Use SRWR algorithm and network pharmacology to predicting the mechanism of the action of Lithospermum erythrorhizon Sieb on atopic dermatitis

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Research Article

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Abstract

The application of network analysis algorithms promoted the development of network pharmacology. This study aimed to combine network pharmacology and signed random walk with restart (SRWR) to reveal the mechanism by which Lithospermum erythrorhizon Sieb (LES) exerts effects on atopic dermatitis (AD), and illustrate our approach and as a proof of principle for the method.

We retrieved the compounds and targets of LES from TCMID and TCMSP and identified important compounds and targets by intersection analysis and PPI network. Then we firstly constructed a human genomic signaling network, which containing KEGG signaling network(including proteins/genes, interactions and signaling pathways in KEGG database), and STRING database(covers of the correlation scores between genes), and ran SRWR and KEGG based on this network, we got the conclusion that the active LES-derived compounds caffeic acid, Isovaleric acid, Arnebinol and Alannan may inhibite PTGS2, HSP90AA1, MAPK14, which are critical mediators involved in PI3K-Akt pathway, Fc epsilon RI signaling pathway, VEGF signaling pathway, Calcium signaling pathway. The application of SRWR could obtain putative LES targets with a lower false-positive rate, and lead to a more reliable foundation and a more suitable TCM herb study. more verification will further illustrate the advantage of this approach in the study of TCM herb.

1. Background

Network pharmacology is a novel approach to explore the interaction between active ingredients and potential targets of drugs, indicating a holistic view of Traditional Chinese Medicine(TCM) [1]. In addition, network pharmacology integrates the interaction into a network and illustrates the action of drugs on the human body from a systematic perspective[2]. Meanwhile, there are also some problems such as the difficulty of data integration, the analysis of network characteristics to be improved. The signed random walk with restart(SRWR) could meet the data-dependent needs, identify targets with high confidence, simulate the propagation of activation or inhibition effects of the drug on the signaling network [3].by the construction of a signed human signaling network and application of SRWR, the most inhibited genes/proteins by LES against AD, and a clearer drug-target-pathway interaction network was constructed.

Based on traditional Chinese medicine (TCM) theory, Lithospermum erythrorhizon Sieb (LES) has the effects of promoting blood circulation, blood cooling, heat-clearing and detoxication has been used to treat AD for hundreds of years in China [4]. Naphthoquinone derivatives shikonin, acetylshikonin and isobutylshikonin are widely present in the epidermis of the roots of Lithospermum erythrorhizon Sieb[5]. Recent studies showed that shikonin could inhibit TNF-α upregulation in mucosal-type bone marrow-derived mast cells by suppressing the activity of calcineurin[6]. Wang and coworkers suggested that shikonin reduced inflammatory cell infiltration and collagen deposition by inhibiting NF-κB signaling pathway and suppressing the expression of MMP9[7]. However, the potential mechanisms of anti-inflammatory and anti-allergy activities of shikonin derivatives on AD have not been completely

elucidated, AD as a multifactorial disease has a high prevalence and affects 15–30% children and 2–10% adults[8], requires different diagnostic and therapeutic approaches. However, currently there are limited numbers of treatment options for AD patients. Therefore, precision medicine approaches to the prevention and management of AD are required. So we combine network pharmacology and SRWR to reveal the mechanism by which LES exerts effects on AD, and illustrate our approach as a proof of principle for the method.

2. Methods

2.1 Targets Chemical compounds and Targets of LES

The compounds and targets of LES were retrieved from Traditional Chinese Medicine Integrated Database (TCMID) [9] and Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) [10]. The bioactive components were selected based on the absorption, distribution, metabolism and excretion (ADME)[11]. The candidate components were determined based on two parameters: (1) Pharmacokinetics GI absorption (2) Drug-likeness (DL): the Lipinski rule of five and the Veber Ghose, Muegge and Egan rules, Compounds that meet more than two of Lipinski's rules will be chosen[12]. Eventually, 60 compounds were retrieved.

2.2 AD-associated genes

AD-associated genes were collected from the DisGeNET[13]and GEO(Gene Expression Omnibus)[14]. 120 AD-associated genes were obtained from DisGeNET, the genomic expression profiles of 72 AD controls from datasets(GSE32924, GSE36842, GSE107361 and GSE130588) were selected in GEO, dataset GSE22255). The corresponding research analyzed human peripheral blood mononuclear cells collected from 111 AD patients and 72 sex and age-matched controls. A total 410 differentially expressed genes were identified, in which 162 were up-regulated and 250 were down-regulated in AD patients.

2.3 FDA-approved drugs and their targets

The FDA-approved drugs for the treatment of AD were used as positive controls to contrast with LES compounds. And their targets were retrieved from the Drugbank database[15].

2.4 Construction of signed human genomic signal networks

We downloaded all signaling pathways(excluding metabolism pathways) data from KEGG database, and then combined proteins/genes and interactions from those signaling pathways to construct a KEGG signaling network. The correlation scores between genes were obtained from STRING database, these data were then integrated together to construct a human genomic signaling network. In this network, nodes denote proteins/genes and links denotes relationships between them. Activative or inhibitory relationships are depicted as either positive and negative links, positive links represent that an upstream protein activates a downstream protein, and a negative link means that an upstream protein inhibits a

downstream protein. Thus, the network is a weighted directed network called signed network. In which the weights of directed edges are between + 1 and − 1, + and - representing activation or inhibition, The constructed network has 3892 nodes and 28459 directed links, in which 21629 and 6830 are positive and negative links.

2.5 Simulating the propagation of the impact of a drug by signed random walk with restart(SRWR)

The SRWR algorithm was proposed in the research of social networks for measuring trust and distrust in signed social networks[16]. Here we used this algorithm to measure how the activation or inhibition of a seed node, which corresponded to a drug target, leaded to the activation or inhibition of other nodes in the human signaling network. A random walk on a graph is defined as an iterative walker's transition from a specific node to a random neighbor starting at a given source node (e.g. "protein A"). In this study, the algorithm of Random Walk with Restart (RWR) we applied in which allow the restart of the walk in every time step at node "protein A" with probability r. The equation for the random walk with restart is defined as:

$$p^{i+1} = (1 - r) Wp^t + rp^0$$

where r is the restart probability, W is the column-normalized adjacency matrix of the network graph, and p^t is a vector of size equal to the number of nodes in the graph where the i-thelement holds the probability of being at node$i$at time step t. The initial probability vector p^0 was constructed such that equal probabilities were assigned to the nodes representing members of the disease, with the sum of the probabilities equal to 1.

Suppose a signed random walker starts at one of the seed nodes *s* and walks on a signed network. The sign of the walker is either positive or negative, meaning that it exerts activation or inhibition to a node, respectively. At each step, the walker either moves to a randomly chosen neighbor node of the current node *v* or it jumps back to its starting seed node *s* and restarts its random walking. When the random walker goes through a negative edge, it changes its sign from positive to negative, or vice versa. Otherwise, it keeps its sign. Once the walker jumps back to its starting node, it regains its original sign. The SRWR can simulate the process that the activation or inhibition of a seed node propagates to other nodes in a signaling network.

In case we have a group of seed nodes such as multiple targets of a drug, we calculate the relative activation value of each activated seed and inhibited seed by finding the shortest path from seed node s to other targets.

3. Results

3.1 Identification of LES's important targets by intersection analysis

We collected two disease gene sets and one drug target set associated with AD as reference. Firstly, we investigated the overlaps between these gene sets. As shown in Fig. 1(A), 69 of the 751 AD disease genes in DisGeNET were differentially expressed in atopic dermatitis patients participated in the experiment of the GEO dataset, on the other hand, drug target genes for anti-AD drugs in Drugbank dataset have 11 genes in disgeNet. Fig. 1(A) shows that the three datasets have no common genes. In Fig. 1(B) we show the overlaps of LES's target genes with AD diseases genes and target genes for anti-AD drugs in DrugBank database. Among LES's 77 target genes, 17 are AD disease genes, there if which are anti-AD drug targets. The three common genes of the three datasets are PTGS2, NR3C1, SLC6A4 Suggesting their important role in treatment of AD. According to the data from TCMSP, PTGS2 were regulated by more than 10 compounds. PTGS2 was regulated by caffeic acid, (2R)-3-oxo-2-phenylbutanenitrile, acetylshikonin, isobutyryl shikonin, deoxyshikonin, palmitic acid, arnebinol, alpha-methyl-n-butylshikonin, alkannan, lithospermidin A, Caffeate, arnebinone, isovanillin, β-acetoxyisovalery lshikonin, lithospermidin B, shikonofuran B.

3.2 Identification of important targets regulated by LES by constructing and analyzing PPI network

We constructed a compound-compound target-AD target- proteins PPI network, including 77 nodes (23 compounds, 37 intersection targets between compound targets and AD targets PPI network, and 17 AD targets) and 441 edges (Fig. 2). nine nodes with an average value of degree ≥25 could be considered as major nodes, including Interleukin-6 (IL-6), prostaglandin endoperoxide synthase2 (PTGS2), nuclear receptor subfamily 3 group C, member 1 (NR3C1, glucocorticoid receptor), Estrogen Receptor 1 (ESR1), interleukin-1β (IL-1β), androgen receptor (AR), interleukin-10 (IL-10), interleukin-4 (IL-4) and heat shock protein 90 alpha family class A member 1 (HSP90AA1).

3.3 Prediction genes significantly inhibited and actived by the SRWR algorithm

The SRWR algorithm was used to measure how the inhibition or activation of a target by a drug propagates to the other nodes in the human signaling network. This could help assess the potential effect of a given drug. AD associated disease genes collected from four GEO datasets (GSE32924, GSE36842, GSE107361 and GSE130588) were used as mechanistic controls to contrast with LES's targets. As well as anti-AD drugs from DrugBank were used to verify and validate the effects of the drugs.

There were 36 targets of DrugBank anti-AD drugs. To simulate the effect of each drug on the human signaling network by SRWR, these 36 targets were first clustered into three groups according to their corresponding drugs (See Table 1). In Table 1 we list the numbers of genes in common between the top genes by each compound and the three validation gene datasets. in listed cases the *p*-values are much smaller than 0.05, indicating the statistically significant enrichment of actived genes in the validation sets, majority active compounds take inhititory effects.11compounds were listed in Table1. We found that an amout of genes in the validation sets were inhibited d by some compounds especially Acetylshikonin, Deoxyshikonin, Isobutyrylshikonin, Alkannan, Caffeic acid. These results suggest that LES exert its anti-AD effects mainly by inhibiting a group of genes associated with AD.

Table 1 The overlap numbers of top inhibited genes by each group of drugs with the three validation gene sets.

Drug class or compound	Target	Targets	AD disease genes	AD drugs targets	GEO up-regulated genes
Anti-histamine	(-)	22	2	11	0
Anti-inflammatory	(-)	7	1	2	0
immunity	(-)	5	1	1	0
Caffeic acid	(-)	28	11	1	4
Arnebinol	(-)	19	4	1	2
Palmitic acid	(-)	26	4	0	1
Acetylshikonin	(-)	28	3	0	8
Deoxyshikonin	(-)	16	3	0	6
Isobutyryl shikonin	(-)	18	2	0	5
Isovaleric acid	(-)	15	2	0	4
Lithospermidin A/B	(-)	13	2	0	4
α-methyl-n-butylshikonin	(-)	15	2	0	4
Lobelanidine	(-)	21	2	2	3
Senecic acid	(-)	6	2	0	2

3.4 KEGG pathway Enrichment Analyses

Pathway enrichment analysis identified a total of 107 KEGG pathways of basic biological process to be significantly enriched with inhibited genes corresponding to LES targets (p-value≤0.05), in which all three anti-AD associated pathways included. Similiary, 13 KEGG pathways were significantly enriched with anti-AD drugs(Fig. 3). metabolism pathways (Tyrosine metabolism, Tryptophan metabolism, Sphingolipid signaling pathway, Arginine and proline pathway), Cancer pathways (Small cell lung cancer, Prostate cancer, Chemical carcinogenesis), PI3K-Art signaling pathway, Neuroactive ligand-receptor interaction, Fc epsilon RI signaling pathway, VEGF signaling pathway, and so on(Table 2).

3 signaling pathways were associated with cancers, indicating that LES has the potential to treat diverse cancers such as lung cancer and prostate cancer as reported previously[17][18]. 4 signaling pathways were associated with metabolism pathways, the findings from metabolomics studies focusing on tyrosine and

tryptophan metabolism, sphingolipids derived metabolites were shown to have the potential to identify AD endotypes, which could beneficially promote personalized prevention and treatment[19].

Phosphoinositide 3-kinase(PI3K) acts as a key signaling protein in T cell activation, proliferation and migration. The proliferation of AD T cells and the secretion of IL-6 and IL-10 were significantly inhibited by inhibiting PI3K pathway. Combined with the results of this study, the major components of LES may inhibit IL-6 and IL-10 through PI3K/Akt pathway. Therefore, we hypothesized that PIK3-Akt signaling pathways may mediate the effects of LES on AD. Overproduction of VEGF in AD lesions has previously been observed, and also known that as a potential marker of AD severity[20], major compounds (Caffeic acid, Alkannan, Arnebinone, eg) may inhibite VEGF signaling pathways through MAPK14, PTGS2 .

FcεRI was the high-affinity receptor of IgE, with in-depth study of FcεRI signaling pathway[21], more and more key moculers on this pathway, for example, Omalizumab, cyclic peptides, some small proteins and natural products were to be the drug candidates against AD[22], in this study, we found Caffeic acid and Alkannan have the potential to be candidate natural drugs to bind PRKCB, BTK, RAC1 and MAPK14 to inhibit FcεRI signaling pathway. Calcineurin inhibition (tacrolimus) was the foundation of the pharmacologic treatment of AD, the inflammation suppressing roles of tacrolimus could be related with it effects of inhibiting T cell activation and blocking the Calcineurin signaling pathway[23]. otherwise, ORAI1/NFAT-calcium pathway was also found to play as an essential regulator with TSLP in AD[24]. Combine with the PPI network, the results indicated Arnebinol, Caffeic acid, Alkannan, Lobelanidine, may inhibit TSLP through ORAI1/NFAT-calcium pathway, and also may have a similar effect to tacrolimus through the Calcineurin signaling pathway.

Table 2 important compounds and associated genes in KEGG pathways

Pathways		Gene	Compouds’
Metabolism	Tyrosine metabolism	MAOB,GOT1,ADH1C,MAOA,ADH1B, ADH1A	Isovanilli, Isovaleric acid, cafferic acid
	Trypopan metabolism	MAOB,MAOA, CYP1A1	Isovanilli,cafferic acid
	Sphingolipid signaling pathways	OPRD1, PRKCB, BCL2, RAC1, MAPK14, CTSD	Lobelanidine, cafferic acid, Palmitic acid, Alkannan,
	Arginine and proline pathway	GATM, MAOB, GOT1, MAOA	Isovanilli, Isovaleric acid
PI3K-Art signaling pathway		COL1A1, GSK3B, BCL2, HSP90AA1, RXRA, RAC1 CHRM1, CDK2, KDR	Palmitic acid, Alkannan, α-methyl-n-butylshikonin, Arnebinol, cafferic acid
VEGF signaling pathway		PRKCB, KDR, RAC1, MAPK14, PTGS2	Caffeic acid, Arnebinone α-methyl-n-butylshikonin, Alkannan
Fc epsilon RI signaling pathway		PRKCB, BTK, RAC1, MAPK14	Caffeic acid, Alkannan
Calcium signaling pathway		CHRM3, CHRM1, PRKCB, ADRA1D, ADRB1, ADRB2, ADRA1B	Arnebinol, Caffeic acid, Alkannan, Lobelanidine,

4 Discussion

4.1 Potential mechanism of LES in treating AD

Using multiple bioinformatics approach, we have systematically investigated anti-AD mechanism of LES from compound, target, pathway, network respectively.we retrieved 23 active compounds from LES and predicted 99 targets. Network analysis suggested that LES exerted effects on AD by regulating such targets as IL-6, PTGS2, ESR1, IL-1β, AR, IL-10, HSP90AA1 and IL-4. Our overlapping analysis for collected data by combining GEO database and DrugBank, suggested that the active LES-derived compounds caffeic acid, Isovaleric acid, Arnebinol, Alannan may inhibite PTGS2, HSP90AA1, MAPK14, which are critical mediators involved in anti-inflammation, anti-histamine pathways. LES has produced its anti-AD effects because its combination of components inhibiting multible targets.

Constructing and analyzing a target-pathway network for putative LES targets showed that LES could modulate several signaling pathways implicated in the pathogenesis of AD, including PI3K-Akt pathway, Fc epsilon RI signaling pathway, VEGF signaling pathway, Calcium signaling pathway.These four signal transduction pathways cross-talk with each other to regulate inflammation, immmuity and allergy, while

the proinflammatory cytokines PTGS2, signal integration MAPK14, antiallergic receptor CHRM1 locate key link of the pathways. These results suggest that LES may take effects by inhibiting a series of proteins in each of these four pathways.

4.2 The Value Of The Proposed Computational Systems Pharmacology Approach

This study employed a computational systems pharmacology approach to elucidate the molecular mechanisms of TCM drug, using LES as an example. The results demonstrated the considerable advantage of this approach in investigating the mode of study of TCM products. The stimulatory or inhibitory activity of natural compounds on protein targets is usually lower than that of specifically designed drug molecules. Instead, pathways enriched with TCM targets are considered most likely to be regulated by the TCM drug. On the other hand, in view of the interactions between proteins/genes, the impact of natural drug on targets can spread to other proteins/genes through protein-protein interaction networks or through downstream signaling pathways. Based on these considerations, proteins/genes that are markedly inhibited or activated because of the network propagation of the targets are reasonably thought as significantly inhibited or activated by that drug. Several propagation-like agorithms, such as random walk with start[25], and diffusion kernel[26] have been applied for the identification of proteins Influenced by drugs or diseases, most of these algorithms are performed on positively weighted graphs, which cannot reflect the complete picture of drug-induced activation and/or inhibition on proteins. Such signaling pathways studied as separate entities, are not very suitable for TCM herb study. The SRWR algorithm was used to simulate the spread of active compound-induced activation or inhibition to a group of targets on a signed human signaling network[27]. The difficulty in the application of the SRWR algorithm is the lack of a readymade signed protein-protein interaction (PPI) network. In this study, we built a new network combining KEGG and STRING databases. In this network, by merging all available pathways, we constructed a signed human signaling network, which included positive and negative regulation relationships between proteins. This network was then used as a background network for conducting the SRWR.

Using the SRWR algorithm, we identified the top 5% genes inhibited by LES, and multiple tools were used to predict the targets of active LES compounds and only prediction results with the highest confidence scores were accepted. This strategy could obtain putative LES targets with a lower false-positive rate and a more reliable foundation for further mechanistic studies. The proposed computational systems pharmacology approach helped decipher and analyze the plausible connection between natural compounds, targets, disease processes, and currently approved single-agent pharmaceuticals in the context of network science, However, this study has limitations because it is based on online datasets. The detailed mechanisms of action of LES on AD should be validated by real-time PCR analysis and function assay. Second, due to the difficulty of data acquisition, the constructed human signaling

network may not include all known protein-protein interactions with direction and/or mode. This situation could be improved in the future when more signaling pathway data are available.

5 Conclusions

In this study, we constructed a signed network, combining KEGG and STRING databases, which included positive and negative regulation relationships between proteins, then we ran SRWR based on this background network. meanwhile, we collected disease gene sets in DisGeNET and GEO as reference, AD drugs from Drugbank as positive control, and only indentified prediction results with the highest confidence scores were accepted. These strategies could obtain putative LES targets with a lower false positive rate, and lead to a more reliable foundation and a more suitable for TCM herb study. Finally, the active LES-derived compounds caffeic acid, Isovaleric acid, Arnebinol, Alannan may inhibite PTGS2, HSP90AA1, MAPK14, which are critical mediators involved in PI3K-Akt pathway, Fc epsilon RI signaling pathway, VEGF signaling pathway, Calcium signaling pathway. From network point of view, through network propagation, LES inhibited a group of genes expressed in target tissues associated with AD, nextly, The deductions drawn from the computational analysis will be validated by our subsequent in silico, in vitro and in vivo experiments. more verification will further illustrate the advantage of this approach in the study of TCM herb.

Declarations

Ethics approval and consent to participate

No ethics statement was required because this study involved no human or animals.

Consent for publication

All authors read and approved the manuscript.

Availability of data and material

All data and material are available upon request.

Competing interests

The authors declare that there are no competing interests associated with the manuscript.

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Authors' contribution

T. W. designed the study. W.Y, L.Z and B.Z collected and analyzed the data.

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Not applicable

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Figures

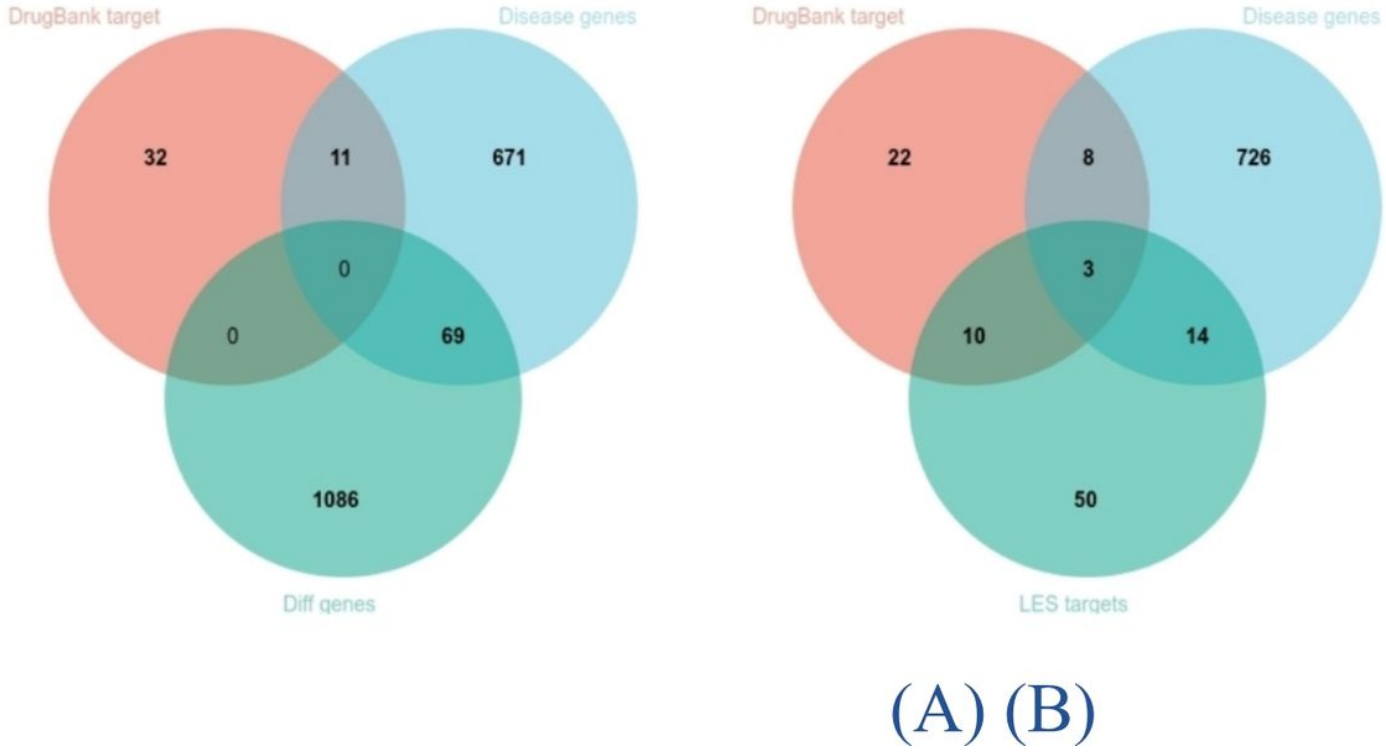

Figure 1

Overlaps between different gene sets under study. (A) Overlaps between diseases genes from DisGeNET (Disease genes), differentially expressed genes in the GEO dataset (Diff genes), drug target genes for anti-AD drugs in DrugBank database (DrugBank targets). (B) Overlaps between diseases genes from DisGeNET, drug target genes for anti-IS drugs in DrugBank database, and LES target genes (LES targets).

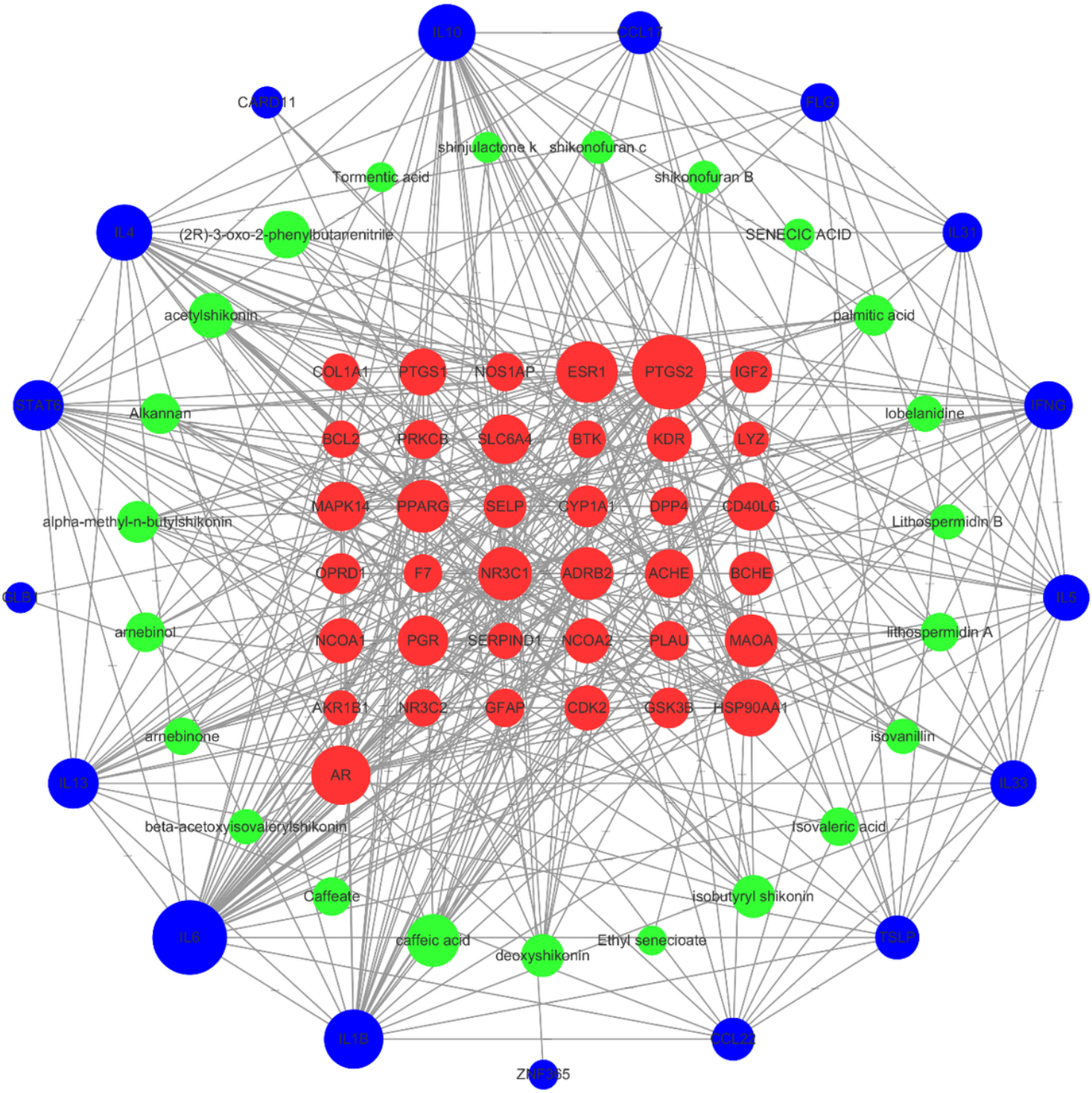

Figure 2

Compound-Compound Target-AD Target-Other Human Protein PPI Network. Green circles indicate compounds with effects on intersection targets between compound targets and AD targets. Red circles indicate intersection targets between compound targets and AD targets. Blue circles indicate targets related to AD.

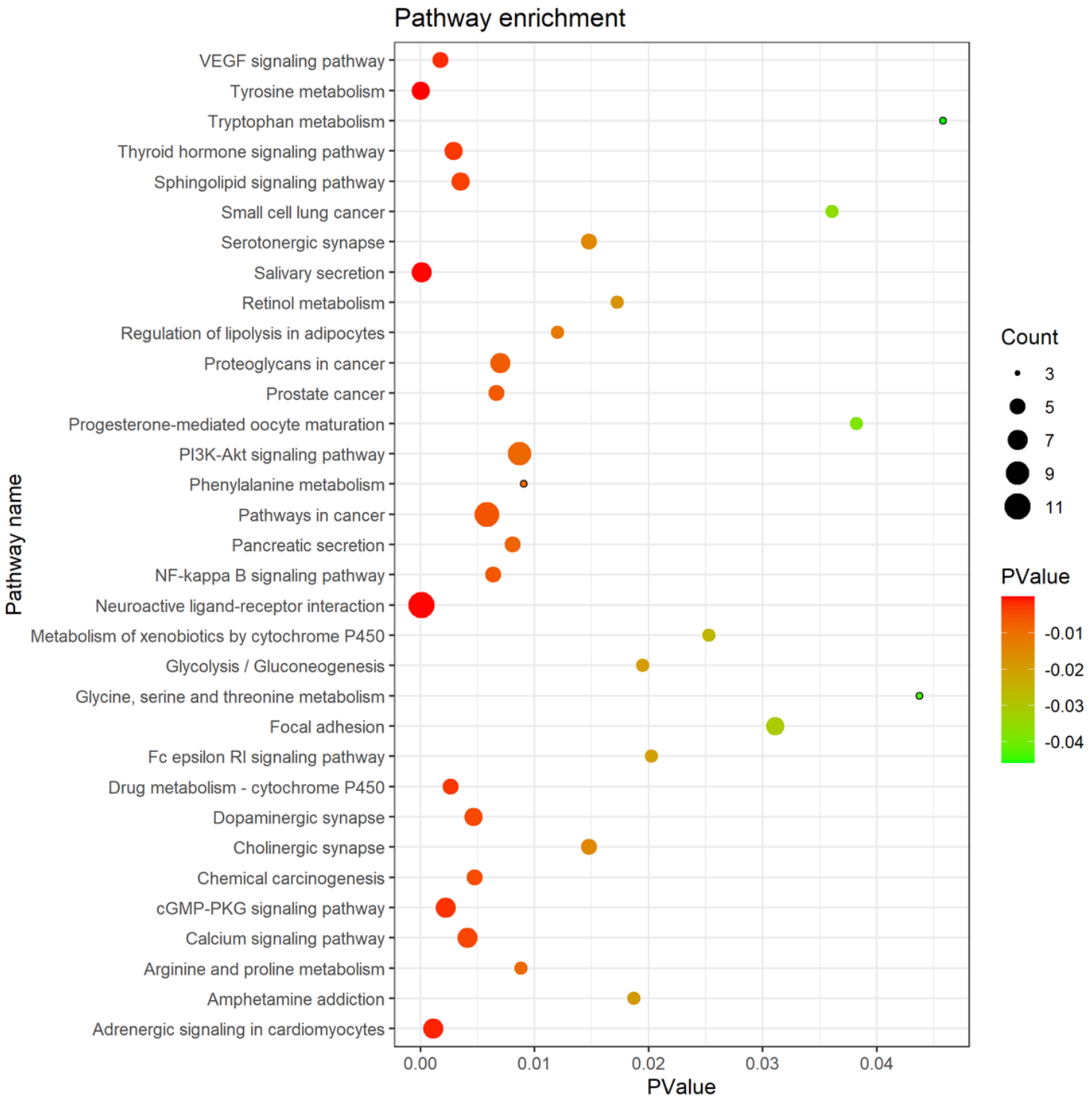

Figure 3

KEGG analysis of major targets of LES. X-axis showed the Rich factor (FDR<0.01), and Y-axis showed significantly enriched KEGG pathways of the targets.