolin-7-O- β -D-glucoside; 3,4-dicaffeoylquinic acid; 3, 5-dicaffeoylquinic acid; 11 β -hydroxyleucodin-11-O- β -glucopyranoside; apigenin-7-O- β -D-glucuronide; ixerin Z; apigenin-7-O- β -D-glucoside; 4, 5-dicaffeoylquinic acid; 11 β -hydroxyleucodin-11-O- β -glucopyranoside isomer; 11 β ,13-dihydroixerin Z; luteolin; 11, 13-dihydro-13-prolyl-ixerin Z1; acacetin-7-O- β -D-rutinoside (HAO-MING *et al.*, 2013; YING *et al.*, 2013).

Retrieval Methods

We logged on to PubChem Homepage (<http://www.ncbi.nlm.nih.gov/pccompound>) and searched for "Uridine". We got the Uridine's CID number (6029) from the site, and we linked back to PubChem homepage and clicked "chemical structure search" below "PubChem Tool". From the display, we clicked on "CID, SMILES, INCHI" below "identity similarity", and input 6029 in the blank, unfold "option" menu. We chose similarity greater than 90 and other options were default. At last, we clicked "search" to enter next level (ZHANG *et al.*, 2013).

On the basis of PubChem database results, there were 1623 results. On the right side of webpage, we saw the item "BioActivity Experiments" under "Refine your results". Then, we clicked "Bioassays Active (53)", and got 53 main active ingredients. Next, we clicked "BioActivity Analysis" under "Action on your results", and finished target analysis for these 53 active components. The item of "target" was the useful result we needed. We then clicked "download" to download the contents. In the downloaded file, data of "active compounds" showed that results 1-5 were meaningful targets. Found with these meaningful targets was a corresponding "sequence GI used in assays", and these GI number was organized for the next step (ZHANG *et al.*, 2013). After it, we found out all the corresponding GI number of main components in *Ixeris sonchifolia* and organized them for the next step.

We logged on to David homepage (<http://david.abcc.ncifcrf.gov/summary.jsp>) and clicked "upload" under "start analysis". We input all the GI numbers, chose "protein GI

Accession” for “step 2”, chose “gene list” for “step 3”, then started search and observation of results. We clicked “genetic association db disease class”, for pop up in another page. Then we could get the Gene ID, Targets and Functions. Finally, we clicked “download file” to completely organize the results. Until now, we totally finished the whole search session and got the aimed results (ZHANG *et al.*, 2013).

RESULTS

About the effective constituents of *Ixeris sonchifolia* Injection, there was no record about 3,4-dihydroxy-caftaric acid in David Database. There was no record of caffeic anhydride; 11, 13-dihydro-13-prolyl-ixerin Z; 3-p-coumaroylquinic acid; 4-caffeoylquinic acid; 5-p-coumaroylquinic acid; 4-feruloylquinic acid; luteolin-7-O- β -D-gentiobioside; sonchifolactone D; 11 β -hydroxyleucodin-11-O- β -glucopyranoside; ixerin Z; 4, 5-dicaffeoylquinic acid; 11 β -hydroxyleucodin-11-O- β -glucopyranoside isomer; 11 β , 13-dihydroixerin Z and 11, 13-dihydro-13-prolyl-ixerin Z1 in PubChem Database. Others results of Gene ID, targets and functions of *Ixeris sonchifolia* injection are shown in Table 1.

Table 1. Gene ID, gene targets and functions of *Ixeris sonchifolia* injection

No.	Gene ID	Gene Targets	Functions
1	2393947	<u>ADAM metallopeptidase domain 10</u>	Neurological
2	42741659	<u>ATP-binding cassette, sub-family B (MDR/TAP), member 1</u>	Aging, cancer, cardiovascular, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, renal, unknown, and vision
3	67462103	<u>ATP-binding cassette, sub-family G (WHITE), member 2</u>	Cancer, cardiovascular, normalvariation, pharmacogenomic
4	231632	<u>B-cell CLL/lymphoma 2</u>	Cancer, developmental, hematological, immune, other
5	2493274	<u>BCL2-antagonist/killer 1; BCL2-like 7 pseudogene 1</u>	Cancer
6	728945	<u>BCL2-associated X protein</u>	Cancer, hematological, immune
7	4557365	<u>Bloom syndrome, RecQ helicase-like</u>	Cancer
8	55977782	<u>CD38 molecule</u>	Immune, metabolic, unknown
9	116241283	<u>CREB binding protein</u>	Neurological, other, pharmacogenomic
10	10864009	<u>CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1</u>	Infection
11	4503351	<u>DNA (cytosine-5-)-methyltransferase 1</u>	Immune
12	125370	<u>FYN oncogene related to SRC, FGR, YES</u>	Cardiovascular, chemdependency, neurological, psychological
13	121945198	<u>HtrA serine peptidase 1</u>	Neurological, vision
14	119579178	<u>Janus kinase 2</u>	Cancer, cardiovascular, developmental, hematological, pharmacogenomic, reproduction

15	124263658	<u>Kruppel-like factor 5 (intestinal)</u>	Metabolic
16	118607	<u>NAD(P)H dehydrogenase, quinone 1</u>	Cancer, chemdependency, hematological, immune, metabolic, neurological, normalvariation, other, pharmacogenomic, renal, reproduction
17	255652944	<u>Niemann-Pick disease, type C1</u>	Other
18	3063388	<u>Parkinson disease (autosomal recessive, juvenile) 2, parkin</u>	Infection, neurological
19	18418623	<u>SMAD family member 3</u>	Cancer, infection, metabolic
20	119579215	<u>SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2</u>	Psych
21	2358024	<u>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</u>	Immune
22	20140568	<u>TAR DNA binding protein</u>	Psych
23	47678753	<u>X-box binding protein 1</u>	Chemdependency, Psychological, unknown
24	113037	<u>Acetylcholinesterase (Yt blood group)</u>	Neurological, normalvariation, other, Psychological, renal, unknown
25	1709543	<u>Acid phosphatase 1, soluble</u>	Cardiovascular, developmental, immune, infection, metabolic, other, psychological, reproduction
26	231473	<u>Adenosine A1 receptor</u>	Cardiovascular, pharmacogenomic, psychological
27	543740	<u>Adenosine A2a receptor</u>	Cardiovascular, chemdependency, neurological, other, pharmacogenomic, psychological
28	6840802	<u>Adenosine kinase</u>	Immune
29	20141702	<u>Adenosylhomocysteinase</u>	Cardiovascular,
30	4501969	<u>Adrenergic, beta-2-, receptor, surface</u>	Aging, cancer, cardiovascular, developmental, immune, infection, metabolic, normalvariation, other, pharmacogenomic, psychological, reproduction, unknown
31	30582681	<u>Aldehyde dehydrogenase 1 family, member A1</u>	Chemdependency, pharmacogenomic
32	113596	<u>Aldo-keto reductase family 1, member B1 (aldose reductase)</u>	Cardiovascular, developmental, immune, metabolic, neurological, other, renal, unknown, vision
33	24497585	<u>Aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha</u>	Metabolic, other

		<u>hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4)</u>	
34	116734717	<u>Alkaline phosphatase, liver/bone/kidney</u>	Cardiovascular, immune, metabolic, other
35	1351933	<u>Amylase, alpha 1A (salivary); amylase, alpha 1B (salivary); amylase, alpha 1C (salivary)</u>	Metabolic, neurological
36	112927, 257380	<u>Amyloid beta (A4) precursor protein</u>	Neurological, psych
37	124375976, 113830	<u>Androgen receptor</u>	Aging, cancer, cardiovascular, developmental, immune, metabolic, neurological, normalvariation, other, psychological, reproduction
38	4885057	<u>Apelin receptor</u>	Cardiovascular
39	13399304	<u>Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G</u>	Infection
40	25987838, 154426292	<u>Arachidonate 12-lipoxygenase</u>	Cancer, cardiovascular, metabolic, psych
41	126396, 1832253	<u>Arachidonate 15-lipoxygenase</u>	Cardiovascular, metabolic
42	126407	<u>Arachidonate 5-lipoxygenase</u>	Cancer, cardiovascular, immune, neurological, pharmacogenomic
43	4502331	<u>Arginine vasopressin receptor 1A</u>	Other, psych
44	4502333	<u>Arginine vasopressin receptor 1B</u>	Psych
45	267256	<u>Arginine vasopressin receptor 2</u>	Metabolic, renal
46	51095037, 4502003	<u>Aryl hydrocarbon receptor</u>	Cancer, cardiovascular, developmental, metabolic, normalvariation, Psychological, reproduction, vision
47	2702319	<u>Aryl hydrocarbon receptor nuclear translocator</u>	Other, reproduction
48	171543895	<u>Ataxin 2</u>	Immune, neurological
49	728984, 1698399	<u>Breast cancer 1, early onset</u>	Cancer, normalvariation, other, pharmacogenomic
50	116353	<u>Butyrylcholinesterase</u>	Cardiovascular, metabolic, neurological, normalvariation, other, pharmacogenomic, psychological
51	62362414	<u>C-abl oncogene 1, receptor tyrosine kinase</u>	Cancer
52	49037474	<u>Calmodulin 3 (phosphorylase kinase, delta); Calmodulin 2 (phosphorylase kinase, delta); Calmodulin 1 (phosphorylase</u>	Cardiovascular, metabolic

		<u>kinase, delta)</u>	
53	153791733	<u>Casein kinase 1, gamma 2</u>	Neurological
54	77416852, 14790119	<u>Caspase 3, apoptosis-related cysteine peptidase</u>	Cancer, developmental
55	28558771	<u>Caspase 9, apoptosis-related cysteine peptidase</u>	Cancer, developmental, immune, metabolic
56	1705894	<u>Chemokine (C-C motif) receptor 4</u>	Immune
57	37622910	<u>Cholinergic receptor, muscarinic 1</u>	Chemdependency, immune, neurological, psychological
58	52426748	<u>Cholinergic receptor, muscarinic 4</u>	Psychological
59	7108336	<u>Cholinergic receptor, muscarinic 5</u>	Psychological
60	180352	<u>Coagulation factor XI</u>	Cancer, cardiovascular, hematological
61	13124873, 13124881	<u>Core-binding factor, beta subunit</u>	Cancer
62	30219	<u>Corticotropin releasing hormone binding protein</u>	Psychological
63	116051	<u>Cyclin-dependent kinase 2</u>	Cancer
64	20072248	<u>Cyclin-dependent kinase 5, regulatory subunit 1 (p35)</u>	Developmental
65	266423	<u>Cyclin-dependent kinase 6</u>	Cancer
66	90421313, 89348172	<u>Cystic fibrosis transmembrane conductance regulator (ATP- binding cassette sub-family C, member 7)</u>	Cancer, cardiovascular, developmental, immune, infection, metabolic, other, reproduction, unknown
67	117139	<u>Cytochrome P450, family 1, subfamily A, polypeptide 1</u>	Aging, cancer, cardiovascular, hematological, immune, infection, metabolic, neurological, normal variation, other, pharmacogenomic, reproduction, unknown, vision
68	117144, 73915100	<u>Cytochrome P450, family 1, subfamily A, Polypeptide 2</u>	Cancer, cardiovascular, chem.- dependency, hematological, immune, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction, unknown, vision
69	48429256	<u>Cytochrome P450, family 1, subfamily B, polypeptide 1</u>	Aging, cancer, chemdependency, developmental, immune, metabolic, neurological, normalvariation, other, pharmacogenomic, reproduction, unknown, vision
70	119597822 , 117293	<u>Cytochrome P450, family 19, subfamily A, polypeptide 1</u>	Cancer, cardiovascular, developmental, immune, metabolic,

			neurological, normalvariation, other, Psychological, reproduction, unknown
71	60416369, 4503219	<u>Cytochrome P450, family 2, subfamily C, polypeptide 19</u>	Cancer, cardiovascular, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction, unknown
72	13699818, 6686268	<u>Cytochrome P450, family 2, subfamily C, polypeptide 9</u>	Cancer, cardiovascular, hematological, immune, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction
73	84028191, 68509921, 40805836	<u>Cytochrome P450, family 2, subfamily D, polypeptide 6</u>	Aging, cancer, cardiovascular, chemdependency, hematological, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, renal, reproduction, unknown, vision
74	116241312 , 13435386	<u>Cytochrome P450, family 3, subfamily A, polypeptide 4</u>	Cancer, cardiovascular, developmental, hematological, immune, infection, metabolic, neurological, normalvariation, pharmacogenomic, renal, reproduction, unknown
75	118447	<u>Deoxycytidine kinase</u>	Cancer, normalvariation, pharmacogenomic
76	17391426	<u>Dihydrolipoamide dehydrogenase</u>	Neurological
77	1352311	<u>Dipeptidyl-peptidase 4</u>	Immune
78	4503383, 299681	<u>Dopamine receptor D1</u>	Cardiovascular, chemdependency, neurological, pharmacogenomic, Psychological
79	4503385	<u>Dopamine receptor D2</u>	Cancer, chemdependency, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction, unknown
80	89191863	<u>Dopamine receptor D3</u>	Cancer, cardiovascular, chemdependency, metabolic, neurological, normalvariation, pharmacogenomic, Psychological
81	21315078	<u>Endoplasmic reticulum aminopeptidase 1</u>	Cardiovascular, other
82	40254439	<u>Endothelial PAS domain protein 1</u>	Normalvariation, other

83	21361095	<u>Enhancer of zeste homolog 2 (Drosophila)</u>	Cancer
84	2811086	<u>Epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)</u>	Cancer, immune, infection, metabolic, normalvariation, other, pharmacogenomic, renal, unknown
85	544257, 118764400	<u>Estrogen receptor 1</u>	Cancer, cardiovascular, chemdependency, developmental, hematological, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction, unknown
86	10835013	<u>Estrogen receptor 2 (ER beta)</u>	Cancer, cardiovascular, hematological, immune, metabolic, neurological, other, pharmacogenomic, Psychological, reproduction
87	168985070	<u>Euchromatic histone-lysine N-methyltransferase 2</u>	Cancer
88	4758356	<u>Flap structure-specific endonuclease 1</u>	Neurological
89	156630887	<u>Fms-related tyrosine kinase 3</u>	Cancer, metabolic, other, pharmacogenomic
90	4503779	<u>Formyl peptide receptor 1</u>	Immune
91	4503895	<u>Galactokinase 1</u>	Metabolic, vision
92	6016094	<u>Galanin receptor 2</u>	Chemdependency
93	4503907	<u>Galanin receptor 3</u>	Chemdependency
94	7705682	<u>Geminin, DNA replication inhibitor</u>	Cancer
95	1724069	<u>Glucagon-like peptide 1 receptor</u>	Metabolic
96	4503951	<u>Glucokinase (hexokinase 4)</u>	Cardiovascular, immune, metabolic, other, unknown, vision
97	119393891	<u>Glucosidase, alpha; acid</u>	Metabolic, other
98	496369	<u>Glucosidase, beta; acid (includes Glucosylceramidase)</u>	Metabolic, neurological, other
99	71051501	<u>Glutaminase</u>	Psychological
100	31933	<u>Glutathione S-transferase mu 1</u>	Aging, cancer, cardiovascular, chemdependency, developmental, hematological, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, renal, reproduction, unknown, vision

101	4758484	<u>Glutathione S-transferase omega 1</u>	Cancer, cardiovascular, neurological, normalvariation, pharmacogenomic
102	7669492	<u>Glyceraldehyde-3-phosphate dehydrogenase-like 6; hypothetical protein LOC100133042; glyceraldehyde-3-phosphate dehydrogenase</u>	Neurological, reproduction
103	21361340	<u>Glycogen synthase kinase 3 beta</u>	Cancer, chemdependency, metabolic, neurological, pharmacogenomic, Psychological
104	134039205	<u>Glyoxalase I</u>	Cardiovascular, immune, infection, other, Psychological, unknown
105	19855073	<u>Heat shock 27kDa protein-like 2 pseudogene; heat shock 27kDa protein 1</u>	Neurological
106	12803275	<u>Heat shock 70kDa protein 1A; heat shock 70kDa protein 1B</u>	Aging, cancer, cardiovascular, immune, infection, metabolic, neurological, other, pharmacogenomic, Psychological, renal, reproduction
107	5729877	<u>Heat shock 70kDa protein 8</u>	Cancer, renal
108	462333	<u>Heat shock transcription factor 1</u>	Cancer
109	4504349	<u>Hemoglobin, beta</u>	Cardiovascular, hematological, infection, metabolic, normalvariation, other, unknown
110	31077205	<u>Hepatocyte nuclear factor 4, alpha</u>	Immune, metabolic
111	90903231	<u>Huntingtin</u>	Neurological, other, Psychological, unknown
112	544152	<u>Hydroxysteroid (17-beta) dehydrogenase 2</u>	Cancer, metabolic
113	222080095	<u>Hypocretin (orexin) receptor 1</u>	Other
114	32879895, 4504385	<u>Hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)</u>	Cancer, cardiovascular, hematological, metabolic, other, vision
115	155969707	<u>Insulin-degrading enzyme</u>	Developmental, metabolic, neurological, Psychological

116	59036749	<u>Insulin-like growth factor 2 (somatomedin A); insulin; INS-IGF2 readthrough transcript</u>	Aging, cancer, cardiovascular, developmental, immune, metabolic, neurological, normalvariation, other, Psychological, reproduction, unknown, vision
117	67191027	<u>Integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)</u>	Cardiovascular, immune
118	108936015	<u>Interleukin 8 receptor, alpha</u>	Cancer, immune, infection, other, vision
119	21327705	<u>Kallikrein-related peptidase 7</u>	Immune
120	1170955	<u>Macrophage migration inhibitory factor (glycosylation-inhibiting factor)</u>	Cardiovascular, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, renal
121	116852	<u>Matrix metallopeptidase 1 (interstitial collagenase)</u>	Aging, cancer, cardiovascular, developmental, immune, infection, metabolic, neurological, normalvariation, other, reproduction, unknown
122	729179	<u>Matrix metallopeptidase 12 (macrophage elastase)</u>	Cancer, cardiovascular, immune, other
123	1168998	<u>Matrix metallopeptidase 13 (collagenase 3)</u>	Cancer, cardiovascular, immune
124	4826834	<u>Matrix metallopeptidase 14 (membrane-inserted)</u>	Immune
125	116856	<u>Matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)</u>	Cancer, cardiovascular, chemdependency, immune, metabolic, other, reproduction
126	116857	<u>Matrix metallopeptidase 3 (stromelysin 1, progelatinase)</u>	Aging, cancer, cardiovascular, developmental, immune, infection, neurological, other, reproduction, vision
127	269849668	<u>Matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)</u>	Cancer, cardiovascular, immune, infection, metabolic, neurological, other, Psychological, renal, reproduction, vision
128	119508433	<u>Melanocortin 4 receptor</u>	Metabolic, normalvariation, Psychological
129	21595776	<u>Methyl-CpG binding domain protein 2</u>	Cancer

130	143811423	<u>Methylthioadenosine phosphorylase</u>	Metabolic
131	40807040	<u>Microphthalmia-associated transcription factor</u>	Metabolic, other
132	92096784	<u>Microtubule-associated protein tau</u>	Developmental, neurological, other, Psychological, unknown
133	18860839	<u>Multiple endocrine neoplasia I</u>	Cancer, metabolic, other
134	46395496	<u>Neuropeptide S receptor 1</u>	Immune
135	4505445	<u>Neuropeptide Y receptor Y1</u>	Developmental, metabolic, normal variation
136	4505447	<u>Neuropeptide Y receptor Y2</u>	Metabolic
137	110611243	<u>Neurotensin receptor 1 (high affinity)</u>	Psychological
138	115298672	<u>Neutrophil cytosolic factor 1; neutrophil cytosolic factor 1C pseudogene</u>	Immune
139	224028257, 20149576	<u>Nuclear factor (erythroid-derived 2)-like 2</u>	Other
140	21620132, 34577122	<u>Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1</u>	Cancer, cardiovascular, immune, infection, neurological, pharmacogenomic
141	22538455	<u>Nuclear receptor coactivator 1</u>	Cardiovascular
142	32307126	<u>Nuclear receptor coactivator 3</u>	Cancer, metabolic, normalvariation, other
143	23503089	<u>Nuclear receptor subfamily 1, group H, member 3</u>	Cardiovascular, metabolic
144	121069, 66528677	<u>Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)</u>	Cancer, cardiovascular, chemdependency, developmental, immune, metabolic, normalvariation, other, pharmacogenomic, Psychological, renal
145	20070193	<u>Nuclear receptor subfamily 5, group A, member 1</u>	Developmental, metabolic
146	116242691	<u>Opioid receptor, kappa 1</u>	Chemdependency
147	2851402, 117940060	<u>Opioid receptor, mu 1</u>	Cancer, chemdependency, metabolic, neurological, other, pharmacogenomic, Psychological
148	118377	<u>Ornithine decarboxylase 1</u>	Cancer, other, pharmacogenomic
149	32307152	<u>Oxytocin receptor</u>	Psychological
150	998701	<u>Paired box 8</u>	Metabolic

151	5453898	<u>Peptidylprolyl cis/trans isomerase, NIMA-interacting 1</u>	Neurological
152	13432234, 216409692, 20336229	<u>Peroxisome proliferator-activated receptor gamma</u>	Aging, cancer, cardiovascular, immune, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction
153	18266879	<u>Phosphatidylinositol-5-phosphate 4-kinase, type II, alpha</u>	Psychological
154	126302584	<u>Phosphoinositide-3-kinase, catalytic, alpha polypeptide</u>	Cancer, pharmacogenomic
155	129483	<u>Phospholipase A2, group IIA (platelets, synovial fluid)</u>	Cancer, cardiovascular, metabolic, Psychological
156	270133071	<u>Phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)</u>	Cardiovascular, immune, metabolic, Psychological
157	223459640	<u>Phospholipase C, gamma 1</u>	Immune, Psychological
158	6648082	<u>Phosphorylase, glycogen, liver</u>	Immune
159	4758878	<u>Platelet-activating factor acetylhydrolase 2, 40kDa</u>	Cardiovascular
160	130781	<u>Poly (ADP-ribose) polymerase 1</u>	Aging, cancer, immune, metabolic, neurological, pharmacogenomic, renal, vision
161	154350220	<u>Polymerase (DNA directed) iota</u>	Cancer
162	7705344	<u>Polymerase (DNA directed) kappa</u>	Cancer
163	544186, 4505931	<u>Polymerase (DNA directed), beta</u>	Cancer, pharmacogenomic
164	50403732	<u>Polymerase (DNA directed), delta 1, catalytic subunit 125kDa</u>	Cancer
165	11093520	<u>Potassium channel, subfamily K, member 3</u>	Psychological
166	32479527	<u>Potassium voltage-gated channel, KQT-like subfamily, member 1</u>	Cardiovascular, chemdependency, other
167	4557729	<u>Potassium voltage-gated channel, subfamily H (eag-related), member 2</u>	Cardiovascular, chemdependency, other
168	4506113	<u>Prion protein</u>	Aging, cancer, metabolic,

			neurological, other, Psychological, reproduction
169	215273868	<u>Prolyl endopeptidase</u>	Psychological
170	31881630	<u>Prostaglandin E receptor 2 (subtype EP2), 53kDa</u>	Cardiovascular, immune
171	3915797	<u>Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)</u>	Cancer, cardiovascular, hematological, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, reproduction
172	131467	<u>Protein tyrosine phosphatase, non-receptor type 1</u>	Cardiovascular, metabolic
173	116242696	<u>Purinergic receptor P2X, ligand-gated ion channel, 4</u>	Cardiovascular, Psychological
174	1352692	<u>Purinergic receptor P2Y, G-protein coupled, 1</u>	Hematological, pharmacogenomic,
175	21263830	<u>Purinergic receptor P2Y, G-protein coupled, 11</u>	Cardiovascular,
176	86301163, 5032039	<u>Regulator of G-protein signaling 4</u>	Neurological, pharmacogenomic, Psychological,
177	18677729	<u>Relaxin/insulin-like family peptide receptor 2</u>	Developmental
178	132608	<u>Ribonucleotide reductase M1</u>	Cancer, pharmacogenomic
179	1730070	<u>Ribosomal protein S6 kinase, 90kDa, polypeptide 3</u>	Developmental
180	187960042	<u>Selectin E</u>	Cancer, cardiovascular, developmental, immune, infection, metabolic, normalvariation, renal, unknown, vision
181	6274552	<u>Signal transducer and activator of transcription 1, 91kDa</u>	Infection
182	13272532	<u>Signal transducer and activator of transcription 3 (acute-phase response factor)</u>	Cardiovascular, immune, pharmacogenomic
183	15724400	<u>Signal transducer and activator of transcription 6, interleukin-4 induced</u>	Immune, infection, pharmacogenomic, renal, reproduction
184	3719421	<u>Similar to Werner syndrome protein; Werner syndrome, RecQ helicase-like</u>	Cancer, cardiovascular, metabolic, pharmacogenomic

185	38258652	<u>Sirtuin (silent mating type information regulation 2 homolog) 5 (S. cerevisiae)</u>	Psychological
186	74732700	<u>Solute carrier family 22 (organic anion/urate transporter), member 12</u>	Metabolic, renal
187	11141885	<u>Solute carrier family 5 (choline transporter), member 7</u>	Cardiovascular, neurological
188	17433306	<u>Solute carrier family 5 (low affinity glucose cotransporter), member 4</u>	Psychological
189	10937869	<u>Survival of motor neuron 1, telomeric; survival of motor neuron 2, centromeric</u>	Neurological, other
190	586067	<u>Synuclein, alpha (non A4 component of amyloid precursor)</u>	Chemdependency, neurological, other, Psychological
191	6226780	<u>Telomerase reverse transcriptase</u>	Cancer, cardiovascular, hematological
192	120660324	<u>Thrombopoietin</u>	Cardiovascular, hematological
193	189491771	<u>Thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian)</u>	Immune, metabolic, other, Psychological
194	38016895	<u>Thyroid stimulating hormone receptor</u>	Cancer, cardiovascular, immune, metabolic, other, vision
195	4507681	<u>Thyrotropin-releasing hormone receptor</u>	Cardiovascular
196	13959709	<u>Topoisomerase (DNA) II alpha 170kDa</u>	Cancer, pharmacogenomic
197	116242818	<u>Transforming growth factor, beta receptor II (70/80kDa)</u>	Cancer, cardiovascular, developmental, metabolic, other, Psychological, renal
198	4507593	<u>Tumor necrosis factor (ligand) superfamily, member 10</u>	Immune, infection
199	224494019	<u>Tumor necrosis factor receptor superfamily, member 10b</u>	Immune, normal variation
200	120407068, 269849759, 23491729	<u>Tumor protein p53</u>	Aging, cancer, cardiovascular, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, Psychological, vision

201	4507949	<u>Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide</u>	Immune
202	119533	<u>V-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)</u>	Cancer, metabolic, pharmacogenomic
203	111305821	<u>Valosin-containing protein</u>	Psychological
204	63054845	<u>Vitamin D (1,25-dihydroxyvitamin D3) receptor</u>	Aging, cancer, cardiovascular, hematological, immune, infection, metabolic, neurological, normalvariation, other, pharmacogenomic, renal, reproduction

DISCUSSION

According to detailed results of each ingredient, the frequency of “aging” function, “hematological”, “renal”, “vision”, “chemdependency”, “unknown”, “infection”, “developmental”, “normalvariation”, “reproduction”, “pharmacogenomic”, “psych”, “immune”, “neurological”, “metabolic”, “other”, “cardiovascular”, and “cancer” is 49, 59, 65, 80, 99, 101, 104, 108, 138, 140, 178, 208, 251, 252, 257, 276, 282, and 361, respectively.

Research conducted by YAOCHUN *et al.* (2009) suggested that flavonoids, particularly luteolin, in *Ilexeris sonchifolia* contribute to the neuroprotective effects, which made the compounds from these herb reasonable candidates for treatment of cerebral ischemia-reperfusion diseases. In our research, we had found that there were 56 genes in the total 154 genes of “luteolin” having the “Neurological” function, and at the same time, there were 16 genes with the function of “Hematological” improvement.

Ilexeris sonchifolia had definite curative effects on ischemic optic neuropathy, which could improve the blood-supply balance and optical microcirculation by changing blood rheological characteristics and hemodynamics with no absolute adverse reaction, so there were greatly significant points on promoting the early recovery and improving the quality of life in patients (HELI, 2013). In our research, we had found that there were 80 genes in the total 3008 genes having the “Vision” function, and at the same time, there were 59 genes in total with the function of “Hematological” improvement. The effects of genes on “Metabolic” function may be able to accelerate the blood cell’s regeneration.

Reports showed that *Ilexeris sonchifolia* Injection could contribute to remove the free radical, restrain the platelet aggregation and enhance the activity of plasmin to protect the ischemia injury (YOUSEF, *et al.*, 2004; JINNA *et al.*, 2006). In our research, we had found that there were 59 genes in the total 3008 genes having the “Hematological” function, and at the same time, there were 257 genes in total with the function of “Metabolic” improvement, which may offer a reasonable evidence for the previous researches.

In Li *et al.*'s research, intravenous drip infusion of *Ixeris sonchifolia* injection was given to 72 patients with atherosclerosis once daily. Levels of prostaglandin I₂ (PGI₂), endothelin (ET) and thromboxane A₂ (TXA₂) were tested from fasting venous blood samples (3 mL) before and after treatment for 1 week. Compared with the previous levels before treatment, significantly *Ixeris sonchifolia* injection decreased TXA₂ and ET respectively, but obviously increased PGI₂ (P<0.01). So *Ixeris sonchifolia* injection could improve and adjust the abnormal secretory function of vascular endothelial cells, so vascular endothelial cells could be considered as one of the targets of *Ixeris sonchifolia* effect (ZHAO-LIANG *et al.*, 2013). In our research, there were 257 genes with the "Metabolic" function and 282 genes with the "Cardiovascular" function. Especially the genes ID 31881630 and 3915797 had significant effects on prostaglandin G/H synthase and cyclooxygenase.

Interleukin-6 (IL-6) was a kind of acute reactive protein, produced by T lymphocytes, mononuclear macrophages, fibroblasts, endothelial cells and muscle cells, which was named as pro-inflammatory cytokine with tumor necrosis factor and interleukin-1, and it could mediate inflammatory and stress reaction. C-reactive protein (CRP) was the firstly discovered acute response protein in body, which was generally believed as a very sensitive inflammatory tissue damage marker. IL - 6 and CRP increased and participated in the occurrence and development of atherosclerosis, playing a very important role. *Ixeris sonchifolia* injection had protective effect on brain tissue by lowering plasma CRP and IL-6 levels, and could improve the total effective rate (QINGLING, 2011). In another experiment, it could reduce the IL-8 and TNF- α levels to improve the COPD Assessment Test in COPD patients (LIFANG and MEIJIAN, 2012). In our research, there were 104 genes with the "Infection" function and 251 genes with the "Immune" function. Especially the genes ID 15724400 and 108936015 had significant effects on IL-4 and IL-8 receptor respectively.

Ixeris sonchifolia could accelerate recovery speed of urinary protein, serum albumin, blood fat, blood coagulation function in primary nephrotic syndrome patients, and had great clinical significance in helping treat the PNS and improve the prognosis of nephrotic syndrome (XIAOJUAN *et al.*, 2013). In our research, there were 65 genes showing the effects on "Renal" function.

Report showed that the quantity of B16 melanoma living cells and survival rate reduced significantly, the expression level of anti-apoptotic protein Bcl-2 downregulated, the expression level of pro-apoptotic protein Bax upregulated, the quantity of apoptotic bodies and evident karyopyknosis rose and the quantity of mitochondria reduced with dose-dependent manner of *Ixeris sonchifolia* injection. So *Ixeris sonchifolia* inhibits malignant melanoma cell growth and enhanced apoptosis cells related to protein Bcl-2/Bax with a linear relationship (WANG *et al.*, 2013). In our research, the highest frequency, 361, of "Cancer" function might lay a solid foundation for the above research.

CONCLUSION

Ixeris sonchifolia Hance has effects on appendicitis, headache, menstruation, blood circulation, blood stasis, pain, fibrinolytic enzymes, thrombus formation, coronary artery, myocardial infarct size, PGI₂, ET, TXA₂, TNF, α -IL-6, and IL-8. In this research, we had detected the gene IDs, gene targets, and their functions about *Ixeris sonchifolia* Injection based on the method of information integration among various databases. 16 kinds of definite functions

had been found, 9 of which had laid a solid foundation for previous reports of *Ixeris sonchifolia* Injection's effects, and according to the frequency of genes ($n > 200$), the effects were focused on the psychological, immune, neurological, metabolic, cardiovascular, and cancer functions. At the same time, according to our results, the *Ixeris sonchifolia* injection may have influences on aging, chemdependency, developmental, normal-variation, reproduction, pharmacogenomic and psychologic functions, which should be verified in the future experiments.

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POTVRDA EFEKTA KOMPONENATA RASTVORA IZOLOVANIH IZ BILJAKA NA CILJNE GENE

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Izvod

Ixeris sonchifolia Hance, normalna perennialna trava ima efekta na upalu slepog creva, glavobolju, menstruaciju, cirkulaciju krvi, zastoj krvi, bolove, fibrinolitičke enzyme, formiranje tromba, koronarne arterije, veličinu miocardalnog infarkta, PGI₂, ET, TXA₂, TNF-, αIL-6, IL-8, etc. Merđutim, nije utvđeno potpuno pokrivanje molekularne osnove i target gena *Ixeris sonchifolia* injectiranja. *PubChem Database* i *DAVID Database* su korišćene zajedno u detekciji gena IDs, ciljnih gena i njihove funkcije. Konačno je nađeno 3008 gena, 16 vrsta konačnih funkcija od kojih je za potvrđeni efekat fokusiran na fiziološke, immune, neurološke, metaboličke i kancerogene funkcije. *Ixeris sonchifolia* je imao širok efekat na različite simptome koji su utvrđeni u ranijim eksperimentima i potvrđene rezultatima istraživanja. Uticaj na starenje, zavisnost na hemikalije, razvojne funkcije, normalno variranje, reprodukciju, farmakogene i psihološke funkcije treba da budu potvrđene u budućim eksperimentima.

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